Review

mTOR signaling in aging: from causality to geroprotective interventions and hallmark-level outcomes

Natalia Bobok[1]

[1]Chief Scientific Officer, INSTYTUTUM AG, Zug 6300, Switzerland

Correspondence to: Natalia Bobok; **email:** Natalia.bobok@instytutum.com
Keywords: mTOR signaling, mTORC1, mTORC2, geroprotective interventions, hallmarks of aging
Received: April 8, 2026 **Accepted:** August 21, 2026 **Published:** September 19, 2026

Copyright: © 2026 Bobok. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

The mechanistic target of rapamycin (mTOR) pathway is an important integrator of processes involved in aging and longevity, coordinating nutrient sensing, metabolic adaptation, and cellular stress responses. This review presents a three-section framework in which mTOR functions as a dynamic signaling hub coordinating multiple biological processes underlying the aging process. Evidence from genetic, experimental, and translational studies supports a causal role for mTOR signaling in lifespan regulation in model organisms, whereas human data remain predominantly associative but biologically consistent. mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) regulate distinct yet complementary aspects of cellular metabolism, proteostasis, autophagy, stress adaptation, and tissue homeostasis. Major geroprotective interventions—including autophagy activation, dietary interventions, physical activity, and senotherapeutics—partly converge on mTOR signaling but also engage parallel pathways. This adaptive regulation restores anabolic–catabolic balance, enhances stress resilience, and improves metabolic flexibility. Collectively, the available evidence identifies mTOR as an important integrative node linking multiple hallmarks of aging and diverse geroprotective interventions. Rather than representing a single therapeutic target, mTOR should be viewed as a context-dependent signaling hub which precise, tissue-specific modulation may promote healthy aging and support future geroscience-based interventions.

INTRODUCTION

Reversible protein phosphorylation is a fundamental mechanism of cellular signaling. It regulates protein activity, stability, localization, and molecular interactions through the coordinated actions of protein kinases and phosphatases. Protein kinases are tightly regulated enzymes that ensure signaling fidelity through precise spatial and temporal control of their activity [1]. Protein kinases constitute one of the largest and most functionally important enzyme families. They regulate virtually all major biological processes by transferring phosphate groups from adenosine triphosphate (ATP) to serine, threonine, or tyrosine residues [2]. This reversible post-translational modification propagates intracellular signaling through phosphorylation cascades, whereas phosphatases terminate signaling by removing phosphate groups from target proteins. Protein kinases account for approximately 2% of the human genome and comprise more than 500 genes. Based on structural and evolutionary characteristics, they are classified into serine/threonine, tyrosine, and dual-specificity kinases [3, 4]. Their structural complexity and regulatory versatility have established protein kinases as central subjects in modern structural biology and as major therapeutic targets, particularly in oncology, where kinase inhibitors have substantially improved clinical outcomes [5]. Within this large kinase superfamily, phosphatidylinositol 3-kinase-related kinases (PIKKs) constitute a specialized family of multidomain serine/threonine kinases. In humans, the PIKK family includes ataxia telangiectasia mutated (ATM), ATM- and Rad3-related (ATR), DNA-dependent protein kinase catalytic subunit (DNA-PKcs), mechanistic

target of rapamycin (mTOR), suppressor with morphological effect on genitalia family member 1 (SMG1), and transformation/transcription domain-associated protein (TRRAP). Canonical PIKKs share a conserved structural organization composed of N-terminal HEAT repeats, followed by the FRAP–ATM–TRRAP (FAT) domain, the catalytic kinase domain, and the C-terminal FATC domain [6]. Functionally, these kinases coordinate cellular adaptation to DNA damage, nutrient availability, oxidative stress, and energetic imbalance [7–9]. Whereas ATM, ATR, and DNA-PKcs primarily maintain genome integrity through DNA damage responses, mTOR occupies a distinct position by integrating nutrient sensing with metabolic regulation, cell growth, and anabolic homeostasis [10–12].

Among PIKK family members, mTOR occupies a central position in aging biology owing to its role in coordinating nutrient sensing, metabolism, and stress adaptation. mTOR is a multidomain serine/threonine kinase (~289 kDa) that integrates environmental and intracellular signals to regulate metabolism, growth, autophagy, and cell survival. It assembles into two functionally distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which differ in molecular composition, upstream regulation, and downstream signaling outputs [13, 14]. Rather than functioning as a linear signaling pathway, mTOR acts as a dynamic signaling hub that coordinates anabolic and catabolic processes in response to nutrient availability, energy status, and cellular stress. Dysregulated or persistent mTOR activation is associated with reduced metabolic flexibility, impaired stress adaptation, and accelerated aging, whereas context-dependent modulation of mTORC1 and mTORC2 supports cellular homeostasis and organismal resilience [15–17]. Consequently, mTOR has become one of the principal molecular targets in geroscience and a promising focus for interventions aimed at promoting healthy aging. This review provides an integrative analysis of the molecular architecture and biological functions of mTOR signaling, with particular emphasis on the emerging role of mTORC2 in aging and longevity. It examines mechanistic, genetic, experimental, and translational evidence linking mTOR signaling to lifespan regulation and critically evaluates current geroprotective interventions that modulate this pathway. Finally, the review discusses the therapeutic opportunities, biological trade-offs, and remaining translational challenges of targeting mTOR signaling to improve healthspan and healthy aging.

MATERIALS AND METHODS

This study was conducted as an integrative narrative review to synthesize current mechanistic, experimental, translational, and clinical evidence regarding the roles of mTORC1 and mTORC2 signaling in aging, longevity, and age-related diseases. An integrative review methodology was selected because the available evidence is highly heterogeneous, encompassing molecular and cellular investigations, animal studies, comparative biology, human genetic studies, translational research, and early-phase clinical trials. Such diversity precludes quantitative evidence synthesis but enables comprehensive integration of mechanistic and translational findings across multiple biological levels.

Literature search

A literature search was performed using MEDLINE (via PubMed), Scopus, Web of Science, and Google Scholar to identify relevant peer-reviewed publications addressing the role of mTOR signaling in aging and longevity. The primary search focused on publications from the preceding 10 years, while earlier seminal studies were retained when necessary to establish fundamental concepts or explain key mechanisms of mTOR biology. The final search covered studies published between November 2001 and April 2026. The final reference list comprised 265 sources, of which 94% were published from 2016 onward, indicating a predominantly recent evidence base. The search strategy combined controlled vocabulary (Medical Subject Headings [MeSH]) with free-text terms. The core PubMed search combined terms related to mTOR signaling and aging/longevity, for example: ((“mTOR”[Title/Abstract] OR “mTORC1” [Title/Abstract] OR “mTORC2”[Title/Abstract] OR “mechanistic target of rapamycin”[Title/Abstract] OR “target of rapamycin”[Title/Abstract]) AND (“aging”[MeSH Terms] OR “aging”[Title/Abstract] OR “ageing”[Title/Abstract] OR “longevity”[Title/Abstract] OR “lifespan”[Title/Abstract] OR “healthspan” [Title/Abstract])). Additional searches incorporated terms related to specific components and downstream pathways, including RAPTOR, RICTOR, SIN1, cellular senescence, hallmarks of aging, autophagy, AMPK, AKT, SGK, PKC, FOXO, caloric restriction, exercise, rapamycin, gero-protection, metabolic adaptation, comparative genomics, and long-lived species. Search strategies were adapted to the indexing systems and search interfaces of the individual databases. Additional relevant publications were identified through citation tracking of influential reviews and primary research articles.

Study selection

The core PubMed search restricted to the preceding 10 years identified approximately 3,000 publications. Titles and abstracts were screened for relevance to the objectives and scope of the review, followed by full-text

assessment of potentially relevant articles. Publications were selected based on their scientific relevance, mechanistic or experimental contribution, and relevance to the central themes of the review. Priority was given to studies providing:

- mechanistic insights into mTORC1 and/or mTORC2 signaling;
- evidence linking mTOR signaling to aging and longevity;
- experimental evaluation of pharmacological, genetic, nutritional, or lifestyle modulation of mTOR pathways;
- translational or clinical evidence relevant to geroprotective interventions.

Seminal studies published before the primary 10-year search window were additionally included when they established fundamental mechanisms or concepts necessary for interpretation of subsequent evidence. Following this process, 265 publications were selected for inclusion in the final reference list.

Evidence synthesis

Because the included studies differed substantially with respect to experimental models, biological systems, methodologies, and outcome measures, formal meta-analysis was not appropriate. Evidence was therefore synthesized using an integrative narrative approach, with emphasis on identifying convergent and divergent findings across molecular, cellular, animal, and human studies. Rather than ranking studies according to a predefined hierarchy of evidence, priority was given to mechanistic consistency, biological plausibility, reproducibility across independent investigations, and translational relevance. Where conflicting findings were identified, these were discussed in the corresponding sections of the review, particularly regarding differential functions of mTORC1 and mTORC2, tissue-specific effects of pathway modulation, and the therapeutic trade-offs associated with chronic versus intermittent mTOR inhibition.

Limitations

As an integrative narrative review, this article is intended to synthesize and interpret current mechanistic, translational, and clinical evidence rather than to provide an exhaustive systematic inventory of all published studies. Because the review integrates evidence from diverse experimental models, including molecular studies, animal models, and clinical investigations, the conclusions should be interpreted in the context of the inherent heterogeneity of the available literature. To provide a balanced perspective, both supportive and conflicting findings were incorporated whenever available. As a nonsystematic narrative review, the analysis may be subject to selection bias.

mTOR complexes: structure and functional specialization

Despite overall structural similarities, the mTOR signaling cascade is organized into two distinct multi-subunit complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). These complexes differ in both composition and functional properties. Notably, mTORC1 is sensitive to rapamycin, whereas mTORC2 is relatively resistant to acute rapamycin exposure. In addition to differences in pharmacological sensitivity, the two complexes exhibit distinct structural and regulatory features [18].

mTORC1: structural determinants and core signaling functions

mTORC1 is the major nutrient-responsive branch of the mTOR network and regulates cellular metabolism, growth, and proteostasis. Persistent or dysregulated mTORC1 activation has been linked to multiple aging-associated phenotypes, although its biological consequences are highly tissue- and context-dependent. Defining its organization and regulation is therefore necessary for interpreting interventions that alter mTOR signaling [9, 15]. Structurally, mTORC1 forms a dimer whose core consists of the kinase mTOR, regulatory-associated protein of mTOR (RAPTOR), and mammalian lethal with SEC13 protein 8 (mLST8/GβL). PRAS40 and DEPTOR are regulatory binding partners rather than invariant, stoichiometric components of the catalytic core. The TTI1–TEL2 complex supports the folding, maturation, and stability of mTOR and other phosphatidylinositol 3-kinase-related kinases but is not itself a structural component of mTORC1 [19, 20]. The C-terminal region of mTOR contains the FAT, FKBP12–rapamycin-binding (FRB), kinase, and FATC domains. The FRB domain binds the FKBP12–rapamycin complex, whereas RAPTOR recognizes TOR signaling (TOS) motifs in selected substrates and facilitates their recruitment to mTOR. These structural features contribute to substrate selectivity and determine the pharmacological sensitivity of mTORC1 to rapamycin, although the extent of inhibition varies among substrates and experimental conditions [21].

Subcellular localization is an important component of mTORC1 regulation. Amino-acid-sensitive Rag GTPases recruit mTORC1 to the lysosomal surface, where Rheb directly stimulates its kinase activity in

response to growth-factor signaling. During acute amino acid deprivation, mTORC1 generally dissociates from lysosomes and becomes cytosolic and inactive rather than accumulating there. mTORC1 or its components have also been detected in the cytoplasm and at the endoplasmic reticulum, Golgi apparatus, mitochondria, and nucleus. These observations suggest that some mTORC1 signaling is spatially distributed. However, the abundance, activity, and physiological relevance of individual non-lysosomal pools are not equally established across cell types, and detection of mTOR alone does not necessarily demonstrate the presence of an intact, active mTORC1 complex. Lysosomal proteolysis and autophagic recycling generate intracellular amino acids that contribute to mTORC1 reactivation after nutrient deprivation. Constitutive lysosomal degradation may also help maintain local amino acid availability under nutrient-replete conditions. This model could explain why a fraction of mTORC1 remains lysosome-associated when extracellular nutrients are available, but its quantitative contribution to basal signaling remains uncertain. The lysosome should therefore be viewed as a major nutrient-sensing and activation platform, not necessarily as the exclusive site of mTORC1 signaling [22–24]. Amino acids activate mTORC1 through Rag-dependent and Rag-independent routes. Leucine, arginine, and glutamine engage distinct upstream sensors and regulators. In addition to canonical Rag-mediated recruitment, glutamine and, in some contexts, asparagine can signal through Arf1-dependent mechanisms. Rab1A-dependent regulation at the Golgi has also been reported. The relative importance of these mechanisms varies according to cell type, nutrient composition, and experimental context [25].

Growth factors regulate mTORC1 mainly through the PI3K–PDK1–AKT pathway. PDK1 contributes to AKT activation, and AKT phosphorylates TSC2, reducing TSC-complex inhibition of Rheb and thereby promoting mTORC1 activation. Energy depletion activates AMP-activated protein kinase (AMPK), which restrains mTORC1 and promotes catabolic adaptation. DNA damage, hypoxia, and other stresses can also modify this network. Rather than functioning as a simple binary switch, these regulatory inputs modulate signaling amplitude, duration, subcellular localization, and substrate selectivity. When nutrients and growth signals are sufficient, mTORC1 promotes protein, lipid, and nucleotide synthesis and supports cell growth. During nutrient or energetic stress, reduced mTORC1 activity permits autophagy and TFEB-dependent lysosomal programs that recycle cellular components. AMPK further promotes autophagy through regulators including ULK1 and Beclin 1. Thus, the balance between mTORC1 and AMPK contributes to the choice between biosynthesis and stress adaptation, although it is only one part of a broader regulatory network [26–32]. Collectively, these inputs enable mTORC1 to integrate nutrient availability, growth factor signaling, cellular energy status, hypoxia, and DNA damage into coordinated metabolic responses. Consequently, the benefits and risks of mTOR modulation are determined by the mode of pathway regulation rather than by inhibition alone.

At the effector level, mTORC1 phosphorylates key substrates, including ribosomal protein S6 kinases (S6K1 and S6K2), eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), and components of the ULK1 autophagy-initiating complex (ULK1, ATG13, and FIP200) [18, 32]. A critical downstream event is phosphorylation of the hydrophobic motif of S6 kinases. mTORC1 phosphorylates the S6K hydrophobic motif, principally Thr389 in S6K1 and the corresponding Thr388 in S6K2. This event is necessary but not sufficient for full activation: it facilitates subsequent PDK1-dependent phosphorylation of the activation loop, including Thr229 in S6K1. Humans express two S6K genes, RPS6KB1 (S6K1) and RPS6KB2 (S6K2), each producing multiple isoforms. S6K1 and S6K2 share substantial sequence similarity and regulatory mechanisms but also have isoform- and context-specific functions. Once activated, S6Ks phosphorylate ribosomal protein S6 and additional substrates involved in translation, cell growth, and metabolic adaptation [33, 34]. S6K signaling contributes to mRNA translation and protein synthesis, although the determinants of transcript selectivity remain incompletely resolved. S6Ks also influence lipid metabolism, glucose homeostasis, insulin signaling, and cell size. Effects on proliferation and apoptosis vary with cell type and physiological context. S6K should therefore be considered one important mTORC1 effector branch rather than a uniform determinant of anabolic output [34–36].

Another major mTORC1 substrate is eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Its phosphorylation is commonly described as a hierarchical process in which Thr37 and Thr46 act as early or priming sites, followed by phosphorylation of Thr70 and Ser65 [37]. However, the precise order and rapamycin sensitivity of individual sites can vary with cellular context and experimental conditions. In its hypophosphorylated state, 4E-BP1 binds eIF4E and prevents formation of the eIF4F complex required for efficient cap-dependent translation. Multisite phosphorylation by mTORC1 reduces the affinity of 4E-BP1 for eIF4E, allowing eIF4F assembly and translation initiation. Accordingly, 4E-BP1 phospho-rylation is an important mechanism through which

mTORC1 increases cap-dependent translation. mTORC1 can phosphorylate free and eIF4E-bound 4E-BP1, although complete dissociation from eIF4E generally requires multisite phosphorylation. Because eIF4E availability can limit translation initiation, the mTORC1–4E-BP1 axis provides a major, but not exclusive, control point for protein synthesis [38–40].

mTORC1 is an important negative regulator of autophagy initiation. It acts primarily by phosphorylating ULK1 and ATG13 within the ULK1–ATG13–FIP200 complex [41]. Under nutrient-replete conditions, mTORC1 phosphorylates human ULK1 at Ser758 (Ser757 in mouse), which disrupts productive interaction between ULK1 and AMPK. Ser638 has also been described as a nutrient-sensitive, mTORC1-regulated site [42]. These modifications reduce the pro-autophagic activity of ULK1 but should not be interpreted as causing complete disassembly of the mammalian ULK1 complex. mTORC1-dependent phosphorylation of ATG13 further reduces ULK1-complex activity and can limit its translocation or productive engagement at autophagosome-initiation sites [43, 44]. Unlike the yeast Atg1 complex, the mammalian ULK1–ATG13–FIP200 complex remains largely assembled under both nutrient-replete and starvation conditions. FIP200 functions as a scaffold that supports interactions among ULK1, ATG13, autophagy receptors, and downstream autophagy machinery; disruption of these interfaces impairs autophagosome formation [45]. The ULK1 complex also participates in selective autophagy, including mitophagy. Autophagy receptors can recruit the complex through FIP200, and FIP200 phosphorylation has been implicated in later stages of mitophagy [46]. These findings establish a role for the ULK1–FIP200 machinery in mitochondrial quality control, but they do not demonstrate that every receptor-mediated or late mitophagy step is directly controlled by mTORC1. Overall, mTORC1 links nutrient availability to protein synthesis, metabolism, and autophagy through distinct S6K, 4E-BP1, and ULK1-complex branches. These outputs are context-dependent and interact other signaling pathways. mTORC1 should therefore be viewed as an important regulatory node within a broader adaptive network (Figure 1).

mTORC2: molecular architecture and regulatory dynamics

Compared with mTORC1, the regulation of mTORC2 remains less completely defined, partly because broadly validated mTORC2-selective pharmacological inhibitors are lacking. Functional evidence therefore relies heavily on genetic perturbation of complex-specific subunits [47, 48]. The core complex contains mTOR, mLST8, RICTOR (rapamycin-insensitive companion of mTOR), and mSIN1 (MAPKAP1). DEPTOR and Protor proteins (PRR5/PRR5L) can associate with the complex, whereas TTI1–TEL2 supports mTOR folding and stability but is not generally considered a defining mTORC2 core subunit. Structural studies show that mTORC2 forms a dimeric assembly in which RICTOR and mSIN1 interact extensively with mTOR. mSIN1 lies near the FRB domain and catalytic cleft, while the RICTOR–mSIN1 module sterically limits FKBP12–rapamycin access to the FRB region. This architecture explains the relative resistance of assembled mTORC2 to acute rapamycin exposure, although prolonged treatment can disrupt mTORC2 in some cell types. Compared with mTORC1, mTORC2 adopts a more compact conformation, reflecting tighter interactions among mTOR, RICTOR, and mSIN1 [20, 49]. RICTOR is required for complex assembly and activity, and its deletion suppresses downstream signaling and can increase sensitivity to stress or pro-apoptotic stimuli in specific experimental systems [50]. mSIN1 contributes to complex stability and substrate recruitment. It contains an N-terminal region, a conserved middle region (CRIM), a Ras-binding domain, and a pleckstrin homology domain. The CRIM domain provides a principal interaction surface for AGC-kinase substrates, although substrate recognition also depends on other contacts and cellular context. Thus, RICTOR and mSIN1 jointly determine mTORC2 architecture, substrate access, and acute rapamycin resistance [51–54].

mTORC2 signaling is also spatially compartmentalized. In the cell systems examined, plasma-membrane mTORC2 activity was relatively independent of acute PI3K activation, whereas growth factors promoted AKT phosphorylation largely by recruiting AKT to membrane-localized mTORC2. By contrast, endosomal and endoplasmic-reticulum-associated mTORC2 pools showed greater PI3K sensitivity. Proposed feedback regulation through AKT and mSIN1 may contribute to these differences, but its general relevance remains uncertain. mTORC2 activity or individual complex components have additionally been reported at mitochondria-associated membranes, lysosomes, peri-nuclear regions, and the nucleus. Evidence for the abundance and function of these pools varies among cell types, and detection of a subunit does not necessarily establish the presence of an intact active complex. Nevertheless, spatial partitioning provides a plausible mechanism for positioning mTORC2 near selected substrates and generating context-dependent signaling outputs [48, 55].

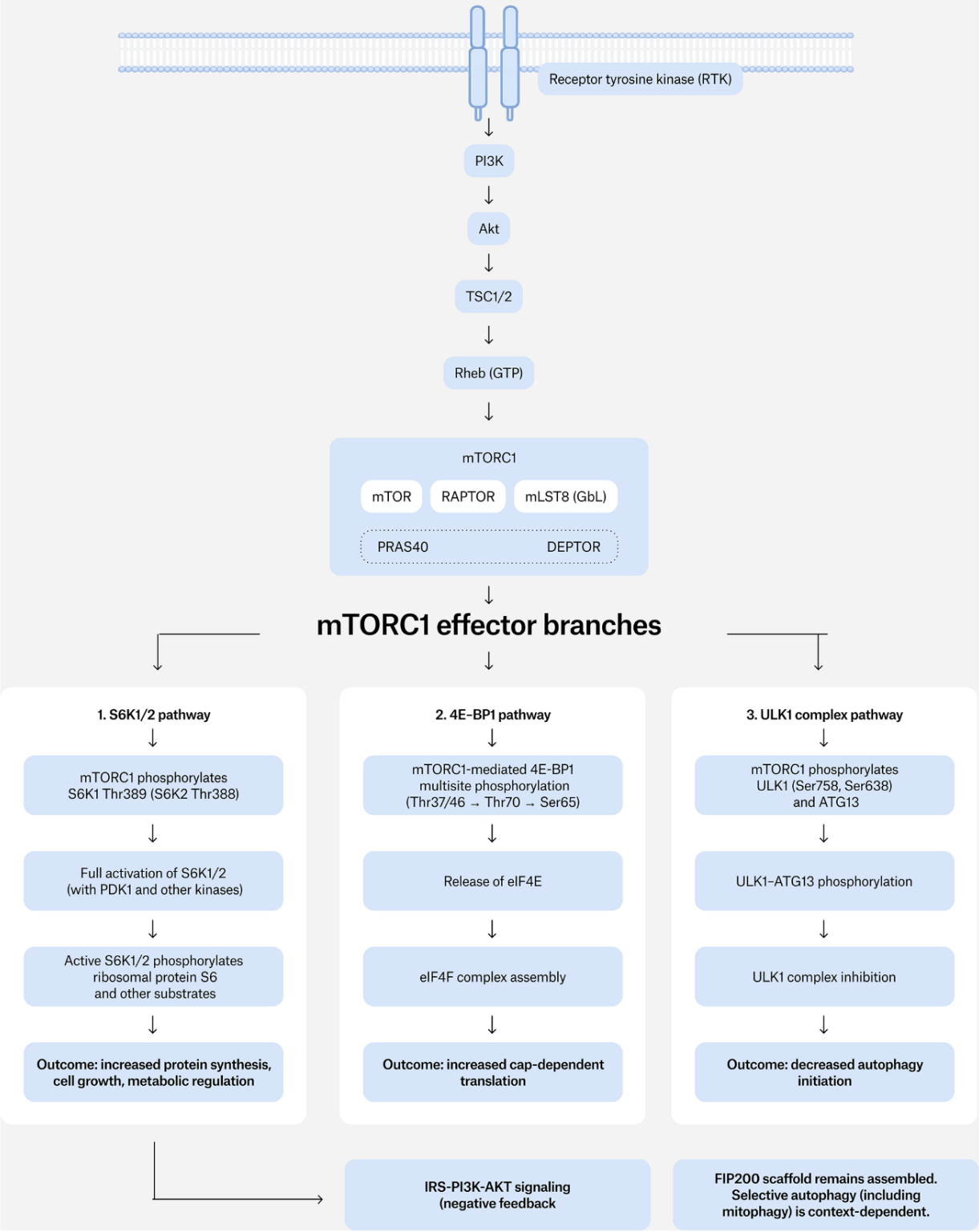


Figure 1. Principal mTORC1 effector pathways. Schematic overview of the principal downstream effector pathways regulated by mTOR complex 1 (mTORC1). Growth factor signaling activates mTORC1 through the PI3K–AKT–TSC1/2–Rheb pathway. The core complex comprises mTOR, RAPTOR, and mLST8 (GβL), whereas PRAS40 and DEPTOR act as regulatory binding partners. Activated mTORC1 regulates three major effector branches: (1) S6K1/2 phosphorylation, promoting protein synthesis, cell growth, metabolic regulation, and negative feedback to IRS–PI3K–AKT signaling; (2) 4E-BP1 phosphorylation, facilitating eIF4F assembly and cap-dependent translation; and (3) ULK1–ATG13 phosphorylation, suppressing autophagy initiation while the FIP200 scaffold remains assembled. Together, these pathways coordinate anabolic metabolism and autophagy in response to growth factor and nutrient availability. This figure was created using Figma.

mTORC2 responds to growth factors, hormones, nutrients, and cellular stress [48]. Insulin and insulin-like growth factors activate PI3K and increase phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3), promoting AKT recruitment and signaling through PI3K-sensitive mTORC2 pools [56, 57]. PIP3 should not, however, be viewed as a universal direct activator because plasma-membrane mTORC2 can remain active independently of acute PI3K stimulation. Adrenergic signals, bioactive lipids, exercise-associated stimuli, and acetylation have also been reported to modulate mTORC2 [58]. Responses to nutrients are less uniform than those of mTORC1. Glucose, amino acids, folate, and lipid species have been linked to mTORC2 activity, but their effects vary by tissue and metabolic state. AMPK, small GTPases, and reactive oxygen species (ROS) provide additional regulatory inputs [48, 59]. During acute energetic stress in cultured-cell models, AMPK directly phosphorylates mTOR and RICTOR and can enhance mTORC2–AKT survival signaling [60]. Small GTPases, including Ras-family proteins, have been reported to regulate mTORC2 through direct interactions and PI3K-dependent mechanisms, although these effects are cell-, model-, and compartment-specific [61, 62]. ROS also provide a context-dependent regulatory input. ROS can activate mTORC2, influencing senescence, fibrosis, and repair responses. These effects are cell type- and context-dependent rather than universal [63, 64].

mTORC2 regulates a broad range of cellular processes through the phosphorylation and functional maturation of AGC kinase family members, including protein kinase B (AKT), protein kinase C (PKC), and serum- and glucocorticoid-induced kinases (SGKs) [48]. Among these, AKT is a central mTORC2 effector that integrates growth-factor and metabolic signals to control cell survival, proliferation, and anabolic metabolism [65–67]. Canonical growth-factor-dependent AKT activation occurs within PI3K signaling. PI3K-derived phosphoinositides, principally phosphatidylinositol (3,4,5)-trisphosphate (PIP3), recruit AKT and phosphoinositide-dependent kinase 1 (PDK1) to membrane compartments. PDK1 phosphorylates AKT at Thr308 within the activation loop, producing substantial catalytic activity. mTORC2 directly phosphorylates AKT at Ser473 within the hydrophobic motif, increasing maximal activity and broadening or modifying substrate engagement; however, the requirement for Ser473 varies among substrates and cell types [68, 69]. Activated AKT regulates pro-apoptotic and stress-response programs through multiple substrates. AKT phosphorylation of FOXO transcription factors promotes 14-3-3 binding, cytoplasmic retention, and reduced transcription of genes involved in apoptosis, stress resistance, and catabolic metabolism [70, 71]. AKT further supports cell survival and metabolic adaptation by phosphorylating BAD and glycogen synthase kinase-3β (GSK-3β). This promotes glycogen synthesis in insulin-responsive tissues and can stabilize β-catenin in specific cellular contexts, although it does not necessarily activate canonical Wnt signaling [72–76]. In skeletal muscle and adipose tissue, AKT promotes glucose uptake by phosphorylating regulators of GLUT4 trafficking, particularly AS160/TBC1D4, thereby facilitating GLUT4 translocation to the plasma membrane [77]. In defined cell types, AKT can further support glycolytic flux through phosphofructokinase-2/fructose-2,6-bisphosphatase signaling and through increased hexokinase II activity or mitochondrial association [78]. AKT also contributes to lipid homeostasis by stimulating lipogenic pathways and, in adipocytes, participating in insulin-mediated suppression of lipolysis, although the relevant mechanisms are context-dependent. Collectively, mTORC2-supported AKT signaling contributes to insulin responsiveness, energy balance, and adaptation to nutrient availability, but individual outputs differ according to AKT isoform, tissue, and signaling context [79].

In addition to AKT, mTORC2 regulates several protein kinase C (PKC) isoforms within the AGC kinase family. The nine mammalian PKC genes comprise conventional (PKCα, PKCβ, PKCγ), novel (PKCδ, PKCε, PKCη, PKCθ), and atypical (PKCζ and PKCι/λ) subclasses. Mature PKCs are autoinhibited by a pseudosubstrate occupying the active site and require ordered priming phosphorylations during biosynthetic maturation. mTORC2 regulates the maturation and stability of protein kinase C (PKC) isoforms through phosphorylation-dependent priming. Loss of mTORC2 impairs PKC maturation and promotes degradation of susceptible isoforms [1, 80]. Once matured, PKCs remain inactive until receptor stimulation activates phospholipase C (PLC), generating diacylglycerol (DAG) and Ca^{2+} signals. Conventional PKCs require both DAG and Ca^{2+}, novel PKCs respond primarily to DAG, whereas atypical PKCs are activated through distinct protein and lipid interactions. Activated PKCs form spatially organized complexes that regulate proliferation, apoptosis, survival, differentiation, migration, and gene expression in an isoform- and context-dependent manner [81, 82]. PKC signaling is closely linked to cytoskeletal organization and cell architecture. Depending on the isoform and cellular context, PKCs phosphorylate regulators of actin dynamics, stress-fiber formation, adhesion turnover, and membrane–cytoskeleton coupling. Representative substrates include MARCKS (myristoylated alanine-rich C kinase substrate), which regulates actin cross-

linking and membrane-associated signaling, and ERM proteins (ezrin, radixin, moesin), which connect membrane proteins to cortical actin [83–87]. PKCs also modulate membrane excitability and ionic homeostasis through isoform- and tissue-specific phosphorylation of ion channels and transport systems, including selected TRP, K^+, Ca^{2+}, Na^+, and Cl^- channels as well as connexins. These effects can alter Ca^{2+} signaling, pH regulation, electrical excitability, and intercellular communication [88, 89]. PKC additionally modulates vesicular trafficking, including exocytosis and endocytosis, with effects on secretion, neurotransmitter release, and hormone signaling. Pharmacological PKC inhibition reduces or delays endocytic flux in some experimental systems, but this response is not universal [90, 91]. PKCs can also signal from nuclear and other intracellular compartments to modify transcriptional programs. Thus, mTORC2-supported PKC maturation contributes to cellular architecture, membrane dynamics, and adaptive signaling; however, individual PKC outputs cannot be attributed uniformly to mTORC2 and depend on isoform, localization, and stimulus [92].

The serum- and glucocorticoid-induced kinase (SGK) family comprises three AGC kinases (SGK1–3) that are structurally related to AKT but differ in their regulatory domains, localization, and biological functions. Their activation requires sequential phosphorylation by mTORC2 and PDK1. mTORC2 is the established hydrophobic-motif kinase for SGK1, whereas regulation of SGK2 and SGK3 is more context-dependent and may involve distinct PI3K–mTOR compartments [93–95]. SGK1 is the most extensively characterized isoform and is widely expressed. Its transcription is rapidly induced by glucocorticoids, mineralocorticoids, osmotic stress, and other stimuli, whereas kinase activity is controlled post-translationally. It regulates channels, transporters, and signaling proteins and can promote survival through FOXO phosphorylation and context-dependent modulation of p53, β-catenin, and NF-κB pathways [95–97]. SGK1-mediated FOXO3 phosphorylation promotes cytoplasmic retention and reduces pro-apoptotic transcription, whereas SGK1 inhibition increases apoptosis in several experimental models [98, 99]. In epithelia, SGK1 increases the activity or membrane abundance of ENaC, Na^+/H^+ exchangers, Na^+/K^+-ATPase, and the sodium–chloride cotransporter, often by inhibiting NEDD4-family ubiquitin ligases [100]. Other SGK1-sensitive transport systems regulate K^+, Ca^{2+}, Cl^-, cell volume, and osmotic balance [101]. SGK1 can also enhance intestinal glucose transport and renal glucose reabsorption. These effects influence systemic glucose handling but may promote hyperglycemia or sodium retention when SGK1 activity is excessive [102, 103]. SGK2 remains less characterized than SGK1. Experimental studies link it to glutamate-receptor trafficking and epithelial ion transport [104]. In renal models, activated SGK2 increases NHE3 surface abundance and Na^+/H^+ exchange [105] and stimulates organic anion transporter 4 through NEDD4-2 [106]. In hepatocytes, pregnane X receptor signaling induces SGK2 and glucose-6-phosphatase, supporting insulin-independent gluconeogenesis [107]. Cold and β_3-adrenergic stimulation also induce SGK2 in brown and beige adipocytes, although deletion has little effect on canonical thermogenesis [108]. Cancer models further link SGK2 to lysosomal acidification and autophagy through ATP6V1H [109] and to FOXO1–GPX4-dependent ferroptosis resistance [110], but these functions are not established in normal tissues. SGK3 is recruited to phosphatidylinositol-3-phosphate-rich endosomes by its phox-homology domain and activated through PDK1 and hydrophobic-motif phosphorylation. It regulates several epithelial transporters, although much evidence comes from heterologous systems [111]. Model-specific functions include BRG1 phosphorylation during adipogenesis [112], preservation of nephrin and podocin during podocyte injury [113, 114], and GSK3β–β-catenin regulation in selected regenerative or cancer models [115]. SGK signaling has also been implicated in developmental neurotoxicity and microglial biology [116, 117]. In PIK3CA-mutant cervical-cancer cells, SGK3 stabilizes catalase [118], but these findings do not establish general neuronal or systemic functions. Collectively, SGKs connect PI3K–mTOR signaling with transport, metabolism, survival, and stress adaptation. In contrast to mTORC1, which predominantly coordinates anabolic growth programs, mTORC2 exhibits broader and more context-dependent functions (Figure 2).

Mechanistic role of mTOR signaling in aging

This section follows a three-part framework that progresses from the mechanistic role of mTOR signaling in aging, through geroprotective interventions targeting mTOR, to its interactions with the hallmarks of aging and age-related diseases. This structure integrates mechanistic evidence, intervention strategies, and biological outcomes to provide a coherent view of mTOR signaling across the aging process (Figure 3).

Causal role of mTOR complexes in aging

mTORC1/2 in aging: convergence of evidence and limits of causal inference

A substantial body of evidence from genetic, experimental, and interventional studies implicates mTOR signaling as an important regulator of aging

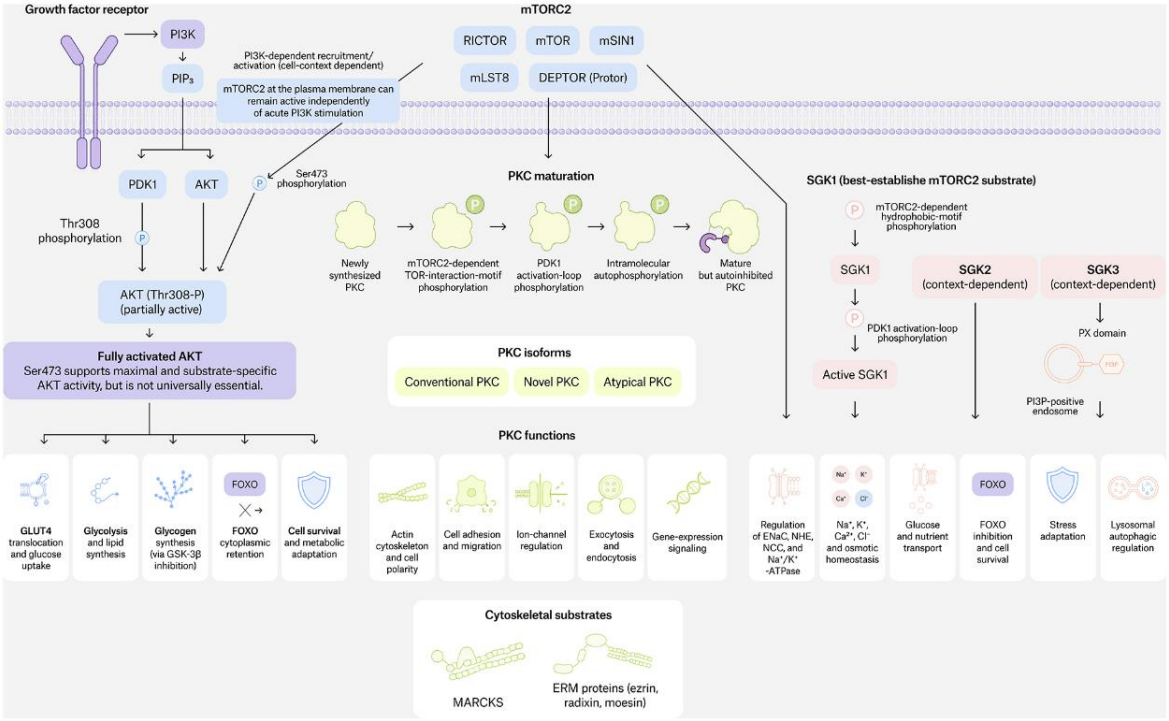


Figure 2. mTORC2 regulation of kinase effectors. Schematic overview of mTORC2 signaling. Growth factor–PI3K signaling promotes context-dependent mTORC2 activation, leading to phosphorylation of AKT, PKC, and SGK family kinases. These downstream pathways regulate cell survival, metabolism, cytoskeletal organization, ion transport, and stress adaptation. This figure was created using Figma.

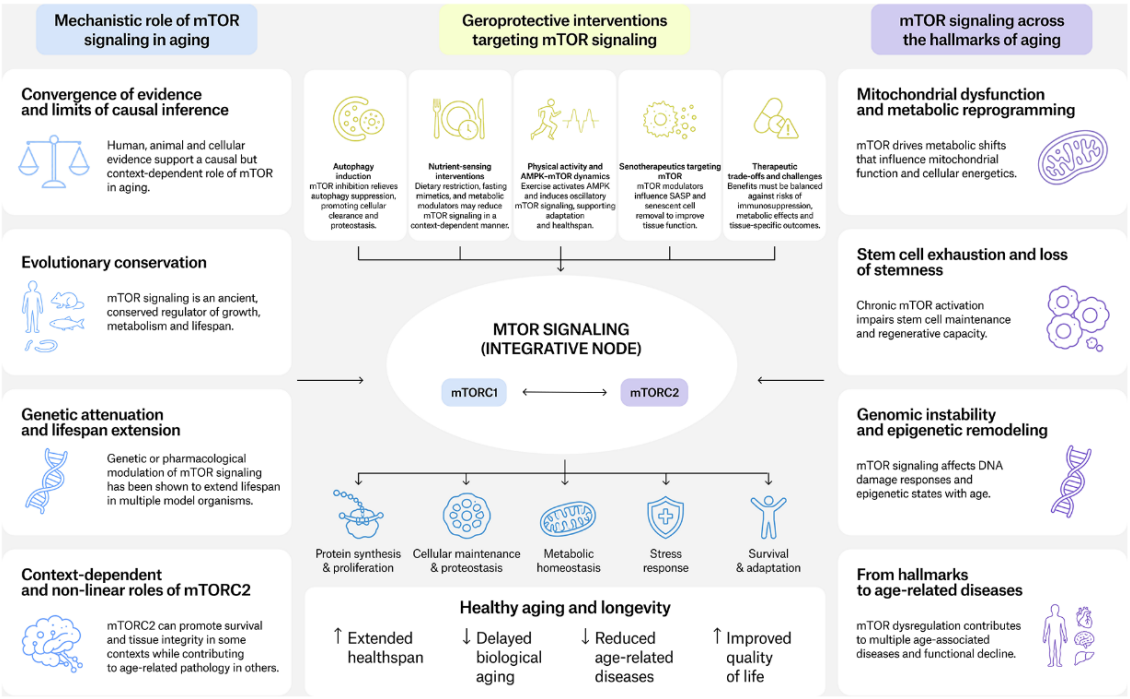


Figure 3. Three-section framework of the section. The figure summarizes the three-section approach, linking the mechanistic role of mTOR signaling in aging, evidence for geroprotective interventions, and mTOR interactions with the hallmarks of aging and age-related diseases. This figure was created using Figma.

biology and longevity. Experimental studies in model organisms support a causal role for mTOR signaling in aging-related processes and lifespan regulation, whereas evidence in humans remains largely associative and translational. Therefore, mTOR may be considered causally involved in aging in experimental model systems and strongly implicated, but not definitively proven as causal, in human aging [119, 120]. First, genetic modulation of mTOR pathway components has been consistently associated with lifespan extension across diverse experimental organisms, supporting a causal contribution of mTOR signaling to longevity in model systems. Evidence from human studies is more indirect. Large-scale whole-exome sequencing analyses of long-lived individuals have identified enrichment of rare coding variants in genes functionally related to mTOR signaling. Variants in genes such as RPS6, FLCN, and SIK3 have been reported among centenarian populations, while RWDD1 has emerged in gene-based analyses. Functional enrichment of mTOR-related pathways further supports the biological relevance of these observations, although it does not establish causality [121]. Importantly, evidence extends beyond physiological aging to accelerated-aging models. In progeroid mouse models, including those recapitulating Hutchinson–Gilford progeria syndrome, genetic attenuation of mTOR signaling prolongs survival and ameliorates multiple aging-related phenotypes, supporting a causal role for mTOR pathway activity in these experimental settings [122]. Second, mTOR signaling regulates several biological processes recognized as hallmarks of aging or closely associated with aging biology [123]. As a central metabolic hub, mTOR integrates nutrient availability, growth-factor signaling, and cellular energy status to coordinate anabolic and catabolic pathways. Under conditions of energy depletion, hypoxia, or DNA damage, AMPK-mediated suppression of mTORC1 promotes adaptive stress responses, highlighting the central role of mTOR in maintaining cellular homeostasis [124, 125]. Experimental studies have shown that modulation of mTOR signaling can influence age-associated physiological dysfunction. In metabolic disease models, attenuation of excessive mTOR activity is associated with preservation of pancreatic β-cell function, improved glucose homeostasis, and reduced cellular senescence [126]. Importantly, early translational studies indicate that these mechanistic effects extend beyond metabolic regulation. In older adults, low-dose inhibition of mTORC1 with the rapalog everolimus (RAD001) significantly enhanced the immune response to influenza vaccination and reduced expression of the T-cell exhaustion marker PD-1, providing early clinical evidence that modulation of mTOR signaling may improve selected features of human immunosenescence [127]. Third, interventional studies indicate that aging-related phenotypes can be modified through pharmacological, genetic, or lifestyle interventions that directly target or secondarily modulate mTOR signaling [128]. In experimental models, beneficial effects have been observed even when interventions are initiated later in life. For example, endothelial-specific reduction of mTOR expression in aged mice improves arterial stiffness, restores endothelial function, and reduces markers of inflammation, oxidative stress, and cellular senescence [129]. Additional mechanistic studies further support the biological relevance of mTOR inhibition in aging tissues. Increased mTOR activity has been demonstrated in hematopoietic stem cells (HSCs) from aged mice, where it contributes to impaired self-renewal, reduced lymphopoiesis, and functional decline. Pharmacological inhibition with rapamycin restored HSC function, rejuvenated hematopoiesis, increased survival following influenza infection, and improved vaccine-induced protective immunity, indicating that modulation of mTOR can reverse some age-associated defects within the hematopoietic system [130]. Nevertheless, these observations primarily derive from animal models, and their direct translation to human aging remains to be fully established. Taken together, genetic, mechanistic, and interventional evidence supports mTOR as an important regulator of aging biology. Its causal role is well supported in model organisms, whereas human data remain associative but translationally relevant [131].

Evolutionary conservation of mTOR signaling in longevity regulation

The TOR signaling pathway is one of the most evolutionarily conserved kinase systems regulating cellular physiology across eukaryotes. From yeast to mammals, TOR integrates intracellular and extracellular cues to coordinate fundamental processes, including gene expression, ribosome biogenesis, proteostasis, autophagy, and mitochondrial metabolism, all of which have been implicated in lifespan and healthspan regulation in experimental model organisms [132]. The organization of TOR signaling into two structurally and functionally distinct complexes, TORC1 and TORC2, across diverse taxa further underscores its evolutionary conservation. TORC1 is broadly conserved throughout eukaryotes, whereas TORC2 is retained in most non-plant eukaryotic lineages. Core complex-specific components, including RAPTOR, RICTOR, and mSIN1, also exhibit substantial structural and functional conservation, consistent with their essential roles in cellular homeostasis [133]. The evolutionary conservation of TOR/mTOR signaling provides a mechanistic framework for interpreting experimental findings across species. Genetic and pharmacological manipulation of this pathway has established causal effects on lifespan and age-associated phenotypes in multiple model organisms. Evolutionary conservation alone, however, does not establish causality

in humans. Evidence linking mTOR signaling to human longevity remains indirect and is derived primarily from genetic association studies, pathway-enrichment analyses, and clinical intervention studies demonstrating improvements in selected age-related physiological outcomes rather than lifespan itself. Therefore, TOR signaling can be considered causally involved in lifespan regulation in experimental systems, whereas its role in human aging is best regarded as strongly implicated but not yet definitively established [134, 135]. Comparative evolutionary analyses provide additional evidence linking the mTOR network to lifespan regulation. A systematic examination of 72 mTOR-associated genes across 48 mammalian species identified pathway components with signatures of positive selection, convergent evolution, or lifespan-associated evolutionary-rate shifts in long-lived mammals. Several implicated genes, including TSC1, TSC2, RPTOR, PIK3CA, PDPK1, and IGF1R, encode core components or upstream regulators of mTOR signaling. Moreover, evolutionary rate analyses demonstrate that variation in specific mTOR network genes correlates with species maximum lifespan, providing evolutionary evidence consistent with a conserved role of this pathway in lifespan regulation [136].

Genetic attenuation of mTOR signaling and lifespan extension

Reduced mTOR signaling has been consistently associated with increased lifespan in experimental model organisms and with longevity-associated molecular signatures in comparative mammalian studies. Genetic or pharmacological attenuation of TOR/mTOR signaling can extend lifespan in multiple experimental model organisms, whereas cross-species analyses indicate that constitutively lower mTORC1 abundance and activity are recurrent features of long-lived mammals. Reduced pathway activity has been reported across multiple tissues and at several regulatory levels, including lower transcript and protein abundance, reduced phosphorylation of selected pathway components, and diminished responsiveness to insulin stimulation. Steady-state levels of core mTORC1 components and upstream activators also tend to be lower in long-lived species than in shorter-lived comparators. Characterization of downstream mTORC1 effectors across species remains less comprehensive than analyses of S6K and ribosomal protein S6. Nevertheless, available evidence suggests that longevity-associated attenuation of mTORC1 extends beyond translational signaling and is associated with modulation of several interconnected processes. These include autophagy initiation through ULK1 and ATG13, mitochondrial biogenesis and function through PGC-1α, lipid metabolism through SREBP1 and Lipin1, phosphatase-dependent regulation involving PP2A, and translational control through 4E-BP1. Collectively, these findings support a model in which long-lived species exhibit coordinated attenuation of mTORC1 signaling across multiple biological processes rather than isolated changes in individual pathway components [137]. Comparative analyses of mammalian species differing in lifespan by more than an order of magnitude further support this association. Long-lived species show reduced expression or abundance of several mTORC1 components and activators, together with a lower basal signaling state, and these relationships remain detectable after accounting for phylogenetic relatedness. Quantitative analyses indicate that variation in mTORC1-related parameters is associated with a substantial proportion of interspecies lifespan variation, although such correlations do not establish that reduced mTORC1 activity is the sole or direct cause of longevity. Reduced FKBP12 abundance has also been observed in some long-lived species. However, FKBP12 is not an autonomous physiological inhibitor of mTORC1; it mediates mTORC1 inhibition when complexed with rapamycin, and the significance of its reduced abundance for natural longevity remains unresolved [138]. Genetic experiments causally link reduced TOR/mTOR signaling to lifespan extension in several model organisms, while comparative studies associate lower mTORC1 activity with mammalian longevity. These findings suggest an evolutionarily conserved contribution, but not a universal or exclusively genetic mechanism.

Context-dependent and non-linear roles of mTORC2 in longevity

The contribution of mTORC2 to aging and longevity is highly context-dependent and cannot be interpreted as uniformly beneficial or detrimental. Their interpretation therefore requires consideration of tissue specificity, environmental conditions, intervention timing, and the balance between adaptive and maladaptive responses. mTORC2 contributes to aging biology through mechanisms that overlap with, but remain distinct from, those of mTORC1. mTORC2 integrates growth-factor, nutrient, and stress signals to regulate metabolism, cytoskeletal organization, stress adaptation, and cell survival. Its activity is primarily stimulated by growth factors but can also be maintained or adaptively regulated under selected nutrient- or stress-associated conditions. Through downstream effectors such as AKT, mTORC2 supports proliferation in nutrient-replete environments and survival during metabolic stress [25]. Evidence from mesenchymal stromal cells (MSCs) suggests that mTORC2 can support regenerative or stress-adaptive programs in specific experimental settings. Selective mTORC1 inhibition suppresses differentiation but induces compensatory mTORC2 activation, shifting MSCs toward a stress-resistant, less differentiated phenotype. This

transition is preceded by autophagy induction and followed by reductions in senescence and apoptosis. Conversely, genetic or pharmacological disruption of mTORC2 signaling, or impairment of autophagic flux, abolishes these responses and promotes calcification, senescence, and cell death. In this context, indirect activation of mTORC2 after mTORC1 inhibition appears to promote AKT-dependent survival signaling, including suppression of FOXO activity [139]. These observations should not, however, be generalized to all tissues or aging contexts. The mTORC2–FOXO axis represents an important interface in stress-responsive and longevity-associated signaling. FOXO transcription factors are regulated by reversible phosphorylation, acetylation, and ubiquitination, enabling rapid adaptation to upstream signals. ATP-competitive mTOR inhibitors that suppress both mTORC1 and mTORC2 induce robust FOXO3 nuclear translocation and transcriptional activation, whereas selective mTORC1 inhibition does not produce comparable effects. These findings are consistent with mTORC2–AKT signaling acting as an upstream constraint on FOXO-dependent transcriptional programs, although they do not establish that this relationship is dominant in every cell type or physiological state [140]. Animal studies further illustrate the tissue-dependent nature of mTORC2 function. Loss of hypothalamic mTORC2 signaling reduces physical activity, increases adiposity and susceptibility to diet-induced obesity, impairs glucose homeostasis, promotes frailty, and shortens lifespan. In experimental models, hypothalamic mTORC2 activity has been reported to increase with age, suggesting a compensatory role in preserving late-life metabolic stability, although this age-associated increase does not itself prove adaptation [141]. Collectively, these findings indicate that preservation or activation of mTORC2 may support longevity-related functions in selected contexts, whereas excessive or inappropriate mTORC2 signaling may be maladaptive elsewhere.

Geroprotective interventions targeting mTOR signaling

Building upon mechanistic and experimental evidence, this section discusses geroprotective interventions that modulate mTOR signaling and evaluates the extent to which mTOR-dependent mechanisms contribute to their beneficial effects (Figure 4).

Autophagy as a central effector of mTOR-dependent geroprotection

Aging is characterized by the progressive accumulation of damaged macromolecules and dysfunctional organelles, while autophagy serves as a fundamental quality-control mechanism by promoting lysosomal degradation and recycling of cellular components. Age-related decline in autophagic capacity contributes to impaired proteostasis, mitochondrial dysfunction, and increased susceptibility to age-associated diseases. Conversely, enhancement of autophagic activity can improve healthspan and, in numerous experimental models, extend lifespan. Several longevity-associated interventions, including caloric restriction, exercise, fasting, NAD^+-modulating strategies, and pharmacological agents, enhance autophagic activity through both mTOR-dependent and mTOR-independent mechanisms involving AMPK, SIRT1, TFEB, Beclin-1/VPS34 complexes, FOXO transcription factors, and other nutrient- and stress-responsive pathways. Thus, mTOR inhibition represents one of several major mechanisms regulating autophagic activity rather than a universal requirement for autophagy-mediated benefit. Within this regulatory network, mTORC1 is the principal mTOR-dependent suppressor of autophagy. Under nutrient-rich conditions, mTORC1 phosphorylates components of the ULK1 initiation complex and TFEB, thereby restraining autophagy initiation, lysosomal biogenesis, and broader catabolic programs. During aging, persistent or inappropriately sustained mTORC1 activity can contribute to reduced autophagic flux, impaired clearance of damaged proteins and organelles, and loss of cellular homeostasis. Physiological or pharmacological attenuation of mTORC1 may restore autophagic function and improve selected age-related phenotypes. However, excessive or prolonged inhibition can compromise protein synthesis, tissue maintenance, repair, and other essential anabolic functions. The net benefit therefore depends on dose, duration, tissue context, and baseline pathway activity [142–145].

Compared with mTORC1, the role of mTORC2 in autophagy regulation is less clearly defined and appears highly context-dependent. Rather than functioning as a primary controller of autophagy initiation, mTORC2 modulates autophagic responses through AGC-kinase signaling, particularly AKT and SGK1, and through FOXO-dependent transcriptional programs. mTORC2-dependent AKT activation has been shown to restrain pro-autophagic signaling through phosphorylation of Beclin-1 and FOXO3 and may influence LAMP2A-dependent chaperone-mediated autophagy through regulation of the GFAP–LAMP2A machinery. In parallel, mTORC2–SGK1 signaling has been linked to macroautophagy, mitophagy, and mitochondrial stress adaptation through effects on FOXO3 and VDAC1. These mechanisms support a modulatory role for mTORC2 but should not be interpreted as uniformly suppressive across all cell types and metabolic conditions [146]. Recent *in vivo* evidence further illustrates coordinated but distinct contributions of both mTOR complexes. In a genetically engineered mouse model with RPE-specific mLST8 overexpression, activation of both mTORC1 and mTORC2 disrupted

autophagosome formation and processing, reduced mitophagy, impaired cellular waste clearance, and promoted retinal pigment epithelium degeneration. Torin1 treatment in cultured cells and experimental normalization of pathway activity improved autophagy-related and cellular phenotypes, indicating that excessive activation of both mTOR complexes can impair autophagic homeostasis in this pathological setting [147]. Effective intervention is therefore more likely to require context-specific restoration of autophagic flux than indiscriminate or sustained suppression of mTOR signaling.

Nutrient-sensing interventions as physiological modulators of mTOR activity

Calorie restriction (CR) is among the most reproducible non-genetic interventions for extending lifespan and healthspan in experimental organisms. In humans, sustained CR without malnutrition improves several cardiometabolic risk factors and biomarkers associated with healthy aging. Related dietary paradigms, including intermittent fasting, time-restricted eating, protein restriction, and selective amino acid restriction, may reproduce some metabolic adaptations associated with CR, although their effects depend on total energy intake, dietary composition, adherence, and population characteristics. These interventions engage an interconnected network involving mTOR, AMPK, insulin/IGF-1 signaling, sirtuins, FOXO transcription factors, FGF21, and the integrated stress response. Accordingly, mTOR modulation should be regarded as one component of a coordinated adaptive response [148–151].

Within this network, suppression of mTORC1 is one of the best-characterized mTOR-dependent responses to reduced nutrient availability. Lower mTORC1 activity can promote autophagy, restrain excessive protein synthesis, improve proteostatic balance, and increase metabolic flexibility. Phosphoproteomic analyses in aging mouse skeletal muscle show that CR and rapamycin remodel partially overlapping but distinct phosphorylation networks, including mTORC1-associated substrates [152]. CR may also influence mTORC2, although this contribution is less direct and remains incompletely defined. Hepatic transcriptomic analyses in male C57BL/6 mice exposed to graded CR identified coordinated changes in gene sets associated with both mTOR complexes, including alterations

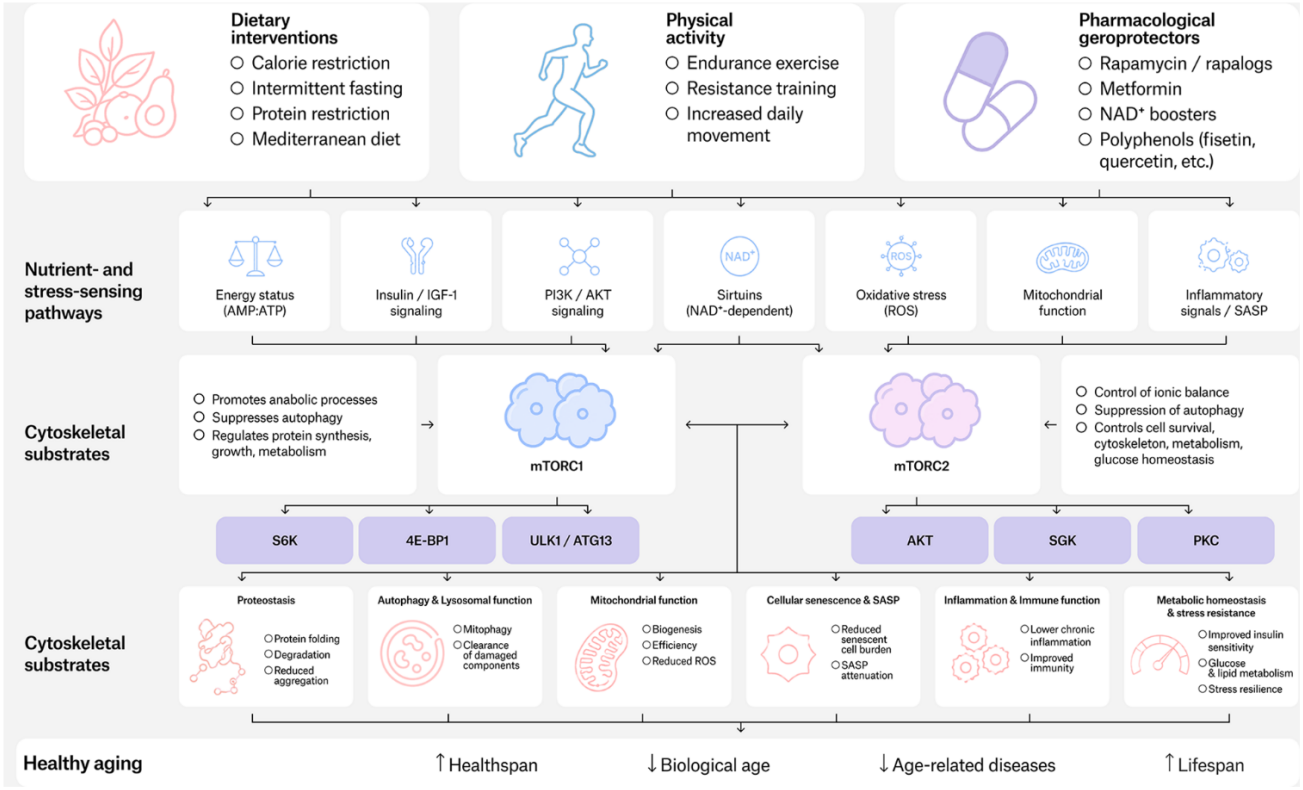


Figure 4. Geroprotective interventions targeting mTOR signaling. Dietary, physical, and pharmacological interventions converge on mTORC1/mTORC2 and related nutrient- and stress-sensing pathways, influencing proteostasis, autophagy, mitochondrial function, senescence, inflammation, and metabolic homeostasis. This figure was created using Figma.

involving Rictor. However, transcript abundance and pathway-enrichment scores do not directly measure mTORC2 kinase activity. The observed changes may arise secondarily from reduced insulin exposure, altered energy metabolism, circadian reorganization, or endocrine adaptation rather than direct nutrient sensing by mTORC2 [153]. Protein quantity and amino acid composition provide additional inputs into longevity-associated signaling. In experimental models, restriction of total protein, methionine, or branched-chain amino acids can reduce mTORC1 signaling and promote autophagy, insulin sensitivity, and metabolic remodeling. Importantly, these interventions simultaneously activate several mTOR-independent adaptive programs, including FGF21 induction, AMPK signaling, altered one-carbon metabolism, and the integrated stress response. Clinical translation these findings therefore requires attention to age, protein quality, total energy intake, physical activity, and preservation of lean mass [154, 155].

The Mediterranean diet illustrates a multifactorial dietary pattern associated with healthy aging. Randomized and observational evidence supports benefits for cardiovascular outcomes and cardiometabolic risk, while associations with lower all-cause mortality are supported primarily by prospective cohort studies [156, 157]. mTOR likely represents one mechanistic node within these broader physiological effects, but direct evidence that the Mediterranean diet improves human outcomes specifically through mTOR inhibition remains limited. Its plant-forward composition, unsaturated fats, fiber, and polyphenols can influence AMPK, insulin signaling, inflammation, oxidative stress, and mitochondrial function, with possible downstream convergence on mTORC1 [158–160]. Taken together, nutrient-sensing interventions act through overlapping but non-identical molecular networks. Within this network, mTOR primarily functions as a metabolic integrator that links nutrient availability to autophagy, proteostasis, and cellular adaptation.

Physical activity and oscillatory AMPK–mTOR signaling dynamics

Regular physical activity is a major contributor to healthy aging. Longitudinal and accelerometer-based studies consistently associate higher activity levels with better physical function, lower all-cause mortality, and longer estimated life expectancy, with benefits observed even after modest increases in daily activity [161–163]. Exercise promotes systemic adaptations through multiple interconnected pathways, including AMPK, PGC-1α-dependent mitochondrial biogenesis, insulin/IGF-1 signaling, myokines, vascular and inflammatory networks. Within this integrated response, mTOR contributes to metabolic adaptation, protein turnover, and tissue remodeling, with its effects influenced by exercise type, intensity, nutritional status, and recovery [164]. At the molecular level, exercise adaptation involves temporal coordination between catabolic and anabolic signaling. During endurance exercise or other conditions of substantial energetic stress, increased AMP:ATP and ADP:ATP ratios activate AMPK, which can transiently restrain mTORC1 through TSC2- and RAPTOR-dependent mechanisms. AMPK activation and reduced mTORC1 signaling jointly facilitate autophagy, substrate mobilization, and metabolic flexibility during energy deficit. During recovery, restoration of energy and nutrient availability, together with mechanical and growth-factor signals, reactivates mTORC1 to support protein synthesis, tissue remodeling, and muscle adaptation. Repeated exercise–recovery cycles can therefore be conceptualized as an oscillatory AMPK–mTORC1 program alternating between cellular maintenance and anabolic regeneration. However, the magnitude and sequence of these responses vary by exercise type [165–168]. Exercise also activates several complementary pathways that operate independently of, or in parallel with, mTOR signaling. AMPK can regulate mitochondrial biogenesis through PGC-1α, promote glucose transport, and activate antioxidant and stress-response pathways without requiring mTOR inhibition. Exercise-induced myokines, improved vascular function, and anti-inflammatory signaling further contribute to systemic metabolic and immune adaptations that are only partially mediated by mTOR [169].

The influence of exercise on mTORC2 is less well defined and appears context-dependent. In cellular models, AMPK can directly facilitate mTORC2 activation during acute energetic stress, enhancing downstream AKT signaling and cell survival [60]. Human skeletal-muscle studies have reported transient exercise-induced phosphorylation of NDRG1, a substrate of SGK1 used as a putative downstream readout of mTORC2 activity, whereas changes in AKT Ser473 and AMPK Thr172 phosphorylation are less consistent. This pattern suggests distinct temporal regulation but does not establish direct mTORC2 activation in every exercise context. Experimental evidence also links mTORC2 signaling to glucose transport and metabolic adaptation during exercise, although its contribution varies by tissue and model [170, 171]. Collectively, exercise promotes healthy aging through dynamic coordination of anabolic and catabolic signaling. Rather than sustained pathway inhibition, physiological benefits arise from the oscillatory regulation of AMPK–mTOR signaling together with complementary adaptive responses.

Senotherapeutics targeting mTOR: from SASP modulation to selective senolysis

Cellular senescence is a core hallmark of aging characterized by stable cell-cycle arrest and extensive phenotypic, metabolic, and secretory remodeling. Although transient senescence supports development, tissue repair, and tumor suppression, persistent senescent cells can impair regeneration and physiological resilience. A major pathogenic mechanism is the senescence-associated secretory phenotype (SASP), a heterogeneous mixture of inflammatory and matrix-remodeling factors that propagates paracrine senescence and chronic inflammation. These observations provide a rationale for senotherapeutic strategies, including senolytics, which preferentially eliminate senescent cells, and senomorphics, which suppress harmful programs such as the SASP without inducing cell death. Evidence remains predominantly preclinical, although both approaches are entering early human studies [172–174]. mTOR is an important regulatory node controlling senescent-cell survival and SASP output. In several primary-cell models, senescence is accompanied by persistent mTORC1 activity and altered autophagy. In specific contexts, autophagic recycling supports mTORC1-dependent synthesis of SASP components, whereas mTORC1 inhibition suppresses key SASP regulators and inflammatory secretion. Autophagy may nevertheless support or restrain senescence depending on the trigger, cell type, and response stage [175]. Physiological hypoxia can also activate AMPK, suppress mTOR and NF-κB signaling, and reduce pro-inflammatory SASP output; hypoxia mimetics reproduce parts of this response experimentally [176]. Disruption of the PI3K–AKT–mTOR survival network may also overcome apoptosis resistance in senescent cells. In a 156-compound screen, the dual PI3K/mTOR inhibitor PF-04691502 preferentially reduced senescent-cell viability, SA-β-gal activity, p16 expression, SASP signaling, and S6K and AKT phosphorylation while inducing apoptosis [177]. However, PF-04691502 remains an experimental candidate, and its selectivity, tolerability, and efficacy require validation *in vivo* and in clinical studies.

Several natural compounds with reported senotherapeutic properties, including fisetin and quercetin, influence PI3K–AKT–mTOR signaling among multiple other molecular targets. Fisetin suppresses AKT/mTOR activity in selected models, while PI3K–AKT–mTOR is among the pathways affected by quercetin [178–180]. Both compounds are pleiotropic, however, and their senotherapeutic effects cannot be attributed solely to mTOR inhibition. Metformin is better regarded as a candidate senomorphic and metabolic modulator than an established senolytic. Through AMPK activation, improved insulin sensitivity, and reduced hyperinsulinemia, it can attenuate inflammatory SASP programs, with mTORC1 suppression representing one component of a broader response. Clinically meaningful senotherapy or slowing of human aging has not been demonstrated [181, 182].

Rapamycin and rapalogs are the best-characterized mTOR inhibitors in geroscience and are predominantly senomorphic [183, 184]. In the National Institute on Aging Interventions Testing Program, dietary rapamycin extended median and maximal lifespan in genetically heterogeneous mice even when initiated at 600 days of age. Similar causes of death across groups supported a broad effect on aging-related mortality rather than prevention of one disease [185]. Rapamycin suppresses SASP signaling and selected senescence markers without directly eliminating senescent cells. In human T cells, low-dose mTOR inhibition reduced DNA-lesion burden and improved survival after genotoxic stress; a small placebo-controlled study also found reduced p21 in immune cells from older adults [186, 187]. These findings support senomorphic activity but not senescent-cell clearance or extension of human healthspan. In the 48-week PEARL randomized trial, intermittent low-dose rapamycin was generally tolerated without a clear excess of serious adverse events. These findings require confirmation in larger trials with prespecified clinical endpoints [188]. Most mTOR-directed senotherapy targets mTORC1, but emerging evidence implicates mTORC2 in selected settings. In a bleomycin-induced pulmonary-fibrosis model, EZY-1, reported as an mTORC2-targeting compound, reduced p16, p21, SA-β-gal activity, and SASP-factor expression alongside inhibition of mTORC2/PI3K/AKT signaling [189]. Independent validation of target selectivity, reproducibility, long-term safety, and therapeutic relevance is required before mTORC2-directed senotherapeutic strategies can be considered for clinical translation.

Therapeutic trade-offs and translational challenges of mTOR modulation

Although mTOR modulation is among the most intensively studied strategies in geroscience, its biological and clinical effects are highly context-dependent. Therapeutic outcomes depend on the degree, selectivity, duration, and tissue distribution of inhibition, baseline physiological state, and the distinct biological functions of mTORC1 and mTORC2 [190]. Dose and duration are major determinants of therapeutic outcome. At doses used in transplantation or oncology, rapamycin and rapalogs suppress immune and proliferative functions and can cause stomatitis, dyslipidemia, impaired wound healing, cytopenias,

infections, and metabolic abnormalities. By contrast, partial mTORC1 inhibition at substantially lower doses may produce different biological outcomes. In older adults, a low-dose combination of the catalytic inhibitor BEZ235 and the allosteric inhibitor RAD001 preferentially inhibited TORC1-related outputs, enhanced antiviral gene expression and influenza-vaccine responses, and was associated with fewer self-reported infections during the subsequent year [191, 192]. These findings support the potential immunological benefits of partial TORC1 inhibition but do not establish long-term geroprotective efficacy.

Treatment schedule may be as important as cumulative exposure. Prolonged daily rapamycin can disrupt mTORC2 assembly and has been associated, particularly in experimental models and at clinically immunosuppressive exposures, with glucose intolerance, insulin resistance, dyslipidemia, impaired hepatic suppression of gluconeogenesis, and pancreatic β-cell dysfunction. Intermittent or short-term administration is mechanistically attractive because it may preserve periods of mTOR activity required for tissue repair and metabolic adaptation. However, human evidence is insufficient to conclude that intermittent dosing provides a superior benefit–risk profile or an effective longevity regimen. Lifespan-extending doses in animals also cannot be translated directly to humans because of interspecies differences in pharmacokinetics, metabolism, and tissue distribution [191].

The consequences of mTOR modulation are also tissue-specific. Moderate attenuation of excessive mTORC1 activity can improve cardiac remodeling, vascular stiffness, endothelial dysfunction, and pressure-overload-associated heart failure, whereas complete cardiac mTORC1 ablation disrupts adaptive protein synthesis and can produce dilated cardiomyopathy [193]. Comparable tissue-specific trade-offs have been reported in skeletal muscle, liver, adipose tissue, the immune system, and the nervous system. Excessive mTORC1 suppression may impair muscle maintenance, regeneration, and wound healing, while prolonged mTORC2 inhibition can compromise insulin signaling, glucose homeostasis, β-cell function, and stress adaptation [194, 195]. Uniform systemic inhibition is therefore unlikely to benefit all organs equally. Human evidence remains preliminary. Survey data from 333 off-label rapamycin users suggest generally favorable self-reported health and tolerability, with transient oral ulcers among the most frequently reported adverse effects. However, self-selection, recall bias, heterogeneous dosing, and the absence of randomized exposure preclude conclusions about efficacy or long-term safety [196]. In a randomized pilot trial of 25 generally healthy adults aged 70–95 years, eight weeks of low-dose daily rapamycin was feasible and did not produce clear short-term deterioration in immune, cognitive, or physical-performance outcomes, although mild hematological and metabolic changes occurred. The study was not powered to evaluate aging, morbidity, or lifespan [197]. Despite compelling preclinical evidence, no adequately powered randomized trial has demonstrated extension of lifespan or broad healthspan in healthy humans. Existing studies are generally small, short, and focused on safety, pharmacodynamics, or selected immune outcomes. Translation is further limited by the absence of validated biomarkers that distinguish beneficial partial mTORC1 inhibition from excessive pathway suppression or clinically relevant mTORC2 disruption. Additional uncertainties include optimal dosing schedules, treatment duration, patient selection, and the lack of regulatory consensus recognizing aging as a therapeutic indication. Common measures such as circulating metabolites, inflammatory markers, phosphorylated S6K or AKT in accessible cells, and composite aging indices may not reflect target engagement in specific organs. Large randomized trials with clinically meaningful endpoints are therefore required before mTOR-targeted interventions can be recommended for routine geroprotective use. Accordingly, the therapeutic objective should be calibrated, tissue-specific modulation of mTOR signaling rather than chronic, indiscriminate pathway suppression [120].

mTOR signaling across the hallmarks of aging

Because mTOR integrates nutrient, growth factor, and energy cues and orchestrates multiple biosynthetic and metabolic programs, its modulation can influence a coordinated set of aging-relevant processes, thereby affecting multiple hallmarks of aging. Mechanistically, mTOR signaling directly regulates protein synthesis, ribosome biogenesis, cell growth, proliferation, and multiple metabolic pathways, thereby influencing several biological processes implicated in aging. The hallmarks of aging framework provide an operational definition of aging drivers based on three criteria:

- their age-associated manifestation;
- acceleration of aging phenotypes upon experimental exacerbation; the feasibility of decelerating, halting, or partially reversing aging phenotypes through therapeutic targeting.

Within this framework, twelve hallmarks have been proposed: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled

macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. These processes are not independent; instead, they form an interconnected network with reciprocal reinforcement. mTOR signaling intersects with several of these hallmark domains [15, 198, 199]. In the context of this review, system-level regulation refers to the capacity of a signaling pathway to coordinate cellular responses across multiple physiological processes and tissue compartments rather than acting as a single upstream cause of aging. Likewise, hallmark integration refers to experimentally supported mechanistic interactions through which a signaling pathway influences multiple hallmarks of aging. Importantly, not all associations between mTOR signaling and aging hallmarks represent direct mechanistic interactions; many instead reflect downstream consequences of broader metabolic and cellular adaptations [9, 199]. Because autophagy and senescence/SASP have already been discussed above as core mechanistic exemplars of mTOR-dependent geroprotective effects, the present section focuses on other hallmarks that better capture outcomes and, importantly, expose potential trade-offs of intervention.

Mitochondrial dysfunction and mTOR-dependent metabolic reprogramming

Mitochondria are central to cellular bioenergetics and metabolism. Age-associated mitochondrial dysfunction includes mtDNA damage, altered fusion–fission dynamics, impaired mitophagy, reduced respiratory capacity, and redox imbalance. Together, these changes can increase reactive oxygen species (ROS), weaken stress adaptation, and contribute to tissue dysfunction [200, 201]. Mitochondrial stress can modify mTORC1 activity through changes in energy status, AMPK signaling, redox balance, and metabolite availability [202]. This relationship is bidirectional and context-dependent: mitochondrial dysfunction does not invariably produce chronic mTOR activation, and mTOR responses vary with tissue, disease state, and stress duration [203]. The strongest mechanistic evidence links mTORC1 to autophagy, mitophagy, and mitochondrial quality control. In selected experimental models, partial pharmacological or genetic attenuation of mTORC1 enhances autophagic flux and mitochondrial turnover. Coordinated AMPK activation and mTORC1 suppression can improve mitochondrial membrane potential, ROS balance, and metabolic flux, although these effects are not uniform across models [204]. MFN2-dependent fusion has also been associated with improved mitochondrial function and AMPK–mTOR remodeling, but much of this evidence comes from disease-specific cellular systems and does not establish a universal causal sequence [205].

Skeletal muscle illustrates the heterogeneity of this response. Aging is associated with variable defects in mitophagy and lysosomal function, but the effects differ among fibers and disease states. In aged mice and human mitochondrial-myopathy samples, mitophagy was enhanced during early pathology but became impaired as respiratory-chain dysfunction progressed. Rapamycin restored mitochondrial turnover in the advanced disease model, supporting mTOR-dependent regulation of mitochondrial recycling in this specific setting [206]. Because preservation of skeletal muscle function is a major determinant of healthspan, these findings suggest that selective modulation of mTOR-dependent autophagy may represent a therapeutic strategy for age-related muscle decline [207]. mTOR inhibition can also impair mitochondrial function. In cultured cardiomyocytes and an inducible cardiac mTOR-knockout model, mTOR suppression promoted prohibitin-1 degradation, OMA1-dependent OPA1 processing, mitochondrial fragmentation, and reductions in oxygen consumption and ATP production, despite lower ROS generation [208]. Thus, mTOR signaling is directly coupled to mitochondrial quality control, but the direction and clinical relevance of its effects depend on tissue, dose, timing, and metabolic context.

Stem cell exhaustion and mTOR-regulated maintenance of stemness

Stem cell exhaustion is a recognized hallmark of aging and contributes to declining tissue maintenance and regenerative capacity [209]. However, aging does not affect every stem-cell compartment uniformly: changes may include reduced self-renewal, altered lineage output, loss of quiescence, defective niche signaling, or impaired activation after injury [210]. In this framework, direct hallmark integration refers to experimentally demonstrated effects of mTOR on stem-cell state or function. Improved tissue repair or organismal health resulting from preserved stem cells should instead be regarded as a downstream consequence [211]. mTOR directly regulates translation, metabolism, growth, proliferation, and differentiation, thereby influencing stem-cell fate across multiple lineages [212]. These effects operate within broader networks involving growth factors, nutrient sensing, mitochondrial quality control, autophagy, epigenetic regulation, and stress responses [213]. The relationship is therefore not adequately described as uniformly beneficial mTOR suppression: both excessive activation and excessive inhibition can impair stem-cell function, depending on lineage and physiological context. Experimental evidence nevertheless shows that

attenuation of excessive mTORC1 activity can preserve stem-cell function in selected settings. In S6K1-deficient mice, hematopoietic stem and progenitor cells showed reduced expression of cell-cycle genes and preservation of functional reconstitution during aging, although the effects differed among transplantation conditions [214]. In pluripotent stem cells, mTORC1–eIF4F-dependent translation regulates ribosomal and mitochondrial programs. Pharmacological mTOR inhibition induces a reversible paused pluripotent state, and inhibition of mitochondrial translation produces overlapping effects, supporting functional coupling between cytosolic translation and mitochondrial proteostasis [215].

Adult epithelial and hematopoietic systems provide further context-specific examples. In cultured human epidermal stem cells, prolonged mTORC1 inhibition reduced clonal conversion and favored maintenance of stem-cell characteristics during *ex vivo* expansion [216]. In hematopoietic stem cells, experimental mTORC1 hyperactivation after loss of TSC1 increased mitochondrial biogenesis, ROS production, and cell-cycle entry while impairing long-term function; rapamycin or antioxidant treatment partly restored these defects [217]. These findings directly link mTOR activity to quiescence and metabolic control, but they do not imply that chronically minimizing mTORC1 is optimal in every adult stem-cell compartment. Oncological effects are also context-dependent. mTOR signaling can support the growth, survival, and therapy resistance of malignant stem-like cells, making pathway inhibition beneficial in some cancer models [218]. In other settings, reduced mTOR activity may accompany dormancy or reversible quiescence, potentially allowing treatment-resistant cells to persist. The outcome depends on tumor genotype, lineage, microenvironment, inhibitor selectivity, and treatment schedule [219–221]. Preservation of normal stem-cell pools must therefore be balanced against the risks of impaired differentiation, inadequate tissue repair, or persistence of malignant cells. Overall, mTOR directly contributes to the regulation of stem-cell quiescence, self-renewal, metabolic state, and differentiation. Broader effects on regeneration and organismal aging arise through interactions with stem-cell niches, mitochondrial and autophagic pathways, and other hallmarks of aging. mTOR should therefore be regarded as an important, context-dependent component of the stem-cell aging network rather than its sole regulator [213, 222].

Genomic instability and epigenetic remodeling in the context of mTOR signaling

Genome integrity progressively declines during aging owing to the accumulation of DNA damage, replication errors, telomere dysfunction, impaired DNA repair, and age-related epigenetic remodeling. Changes in chromatin organization, heterochromatin loss, and epigenetic drift further compromise genome stability by weakening DNA repair and chromosome maintenance [223, 224]. Although genomic instability and epigenetic alterations represent distinct hallmarks of aging, they are closely interconnected. Current evidence suggests that mTOR signaling influences several components of these processes, although most mechanistic data derive from experimental models. mTOR participates in the cellular response to DNA damage through interactions with ATM, ATR, DNA-PK, and other stress-response pathways, with the direction of regulation depending on the type of damage and cellular context [225]. In models of defective DNA repair, persistent genomic stress activates mTORC1, while pharmacological modulation of mTORC1 alters disease progression, indicating that mTOR signaling both responds to and influences genome instability [226]. Conversely, excessive mTORC1 activity can impair repair efficiency by suppressing recruitment of DNA-repair proteins such as RNF168, illustrating that prolonged pathway activation may become maladaptive [227, 228].

Beyond DNA-damage signaling, mTOR also contributes to replication-stress responses. Experimental studies link mTOR to replication-fork stability, nucleotide availability, checkpoint regulation, and FANCD2-dependent recovery of stalled replication forks [227, 229]. Evidence for mTORC2 is more limited but suggests a role in maintaining repair capacity and cell survival. RICTOR depletion impairs recruitment of the repair factor 53BP1 and reduces non-homologous end joining, while cancer models further associate mTORC2 with nucleotide synthesis and repair signaling [230–234]. These observations indicate that mTORC2 may support genome maintenance under specific conditions, although these findings cannot yet be generalized to normal aging tissues.

Overall, available evidence suggests that mTOR influences genomic stability through multiple context-dependent mechanisms. Excessive mTORC1 activity may exacerbate genomic damage or impair selected repair pathways, whereas mTORC2 appears to support repair and stress adaptation in certain experimental settings. However, most evidence remains preclinical, and the contribution of mTOR signaling to genomic instability and epigenetic remodeling during human aging has yet to be fully established [235–237].

From hallmarks to age-related diseases: consequences of mTOR dysregulation

mTOR dysregulation contributes to multiple age-related diseases, but its effects vary by signaling branch, tissue, and disease stage. mTORC1 coordinates protein, lipid,

nucleotide, and glucose metabolism, whereas mTORC2 regulates overlapping functions through AKT, SGK, and PKC. Aging therefore produces tissue-specific imbalances rather than a uniform change in mTOR activity. Therapeutic modulation may suppress harmful mTORC1 outputs while disrupting beneficial anabolic, metabolic, or mTORC2-dependent functions [25, 123, 238].

- Cardiovascular disease. Vascular aging involves endothelial dysfunction, arterial stiffness, inflammation, oxidative stress, impaired autophagy, and VSMC remodeling. Excessive mTORC1 activity can promote anabolic and inflammatory programs while suppressing lysosomal clearance. In aged mice, endothelial mTOR reduction improved arterial and metabolic function, although basal signaling remains necessary for nitric-oxide production and vasodilation in other contexts [129, 193, 239–242]. In experimental atherosclerosis, macrophage mTORC1 activation promotes defective autophagy, inflammation, foam-cell pathology, and plaque-cell death. High-protein feeding and leucine accelerated atherogenesis through a macrophage mTORC1–autophagy mechanism in defined models [242]. VSMC mTORC1 activation has similarly been linked to phenotypic switching, extracellular-matrix remodeling, and medial degeneration [243], but these findings do not establish universal dietary thresholds or identical mechanisms across vascular disorders. The heart further demonstrates the need for calibrated modulation. Partial mTORC1 attenuation can improve pathological hypertrophy and cardiac aging, whereas complete ablation disrupts adaptive protein synthesis [193]. Macrophage mTORC2 can restrain FOXO1-dependent inflammasome signaling [244], and cardiac RICTOR/mTORC2 supports pressure-overload adaptation partly by limiting MST1/Hippo activation [245]. Conversely, excessive endothelial mTORC2–AKT signaling may promote senescence by suppressing Nrf2-dependent stress resistance [246]. TLR4-driven activation of the macrophage mTORC2–AKT–mTORC1 axis can also enhance scavenger-receptor expression, lipid uptake, and foam-cell formation, while mTORC2 inhibition attenuates these responses [247].
- Neurodegenerative disease. Hyperactive mTORC1 can impair autophagic and lysosomal clearance, potentially favoring amyloid-β, pathological tau, and α-synuclein persistence. Altered mTOR signaling is also associated with mitochondrial dysfunction, microglial activation, and neuroinflammation in Alzheimer's and Parkinson's disease models [248–251]. Nevertheless, basal mTOR activity supports synaptic maintenance, stress adaptation, and repair. Selective mTORC1 inhibition may enhance aggregate clearance, whereas prolonged inhibition may compromise neuronal, immune, or regenerative functions. RICTOR/mTORC2 supports cytoskeletal, lysosomal, and survival pathways; its loss increased neural stem-cell necroptotic vulnerability and impaired recovery in spinal-cord-injury models [251–253].
- Metabolic disease. Nutrient excess, obesity, and hyperinsulinemia can sustain mTORC1–S6K signaling, inhibit insulin-receptor substrates, and promote insulin resistance. In pancreatic β-cells, mTORC1 initially supports compensatory growth and insulin production but may become maladaptive when prolonged through impaired autophagy and stress sensitivity [20, 254–256]. Excessive hepatic and adipose mTORC1 activity also promote lipogenesis and ectopic lipid accumulation. By contrast, mTORC2 supports AKT-dependent insulin action, β-cell adaptation, adipose metabolism, and hepatic glucose control. Tissue-specific RICTOR loss can worsen glucose intolerance or lipid accumulation, suggesting that mTORC1-biased inhibition may be preferable to pan-mTOR inhibition [257–259], although this remains unproven clinically.
- Sarcopenia and frailty. Transient mTORC1 activation is required for muscle protein synthesis and adaptation, whereas persistent activation in aged muscle is associated with defective autophagy, mitochondrial stress, and declining quality. Partial mTORC1 inhibition improved selected outcomes in aged rodents [260–263], but prolonged systemic inhibition can reduce muscle mass or blunt anabolic responses. mTORC2 contributes to muscle stem-cell replenishment after repeated injury and maintenance during aging [264, 265]. Excessive suppression of either complex may therefore worsen frailty. Overall, mTOR dysregulation links aging hallmarks with vascular, neurological, metabolic, and musculoskeletal disease, but its effects depend on cell type, tissue and disease stage (Figure 5). Geroprotective strategies should rebalance specific outputs rather than indiscriminately suppress the pathway. Human efficacy remains to be demonstrated using validated biomarkers and clinically meaningful outcomes.

CONCLUSIONS

mTOR network is a major regulator of aging biology, integrating nutrients, cellular energy, and stress signals to control translation, autophagy, mitochondrial function, proteostasis, senescence, stem-cell activity, and genome maintenance. Experimental evidence supports a causal role in lifespan regulation across model organisms, while human evidence remains predominantly translational. mTOR should therefore be viewed as a dynamic, context-dependent network rather

than a binary switch. Distinguishing mTORC1 from mTORC2 is essential. Excessive mTORC1 activity is associated with multiple aging-related dysfunctions, whereas mTORC2 has context-dependent roles in metabolism, survival, repair, and stress adaptation. Gerotherapeutic strategies must consequently favor selective and temporally controlled modulation over uniform pathway inhibition. Dietary restriction, physical activity, autophagy-directed approaches, and senotherapeutics converge on mTOR-associated networks but also engage parallel pathways. Their benefits appear to reflect restored signaling flexibility—reduced excessive anabolic activity combined with improved maintenance and stress resilience—rather than sustained mTOR suppression. Because mTOR modulation can also impair metabolism, immunity, or regeneration, therapeutic benefit depends on tissue, dose, timing, and baseline physiological state. Future research should define tissue-specific responses, establish biomarkers of mTORC1 and mTORC2 activity, and compare continuous inhibition with intermittent or physiologically mimetic schedules. Resolving mTORC1–mTORC2 asymmetry and validating clinically meaningful outcomes will be essential before mTOR-directed interventions can be used to extend human healthspan.

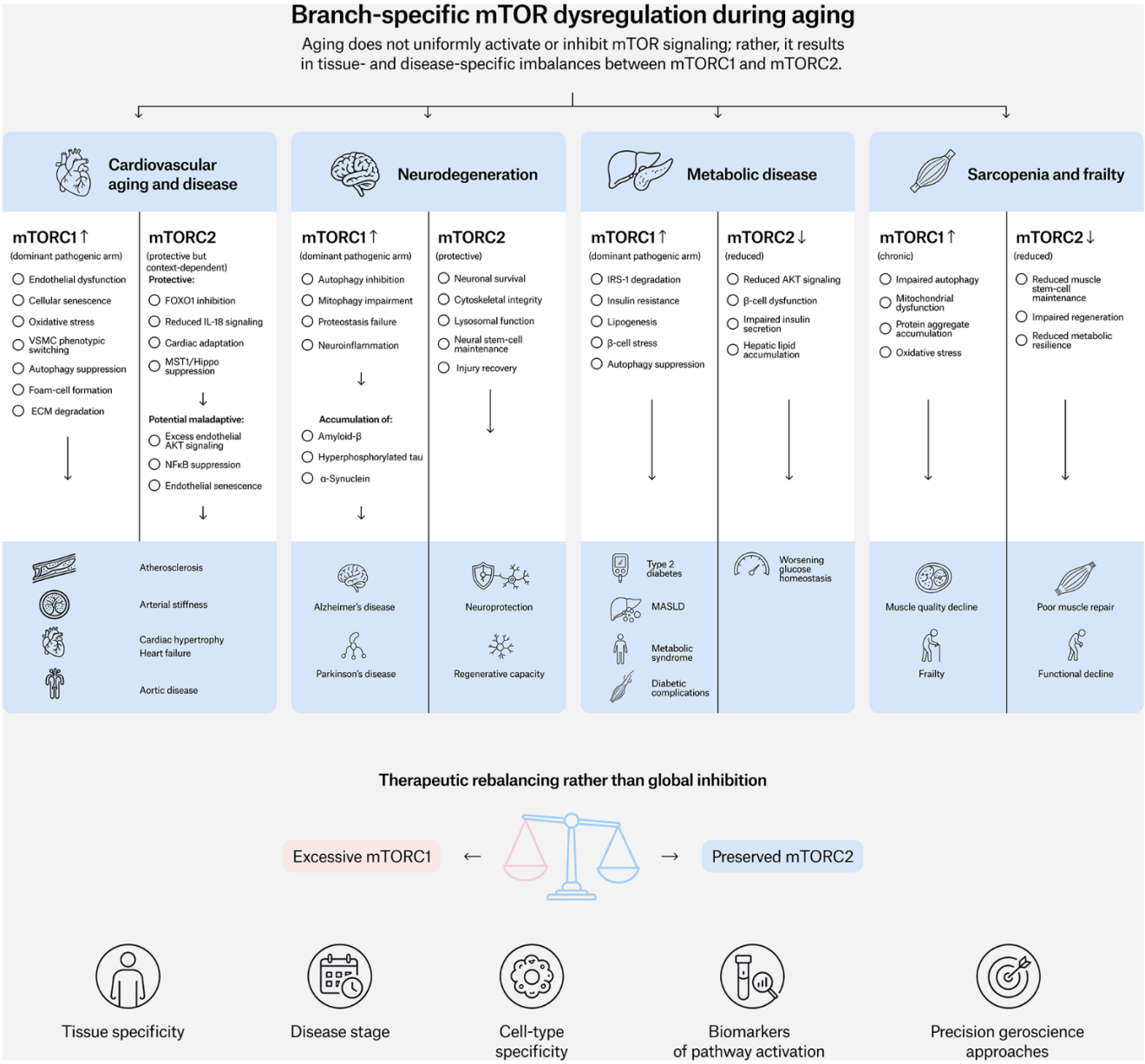


Figure 5. Branch-specific mTOR dysregulation in aging and age-related diseases.

AUTHOR CONTRIBUTIONS

N.B. (Natalia Bobok) conceptualized the study, developed the methodology, performed validation, and wrote and edited the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Baffi TR, Newton AC. Protein kinase C: release from quarantine by mTORC2. Trends Biochem Sci. 2022; 47:518–30. https://doi.org/10.1016/j.tibs.2022.03.003 PMID:35361526

2. Ardito F, Giuliani M, Perrone D, Troiano G, Lo Muzio L. The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy (Review). Int J Mol Med. 2017; 40:271–80. https://doi.org/10.3892/ijmm.2017.3036 PMID:28656226

3. Zerihun M, Rubin SJ, Silnitsky S, Qvit N. An Update on Protein Kinases as Therapeutic Targets-Part II: Peptides as Allosteric Protein Kinase C Modulators Targeting Protein-Protein Interactions. Int J Mol Sci. 2023; 24:17504. https://doi.org/10.3390/ijms242417504 PMID:38139336

4. Dhal AK, Ritaparna P. An insight on protein kinases and their therapeutic perspective. In: Metabolism—Annual Volume 2024. IntechOpen. 2024. https://doi.org/10.5772/intechopen.113285

5. Arter C, Trask L, Ward S, Yeoh S, Bayliss R. Structural features of the protein kinase domain and targeted binding by small-molecule inhibitors. J Biol Chem. 2022; 298:102247. https://doi.org/10.1016/j.jbc.2022.102247 PMID:35830914

6. Angira D, Shaik A, Thiruvenkatam V. Structural and strategic landscape of PIKK protein family and their inhibitors: an overview. Front Biosci (Landmark Ed). 2020; 25:1538–67. https://doi.org/10.2741/4867 PMID:32114444

7. Alemi F, Raei Sadigh A, Malakoti F, Elhaei Y, Ghaffari SH, Maleki M, Asemi Z, Yousefi B, Targhazeh N, Majidinia M. Molecular mechanisms involved in DNA repair in human cancers: An overview of PI3k/Akt signaling and PIKKs crosstalk. J Cell Physiol. 2022; 237:313–28. https://doi.org/10.1002/jcp.30573 PMID:34515349

8. Xu J, Bradley N, He Y. Structure and function of the apical PIKKs in double-strand break repair. Curr Opin Struct Biol. 2023; 82:102651. https://doi.org/10.1016/j.sbi.2023.102651 PMID:37437397

9. Fernandes SA, Demetriades C. The Multifaceted Role of Nutrient Sensing and mTORC1 Signaling in Physiology and Aging. Front Aging. 2021; 2:707372. https://doi.org/10.3389/fragi.2021.707372 PMID:35822019

10. Maréchal A, Zou L. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol. 2013; 5:a012716. https://doi.org/10.1101/cshperspect.a012716 PMID:24003211

11. Enriquez-Rios V, Dumitrache LC, Downing SM, Li Y, Brown EJ, Russell HR, McKinnon PJ. DNA-PKcs, ATM, and ATR Interplay Maintains Genome Integrity during Neurogenesis. J Neurosci. 2017; 37:893–905. https://doi.org/10.1523/JNEUROSCI.4213-15.2016 PMID:28123024

12. Wang J, Huang Y, Wang Z, Liu J, Liu Z, Yang J, He Z. The mTOR Signaling Pathway: Key Regulator and Therapeutic Target for Heart Disease. Biomedicines. 2025; 13:397. https://doi.org/10.3390/biomedicines13020397 PMID:40002810

13. Mao B, Zhang Q, Ma L, Zhao DS, Zhao P, Yan P. Overview of Research into mTOR Inhibitors. Molecules. 2022; 27:5295. https://doi.org/10.3390/molecules27165295 PMID:36014530

14. He L, Cho S, Blenis J. mTORC1, the maestro of cell metabolism and growth. Genes Dev. 2025; 39:109–31. https://doi.org/10.1101/gad.352084.124 PMID:39572234

15. Papadopoli D, Boulay K, Kazak L, Pollak M, Mallette FA, Topisirovic I, Hulea L. mTOR as a central regulator of lifespan and aging. F1000Res. 2019; 8:F1000 Faculty Rev-998. https://doi.org/10.12688/f1000research.17196.1 PMID:31316753

16. Zhang H, Xiao X, Pan Z, Dokudovskaya S. mTOR signaling networks: mechanistic insights and translational frontiers in disease therapeutics. Signal Transduct Target Ther. 2025; 10:428. https://doi.org/10.1038/s41392-025-02493-4 PMID:41469379

17. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017; 168:960–76. https://doi.org/10.1016/j.cell.2017.02.004 PMID:28283069

18. Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, Sengupta S, Kumar D, Garg M. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduct Target Ther. 2023; 8:375. https://doi.org/10.1038/s41392-023-01608-z PMID:37779156

19. Yip CK, Murata K, Walz T, Sabatini DM, Kang SA. Structure of the human mTOR complex I and its implications for rapamycin inhibition. Mol Cell. 2010; 38:768–74. https://doi.org/10.1016/j.molcel.2010.05.017 PMID:20542007

20. Marafie SK, Al-Mulla F, Abubaker J. mTOR: Its Critical Role in Metabolic Diseases, Cancer, and the Aging Process. Int J Mol Sci. 2024; 25:6141. https://doi.org/10.3390/ijms25116141 PMID:38892329

21. Yuan HX, Guan KL. Structural insights of mTOR complex 1. Cell Res. 2016; 26:267–8. https://doi.org/10.1038/cr.2016.10 PMID:26794870

22. Betz C, Hall MN. Where is mTOR and what is it doing there? J Cell Biol. 2013; 203:563–74. https://doi.org/10.1083/jcb.201306041 PMID:24385483

23. Fernandes SA, Angelidaki DD, Nüchel J, Pan J, Gollwitzer P, Elkis Y, Artoni F, Wilhelm S, Kovacevic-Sarmiento M, Demetriades C. Spatial and functional separation of mTORC1 signalling in response to different amino acid sources. Nat Cell Biol. 2024; 26:1918–33. https://doi.org/10.1038/s41556-024-01523-7 PMID:39385049

24. Acharya A, Demetriades C. mTORC1 activity licenses its own release from the lysosomal surface. Mol Cell. 2024; 84:4385–400.e7. https://doi.org/10.1016/j.molcel.2024.10.008 PMID:39486418

25. Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. Physiol Rev. 2021; 101:1371–426. https://doi.org/10.1152/physrev.00026.2020 PMID:33599151

26. Manifava M, Smith M, Rotondo S, Walker S, Niewczas I, Zoncu R, Clark J, Ktistakis NT. Dynamics of mTORC1 activation in response to amino acids. Elife. 2016; 5:e19960. https://doi.org/10.7554/eLife.19960 PMID:27725083

27. Zhuang Y, Wang XX, He J, He S, Yin Y. Recent advances in understanding of amino acid signaling to mTORC1 activation. Front Biosci (Landmark Ed). 2019; 24:971–82. https://doi.org/10.2741/4762 PMID:30844724

28. Takahara T, Amemiya Y, Sugiyama R, Maki M, Shibata H. Amino acid-dependent control of mTORC1 signaling: a variety of regulatory modes. J Biomed Sci. 2020; 27:87. https://doi.org/10.1186/s12929-020-00679-2 PMID:32799865

29. Smiles WJ, Ovens AJ, Kemp BE, Galic S, Petersen J, Oakhill JS. New developments in AMPK and mTORC1 cross-talk. Essays Biochem. 2024; 68:321–36. https://doi.org/10.1042/EBC20240007 PMID:38994736

30. Wang S, Li H, Yuan M, Fan H, Cai Z. Role of AMPK in autophagy. Front Physiol. 2022; 13:1015500. https://doi.org/10.3389/fphys.2022.1015500 PMID:36505072

31. Holczer M, Hajdú B, Lőrincz T, Szarka A, Bánhegyi G, Kapuy O. Fine-tuning of AMPK-ULK1-mTORC1 regulatory triangle is crucial for autophagy oscillation. Sci Rep. 2020; 10:17803. https://doi.org/10.1038/s41598-020-75030-8 PMID:33082544

32. Kajiwara M, Masuda S. Role of mTOR Inhibitors in Kidney Disease. Int J Mol Sci. 2016; 17:975. https://doi.org/10.3390/ijms17060975 PMID:27338360

33. Sridharan S, Basu A. Distinct Roles of mTOR Targets S6K1 and S6K2 in Breast Cancer. Int J Mol Sci. 2020; 21:1199. https://doi.org/10.3390/ijms21041199 PMID:32054043

34. Wu X, Xie W, Xie W, Wei W, Guo J. Beyond controlling cell size: functional analyses of S6K in tumorigenesis. Cell Death Dis. 2022; 13:646. https://doi.org/10.1038/s41419-022-05081-4 PMID:35879299

35. Bohlen J, Roiuk M, Teleman AA. Phosphorylation of ribosomal protein S6 differentially affects mRNA translation based on ORF length. Nucleic Acids Res. 2021; 49:13062–74. https://doi.org/10.1093/nar/gkab1157 PMID:34871442

36. Magnuson B, Ekim B, Fingar DC. Regulation and function of ribosomal protein S6 kinase (S6K) within mTOR signalling networks. Biochem J. 2012; 441:1–21. https://doi.org/10.1042/BJ20110892 PMID:22168436

37. Gingras AC, Raught B, Gygi SP, Niedzwiecka A, Miron M, Burley SK, Polakiewicz RD, Wyslouch-Cieszynska A, Aebersold R, Sonenberg N. Hierarchical phosphorylation of the translation inhibitor 4E-BP1. Genes Dev. 2001; 15:2852–64.

https://doi.org/10.1101/gad.912401 PMID:11691836

38. Qin X, Jiang B, Zhang Y. 4E-BP1, a multifactor regulated multifunctional protein. Cell Cycle. 2016; 15:781–6. https://doi.org/10.1080/15384101.2016.1151581 PMID:26901143

39. Böhm R, Imseng S, Jakob RP, Hall MN, Maier T, Hiller S. The dynamic mechanism of 4E-BP1 recognition and phosphorylation by mTORC1. Mol Cell. 2021; 81:2403–16.e5. https://doi.org/10.1016/j.molcel.2021.03.031 PMID:33852892

40. Maracci C, Motta S, Romagnoli A, Costantino M, Perego P, Di Marino D. The mTOR/4E-BP1/eIF4E Signalling Pathway as a Source of Cancer Drug Targets. Curr Med Chem. 2022; 29:3501–29. https://doi.org/10.2174/0929867329666220224112042 PMID:35209811

41. Hama Y, Fujioka Y, Yamamoto H, Mizushima N, Noda NN. The triad interaction of ULK1, ATG13, and FIP200 is required for ULK complex formation and autophagy. Elife. 2025; 13:RP101531. https://doi.org/10.7554/eLife.101531 PMID:40552710

42. Galhuber M, Thedieck K. ODE-based models of signaling networks in autophagy. Curr Opin Syst Biol. 2024; 39:100519. https://doi.org/10.1016/j.coisb.2024.100519

43. Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. Essays Biochem. 2017; 61:585–96. https://doi.org/10.1042/EBC20170021 PMID:29233870

44. Noda T. Regulation of Autophagy through TORC1 and mTORC1. Biomolecules. 2017; 7:52. https://doi.org/10.3390/biom7030052 PMID:28686223

45. Shi X, Yokom AL, Wang C, Young LN, Youle RJ, Hurley JH. ULK complex organization in autophagy by a C-shaped FIP200 N-terminal domain dimer. J Cell Biol. 2020; 219:e201911047. https://doi.org/10.1083/jcb.201911047 PMID:32516362

46. Eickhorst C, Babic R, Rush-Kittle J, Lucya L, Imam FL, Sánchez-Martín P, Hollenstein DM, Michaelis J, Münch C, Meisinger C, Slade D, Gámez-Díaz L, Kraft C. FIP200 Phosphorylation Regulates Late Steps in Mitophagy. J Mol Biol. 2024; 436:168631. https://doi.org/10.1016/j.jmb.2024.168631 PMID:38821350

47. Fu W, Hall MN. Regulation of mTORC2 Signaling. Genes (Basel). 2020; 11:1045. https://doi.org/10.3390/genes11091045 PMID:32899613

48. Ragupathi A, Kim C, Jacinto E. The mTORC2 signaling network: targets and cross-talks. Biochem J. 2024; 481:45–91. https://doi.org/10.1042/BCJ20220325 PMID:38270460

49. Chen X, Liu M, Tian Y, Li J, Qi Y, Zhao D, Wu Z, Huang M, Wong CC, Wang HW, Wang J, Yang H, Xu Y. Cryo-EM structure of human mTOR complex 2. Cell Res. 2018; 28:518–28. https://doi.org/10.1038/s41422-018-0029-3 PMID:29567957

50. Babaev VR, Huang J, Ding L, Zhang Y, May JM, Linton MF. Loss of Rictor in Monocyte/Macrophages Suppresses Their Proliferation and Viability Reducing Atherosclerosis in LDLR Null Mice. Front Immunol. 2018; 9:215. https://doi.org/10.3389/fimmu.2018.00215 PMID:29487597

51. Yu Z, Chen J, Takagi E, Wang F, Saha B, Liu X, Joubert LM, Gleason CE, Jin M, Li C, Nowotny C, Agard D, Cheng Y, Pearce D. Interactions between mTORC2 core subunits Rictor and mSin1 dictate selective and context-dependent phosphorylation of substrate kinases SGK1 and Akt. J Biol Chem. 2022; 298:102288. https://doi.org/10.1016/j.jbc.2022.102288 PMID:35926713

52. Ruan C, Ouyang X, Liu H, Li S, Jin J, Tang W, Xia Y, Su B. Sin1-mediated mTOR signaling in cell growth, metabolism and immune response. Natl Sci Rev. 2019; 6:1149–62. https://doi.org/10.1093/nsr/nwz171 PMID:34691993

53. Ezine E, Lebbe C, Dumaz N. Unmasking the tumourigenic role of SIN1/MAPKAP1 in the mTOR complex 2. Clin Transl Med. 2023; 13:e1464. https://doi.org/10.1002/ctm2.1464 PMID:37877351

54. Tatebe H, Murayama S, Yonekura T, Hatano T, Richter D, Furuya T, Kataoka S, Furuita K, Kojima C, Shiozaki K. Substrate specificity of TOR complex 2 is determined by a ubiquitin-fold domain of the Sin1 subunit. Elife. 2017; 6:e19594. https://doi.org/10.7554/eLife.19594 PMID:28264193

55. Ebner M, Sinkovics B, Szczygieł M, Ribeiro DW, Yudushkin I. Localization of mTORC2 activity inside cells. J Cell Biol. 2017; 216:343–53. https://doi.org/10.1083/jcb.201610060 PMID:28143890

56. Hawse WF, Cattley RT. T cells transduce T-cell receptor signal strength by generating different phosphatidylinositols. J Biol Chem. 2019; 294:4793–805.

https://doi.org/10.1074/jbc.RA118.006524 PMID:30692200

57. Kazyken D, Lentz SI, Wadley M, Fingar DC. Alkaline intracellular pH (pHi) increases PI3K activity to promote mTORC1 and mTORC2 signaling and function during growth factor limitation. J Biol Chem. 2023; 299:105097. https://doi.org/10.1016/j.jbc.2023.105097 PMID:37507012

58. Knudsen JR, Fritzen AM, James DE, Jensen TE, Kleinert M, Richter EA. Growth Factor-Dependent and -Independent Activation of mTORC2. Trends Endocrinol Metab. 2020; 31:13–24. https://doi.org/10.1016/j.tem.2019.09.005 PMID:31699566

59. An P, Xu W, Luo J, Luo Y. Expanding TOR Complex 2 Signaling: Emerging Regulators and New Connections. Front Cell Dev Biol. 2021; 9:713806. https://doi.org/10.3389/fcell.2021.713806 PMID:34395443

60. Kazyken D, Magnuson B, Bodur C, Acosta-Jaquez HA, Zhang D, Tong X, Barnes TM, Steinl GK, Patterson NE, Altheim CH, Sharma N, Inoki K, Cartee GD, et al. AMPK directly activates mTORC2 to promote cell survival during acute energetic stress. Sci Signal. 2019; 12:eaav3249. https://doi.org/10.1126/scisignal.aav3249 PMID:31186373

61. Senoo H, Wai M, Matsubayashi HT, Sesaki H, Iijima M. Hetero-oligomerization of Rho and Ras GTPases Connects GPCR Activation to mTORC2-AKT Signaling. Cell Rep. 2020; 33:108427. https://doi.org/10.1016/j.celrep.2020.108427 PMID:33238110

62. Smith SF, Collins SE, Charest PG. Ras, PI3K and mTORC2 - three's a crowd? J Cell Sci. 2020; 133:jcs234930. https://doi.org/10.1242/jcs.234930 PMID:33033115

63. Bernard M, Yang B, Migneault F, Turgeon J, Dieudé M, Olivier MA, Cardin GB, El-Diwany M, Underwood K, Rodier F, Hébert MJ. Autophagy drives fibroblast senescence through MTORC2 regulation. Autophagy. 2020; 16:2004–16. https://doi.org/10.1080/15548627.2020.1713640 PMID:31931659

64. Kma L, Baruah TJ. The interplay of ROS and the PI3K/Akt pathway in autophagy regulation. Biotechnol Appl Biochem. 2022; 69:248–64. https://doi.org/10.1002/bab.2104 PMID:33442914

65. Nitulescu GM, Van De Venter M, Nitulescu G, Ungurianu A, Juzenas P, Peng Q, Olaru OT, Grădinaru D, Tsatsakis A, Tsoukalas D, Spandidos DA, Margina D. The Akt pathway in oncology therapy and beyond (Review). Int J Oncol. 2018; 53:2319–31. https://doi.org/10.3892/ijo.2018.4597 PMID:30334567

66. Duggal S, Jailkhani N, Midha MK, Agrawal N, Rao KV, Kumar A. Defining the Akt1 interactome and its role in regulating the cell cycle. Sci Rep. 2018; 8:1303. https://doi.org/10.1038/s41598-018-19689-0 PMID:29358593

67. Wang L, Huang D, Jiang Z, Luo Y, Norris C, Zhang M, Tian X, Tang Y. Akt3 is responsible for the survival and proliferation of embryonic stem cells. Biol Open. 2017; 6:850–61. https://doi.org/10.1242/bio.024505 PMID:28483982

68. Omolekan TO, Chamcheu JC, Buerger C, Huang S. PI3K/AKT/mTOR Signaling Network in Human Health and Diseases. Cells. 2024; 13:1500. https://doi.org/10.3390/cells13171500 PMID:39273070

69. Dan HC, Antonia RJ, Baldwin AS. PI3K/Akt promotes feedforward mTORC2 activation through IKKα. Oncotarget. 2016; 7:21064–75. https://doi.org/10.18632/oncotarget.8383 PMID:27027448

70. Zhang X, Tang N, Hadden TJ, Rishi AK. Akt, FoxO and regulation of apoptosis. Biochim Biophys Acta. 2011; 1813:1978–86. https://doi.org/10.1016/j.bbamcr.2011.03.010 PMID:21440011

71. Pan CW, Jin X, Zhao Y, Pan Y, Yang J, Karnes RJ, Zhang J, Wang L, Huang H. AKT-phosphorylated FOXO1 suppresses ERK activation and chemoresistance by disrupting IQGAP1-MAPK interaction. EMBO J. 2017; 36:995–1010. https://doi.org/10.15252/embj.201695534 PMID:28279977

72. Meco M, Giustiniano E, Nisi F, Zulli P, Agosteo E. MAPK, PI3K/Akt Pathways, and GSK-3β Activity in Severe Acute Heart Failure in Intensive Care Patients: An Updated Review. J Cardiovasc Dev Dis. 2025; 12:266. https://doi.org/10.3390/jcdd12070266 PMID:40710791

73. Domoto T, Uehara M, Bolidong D, Minamoto T. Glycogen Synthase Kinase 3β in Cancer Biology and Treatment. Cells. 2020; 9:1388. https://doi.org/10.3390/cells9061388 PMID:32503133

74. Marcella BM, Hockey BL, Braun JL, Whitley KC, Geromella MS, Baranowski RW, Watson CJ, Silvera S, Hamstra SI, Wasilewicz LJ, Crozier RW, Marais AA, Kim KH, et al. GSK3 inhibition improves skeletal muscle function and whole-body metabolism in male mouse models of Duchenne muscular dystrophy. Nat Commun. 2024; 15:10210.

https://doi.org/10.1038/s41467-024-53886-y PMID:39587049

75. Gupte M, Umbarkar P, Singh AP, Zhang Q, Tousif S, Lal H. Deletion of Cardiomyocyte Glycogen Synthase Kinase-3 Beta (GSK-3β) Improves Systemic Glucose Tolerance with Maintained Heart Function in Established Obesity. Cells. 2020; 9:1120. https://doi.org/10.3390/cells9051120 PMID:32365965

76. Law SM, Zheng JJ. Premise and peril of Wnt signaling activation through GSK-3β inhibition. iScience. 2022; 25:104159. https://doi.org/10.1016/j.isci.2022.104159 PMID:35434563

77. Li X, Hu S, Cai Y, Liu X, Luo J, Wu T. Revving the engine: PKB/AKT as a key regulator of cellular glucose metabolism. Front Physiol. 2024; 14:1320964. https://doi.org/10.3389/fphys.2023.1320964 PMID:38264327

78. Li M, Wu X, Pan Y, Song M, Yang X, Xu J, Plikus MV, Lv C, Yu L, Yu Z. mTORC2-AKT signaling to PFKFB2 activates glycolysis that enhances stemness and tumorigenicity of intestinal epithelial cells. FASEB J. 2024; 38:e23532. https://doi.org/10.1096/fj.202301833RR PMID:38451470

79. Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 2018; 14:1483–96. https://doi.org/10.7150/ijbs.27173 PMID:30263000

80. Baffi TR, Lordén G, Wozniak JM, Feichtner A, Yeung W, Kornev AP, King CC, Del Rio JC, Limaye AJ, Bogomolovas J, Gould CM, Chen J, Kennedy EJ, et al. mTORC2 controls the activity of PKC and Akt by phosphorylating a conserved TOR interaction motif. Sci Signal. 2021; 14:eabe4509. https://doi.org/10.1126/scisignal.abe4509 PMID:33850054

81. Aslam N, Alvi F. Protein Kinase C Life Cycle: Explained Through Systems Biology Approach. Front Physiol. 2022; 13:818688. https://doi.org/10.3389/fphys.2022.818688 PMID:35492590

82. Kanemaru K, Nakamura Y. Activation Mechanisms and Diverse Functions of Mammalian Phospholipase C. Biomolecules. 2023; 13:915. https://doi.org/10.3390/biom13060915 PMID:37371495

83. Li Y, Jiang Y, Hu Z, Yang S, Li L, Xiong C, Gao Y, Sun W, Zhang Y. Protein Kinase C Family: Structures, Biological Functions, Diseases, and Pharmaceutical Interventions. MedComm (2020). 2025; 6:e70474. https://doi.org/10.1002/mco2.70474 PMID:41244006

84. Hamshaw I, Ellahouny Y, Malusickis A, Newman L, Ortiz-Jacobs D, Mueller A. The role of PKC and PKD in CXCL12 and CXCL13 directed malignant melanoma and acute monocytic leukemic cancer cell migration. Cell Signal. 2024; 113:110966. https://doi.org/10.1016/j.cellsig.2023.110966 PMID:37949381

85. Michalczyk I, Sikorski AF, Kotula L, Junghans RP, Dubielecka PM. The emerging role of protein kinase Cθ in cytoskeletal signaling. J Leukoc Biol. 2013; 93:319–27. https://doi.org/10.1189/jlb.0812371 PMID:23192428

86. El Amri M, Fitzgerald U, Schlosser G. MARCKS and MARCKS-like proteins in development and regeneration. J Biomed Sci. 2018; 25:43. https://doi.org/10.1186/s12929-018-0445-1 PMID:29788979

87. García-Ortiz A, Serrador JM. ERM Proteins at the Crossroad of Leukocyte Polarization, Migration and Intercellular Adhesion. Int J Mol Sci. 2020; 21:1502. https://doi.org/10.3390/ijms21041502 PMID:32098334

88. Gada KD, Logothetis DE. PKC regulation of ion channels: The involvement of PIP_2. J Biol Chem. 2022; 298:102035. https://doi.org/10.1016/j.jbc.2022.102035 PMID:35588786

89. Keck M, Pöll S, Schmelzer H, Kressmann T, Hermann C, Mederos Y Schnitzler M, Storch U. Impact of C-Terminal PKC Phosphorylation on TRPC6 Current Kinetics. Int J Mol Sci. 2025; 26:11482. https://doi.org/10.3390/ijms262311482 PMID:41373637

90. Bayonés L, Alfonso-Bueno S, Montenegro M, Moya-Díaz J, Caspe O, Gallo LI, Marengo FD. Membrane retrieval after Immediately Releasable Pool (IRP) exocytosis is produced by dynamin-dependent and dynamin-independent/protein kinase C-dependent mechanisms. J Neurochem. 2022; 163:391–405. https://doi.org/10.1111/jnc.15710 PMID:36254753

91. Ma H. PKC in the perspective of dopamine receptor signaling. Acta Biochim Pol. 2025; 72:14488. https://doi.org/10.3389/abp.2025.14488 PMID:40552006

92. Kazanietz MG, Cooke M. Protein kinase C signaling "in" and "to" the nucleus: Master kinases in transcriptional regulation. J Biol Chem. 2024; 300:105692. https://doi.org/10.1016/j.jbc.2024.105692 PMID:38301892

93. Gong GQ, Wang K, Dai XC, Zhou Y, Basnet R, Chen Y, Yang DH, Lee WJ, Buchanan CM, Flanagan JU,

Shepherd PR, Chen Y, Wang MW. Identification, structure modification, and characterization of potential small-molecule SGK3 inhibitors with novel scaffolds. Acta Pharmacol Sin. 2018; 39:1902–12. https://doi.org/10.1038/s41401-018-0087-6 PMID:30038340

94. Basnet R, Gong GQ, Li C, Wang MW. Serum and glucocorticoid inducible protein kinases (SGKs): a potential target for cancer intervention. Acta Pharm Sin B. 2018; 8:767–71. https://doi.org/10.1016/j.apsb.2018.07.001 PMID:30245963

95. Jang H, Park Y, Jang J. Serum and glucocorticoid-regulated kinase 1: Structure, biological functions, and its inhibitors. Front Pharmacol. 2022; 13:1036844. https://doi.org/10.3389/fphar.2022.1036844 PMID:36457711

96. Cicenas J, Meskinyte-Kausiliene E, Jukna V, Rimkus A, Simkus J, Soderholm D. SGK1 in Cancer: Biomarker and Drug Target. Cancers (Basel). 2022; 14:2385. https://doi.org/10.3390/cancers14102385 PMID:35625991

97. Chen X, Kang H, Xiao Y. The role of SGK1 in neurologic diseases: A friend or foe? IBRO Neurosci Rep. 2024; 17:503–12. https://doi.org/10.1016/j.ibneur.2024.12.003 PMID:39737082

98. Liu W, Wang X, Liu Z, Wang Y, Yin B, Yu P, Duan X, Liao Z, Chen Y, Liu C, Li X, Dai Y, Tao Z. SGK1 inhibition induces autophagy-dependent apoptosis via the mTOR-Foxo3a pathway. Br J Cancer. 2017; 117:1139–53. https://doi.org/10.1038/bjc.2017.293 PMID:29017179

99. González-Herrera F, Catalán M, Anfossi R, Maya JD, Pedrozo Z, Díaz-Araya G, Vivar R. SGK1 is necessary to FoxO3a negative regulation, oxidative stress and cardiac fibroblast activation induced by TGF-β1. Cell Signal. 2023; 109:110778. https://doi.org/10.1016/j.cellsig.2023.110778 PMID:37343898

100. Lou Y, Zhang F, Luo Y, Wang L, Huang S, Jin F. Serum and Glucocorticoid Regulated Kinase 1 in Sodium Homeostasis. Int J Mol Sci. 2016; 17:1307. https://doi.org/10.3390/ijms17081307 PMID:27517916

101. E-Fatima J, Khan FI, Lai D. Exploring serum and glucocorticoid-regulated kinase 1: A promising target for COVID-19 and atrial fibrillation treatment. Heart Rhythm O2. 2025; 6:720–32. https://doi.org/10.1016/j.hroo.2025.02.015 PMID:40496592

102. Mason JA, Cockfield JA, Pape DJ, Meissner H, Sokolowski MT, White TC, Valentín López JC, Liu J, Liu X, Martínez-Reyes I, Chandel NS, Locasale JW, Schafer ZT. SGK1 signaling promotes glucose metabolism and survival in extracellular matrix detached cells. Cell Rep. 2021; 34:108821. https://doi.org/10.1016/j.celrep.2021.108821 PMID:33730592

103. Yang C, Li J, Sun F, Zhou H, Yang J, Yang C. The functional duality of SGK1 in the regulation of hyperglycemia. Endocr Connect. 2020; 9:R187–94. https://doi.org/10.1530/EC-20-0225 PMID:32621586

104. Qin L, Ma K, Yan Z. Chemogenetic Activation of Prefrontal Cortex in Shank3-Deficient Mice Ameliorates Social Deficits, NMDAR Hypofunction, and Sgk2 Downregulation. iScience. 2019; 17:24–35. https://doi.org/10.1016/j.isci.2019.06.014 PMID:31247448

105. Pao AC, Bhargava A, Di Sole F, Quigley R, Shao X, Wang J, Thomas S, Zhang J, Shi M, Funder JW, Moe OW, Pearce D. Expression and role of serum and glucocorticoid-regulated kinase 2 in the regulation of Na+/H+ exchanger 3 in the mammalian kidney. Am J Physiol Renal Physiol. 2010; 299:F1496–506. https://doi.org/10.1152/ajprenal.00075.2010 PMID:20926631

106. Wang H, Xu D, Toh MF, Pao AC, You G. Serum- and glucocorticoid-inducible kinase SGK2 regulates human organic anion transporters 4 via ubiquitin ligase Nedd4-2. Biochem Pharmacol. 2016; 102:120–9. https://doi.org/10.1016/j.bcp.2015.11.024 PMID:26740304

107. Gotoh S, Negishi M. Serum- and glucocorticoid-regulated kinase 2 determines drug-activated pregnane X receptor to induce gluconeogenesis in human liver cells. J Pharmacol Exp Ther. 2014; 348:131–40. https://doi.org/10.1124/jpet.113.209379 PMID:24204015

108. Park CH, Moon J, Park M, Cheng H, Lee J, Chang JS. Protein Kinase SGK2 Is Induced by the β_3 Adrenergic Receptor-cAMP-PKA-PGC-1α/NT-PGC-1α Axis but Dispensable for Brown/Beige Adipose Tissue Thermogenesis. Front Physiol. 2021; 12:780312. https://doi.org/10.3389/fphys.2021.780312 PMID:34899399

109. Ranzuglia V, Lorenzon I, Pellarin I, Sonego M, Dall'Acqua A, D'Andrea S, Lovisa S, Segatto I, Coan M, Polesel J, Serraino D, Sabatelli P, Spessotto P, et al. Serum- and glucocorticoid- inducible kinase 2, SGK2, is a novel autophagy regulator and modulates platinum drugs response in cancer cells. Oncogene. 2020; 39:6370–86.

https://doi.org/10.1038/s41388-020-01433-6 PMID:32848212

110. Cheng L, He Q, Liu B, Chen L, Lv F, Li X, Li Y, Liu C, Song Y, Xing Y. SGK2 promotes prostate cancer metastasis by inhibiting ferroptosis via upregulating GPX4. Cell Death Dis. 2023; 14:74. https://doi.org/10.1038/s41419-023-05614-5 PMID:36720852

111. Liao QQ, Dong QQ, Zhang H, Shu HP, Tu YC, Yao LJ. Contributions of SGK3 to transporter-related diseases. Front Cell Dev Biol. 2022; 10:1007924. https://doi.org/10.3389/fcell.2022.1007924 PMID:36531961

112. Chen Q, Guo J, Liu Y, Du T, Liu J, Zhang Y, Dai Y, Zhang M, Zhou Z, Zhang Q, Wei C, Ding Q, Qin J, et al. Serum- and glucocorticoid-induced kinase 3 orchestrates glucocorticoid signaling to facilitate chromatin remodeling during murine adipogenesis. J Clin Invest. 2025; 135:e186534. https://doi.org/10.1172/JCI186534 PMID:40767604

113. Dong QQ, Li ZF, Zhang H, Shu HP, Tu YC, Liao QQ, Yao LJ. Serum and Glucocorticoid-Inducible Kinase 3/Nedd4-2 Signaling Pathway Participates in Podocyte Injury by Regulating the Stability of Nephrin. Front Physiol. 2022; 12:810473. https://doi.org/10.3389/fphys.2021.810473 PMID:35126185

114. Peng LQ, Zhao H, Liu S, Yuan YP, Yuan CY, Mwamunyi MJ, Pearce D, Yao LJ. Lack of serum- and glucocorticoid-inducible kinase 3 leads to podocyte dysfunction. FASEB J. 2018; 32:576–87. https://doi.org/10.1096/fj.201700393RR PMID:28935820

115. Li YF, Wei TW, Fan Y, Shan TK, Sun JT, Chen BR, Wang ZM, Gu LF, Yang TT, Liu L, Du C, Ma Y, Wang H, et al. Serine/Threonine-Protein Kinase 3 Facilitates Myocardial Repair After Cardiac Injury Possibly Through the Glycogen Synthase Kinase-3β/β-Catenin Pathway. J Am Heart Assoc. 2021; 10:e022802. https://doi.org/10.1161/JAHA.121.022802 PMID:34726469

116. Ham O, Jung S, Kim YJ, Woo DH, Jeong JS, Kim W, Kim S, Quah Y, Lee S, Yu WJ. Methotrexate-induced disruption of the serum-glucocorticoid inducible protein kinase 3 signaling pathway and its effects on brain development. J Hazard Mater. 2025; 494:138438. https://doi.org/10.1016/j.jhazmat.2025.138438 PMID:40327939

117. Inoue K, Sakuma E, Morimoto H, Asai H, Koide Y, Leng T, Wada I, Xiong ZG, Ueki T. Serum- and glucocorticoid-inducible kinases in microglia. Biochem Biophys Res Commun. 2016; 478:53–9. https://doi.org/10.1016/j.bbrc.2016.07.094 PMID:27457803

118. Wang M, Liu J, Liao X, Yi Y, Xue Y, Yang L, Cheng H, Liu P. The SGK3-Catalase antioxidant signaling axis drives cervical cancer growth and therapy resistance. Redox Biol. 2023; 67:102931. https://doi.org/10.1016/j.redox.2023.102931 PMID:37866161

119. Raghuvanshi K, Raghuvanshi D, Kumar D, Nepovimova E, Valko M, Kuca K, Verma R. Exploring the role of mTOR pathway in aging and age-related disorders. EXCLI J. 2025; 24:992–1015. https://doi.org/10.17179/excli2025-8384 PMID:40933955

120. Hands JM, Lustgarten MS, Frame LA, Rosen B. What is the clinical evidence to support off-label rapamycin therapy in healthy adults? Aging (Albany NY). 2025; 17:2079–88. https://doi.org/10.18632/aging.206300 PMID:40778880

121. Kolbe D, Dose J, Putter P, Ziemann M, Laudes M, Slagboom PE, Franke A, Deelen J, Nebel A, and Regeneron Genetics Center. German longevity study reveals novel rare pro-longevity alleles clustering in mTOR signaling pathway. Geroscience. 2025; 47:4955–71. https://doi.org/10.1007/s11357-025-01640-7 PMID:40232348

122. Cabral WA, Tavarez UL, Beeram I, Yeritsyan D, Boku YD, Eckhaus MA, Nazarian A, Erdos MR, Collins FS. Genetic reduction of mTOR extends lifespan in a mouse model of Hutchinson-Gilford Progeria syndrome. Aging Cell. 2021; 20:e13457. https://doi.org/10.1111/acel.13457 PMID:34453483

123. Kennedy BK, Lamming DW. The Mechanistic Target of Rapamycin: The Grand ConducTOR of Metabolism and Aging. Cell Metab. 2016; 23:990–1003. https://doi.org/10.1016/j.cmet.2016.05.009 PMID:27304501

124. Wu CW, Storey KB. mTOR Signaling in Metabolic Stress Adaptation. Biomolecules. 2021; 11:681. https://doi.org/10.3390/biom11050681 PMID:34062764

125. Pungsrinont T, Kallenbach J, Baniahmad A. Role of PI3K-AKT-mTOR Pathway as a Pro-Survival Signaling and Resistance-Mediating Mechanism to Therapy of Prostate Cancer. Int J Mol Sci. 2021; 22:11088. https://doi.org/10.3390/ijms222011088 PMID:34681745

126. Hoseini R, Hoseini Z, Kamangar A. The role of the SIRT1 and mTOR pathways in exercise-induced β-cell

senescence reduction in type 2 diabetes mellitus. Cell Mol Life Sci. 2025; 82:374. https://doi.org/10.1007/s00018-025-05836-0 PMID:41165878

127. Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014; 6:268ra179. https://doi.org/10.1126/scitranslmed.3009892 PMID:25540326

128. Walters HE, Deneka-Hannemann S, Cox LS. Reversal of phenotypes of cellular senescence by pan-mTOR inhibition. Aging (Albany NY). 2016; 8:231–44. https://doi.org/10.18632/aging.100872 PMID:26851731

129. Islam MT, Hall SA, Dutson T, Bloom SI, Bramwell RC, Kim J, Tucker JR, Machin DR, Donato AJ, Lesniewski LA. Endothelial cell-specific reduction in mTOR ameliorates age-related arterial and metabolic dysfunction. Aging Cell. 2024; 23:e14040. https://doi.org/10.1111/acel.14040 PMID:38017701

130. Chen C, Liu Y, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Sci Signal. 2009; 2:ra75. https://doi.org/10.1126/scisignal.2000559 PMID:19934433

131. Xu S, Cai Y, Wei Y. mTOR Signaling from Cellular Senescence to Organismal Aging. Aging Dis. 2013; 5:263–73. https://doi.org/10.14336/AD.2014.0500263 PMID:25110610

132. Bjedov I, Rallis C. The Target of Rapamycin Signalling Pathway in Ageing and Lifespan Regulation. Genes (Basel). 2020; 11:1043. https://doi.org/10.3390/genes11091043 PMID:32899412

133. Tatebe H, Shiozaki K. Evolutionary Conservation of the Components in the TOR Signaling Pathways. Biomolecules. 2017; 7:77. https://doi.org/10.3390/biom7040077 PMID:29104218

134. Passtoors WM, Beekman M, Deelen J, van der Breggen R, Maier AB, Guigas B, Derhovanessian E, van Heemst D, de Craen AJ, Gunn DA, Pawelec G, Slagboom PE. Gene expression analysis of mTOR pathway: association with human longevity. Aging Cell. 2013; 12:24–31. https://doi.org/10.1111/acel.12015 PMID:23061800

135. Podder A, Raju A, Schork NJ. Cross-Species and Human Inter-Tissue Network Analysis of Genes Implicated in Longevity and Aging Reveal Strong Support for Nutrient Sensing. Front Genet. 2021; 12:719713. https://doi.org/10.3389/fgene.2021.719713 PMID:34512728

136. Yang F, Liu X, Li Y, Yu Z, Huang X, Yang G, Xu S. Evolutionary analysis of the mTOR pathway provide insights into lifespan extension across mammals. BMC Genomics. 2023; 24:456. https://doi.org/10.1186/s12864-023-09554-4 PMID:37582720

137. Mota-Martorell N, Jové M, Pamplona R. mTOR Complex 1 Content and Regulation Is Adapted to Animal Longevity. Int J Mol Sci. 2022; 23:8747. https://doi.org/10.3390/ijms23158747 PMID:35955882

138. Mota-Martorell N, Jove M, Pradas I, Berdún R, Sanchez I, Naudi A, Gari E, Barja G, Pamplona R. Gene expression and regulatory factors of the mechanistic target of rapamycin (mTOR) complex 1 predict mammalian longevity. Geroscience. 2020; 42:1157–73. https://doi.org/10.1007/s11357-020-00210-3 PMID:32578071

139. Schaub T, Gürgen D, Maus D, Lange C, Tarabykin V, Dragun D, Hegner B. mTORC1 and mTORC2 Differentially Regulate Cell Fate Programs to Coordinate Osteoblastic Differentiation in Mesenchymal Stromal Cells. Sci Rep. 2019; 9:20071. https://doi.org/10.1038/s41598-019-56237-w PMID:31882658

140. Jimenez L, Amenabar C, Mayoral-Varo V, Mackenzie TA, Ramos MC, Silva A, Calissi G, Grenho I, Blanco-Aparicio C, Pastor J, Megías D, Ferreira BI, Link W. mTORC2 Is the Major Second Layer Kinase Negatively Regulating FOXO3 Activity. Molecules. 2022; 27:5414. https://doi.org/10.3390/molecules27175414 PMID:36080182

141. Chellappa K, Brinkman JA, Mukherjee S, Morrison M, Alotaibi MI, Carbajal KA, Alhadeff AL, Perron IJ, Yao R, Purdy CS, DeFelice DM, Wakai MH, Tomasiewicz J, et al. Hypothalamic mTORC2 is essential for metabolic health and longevity. Aging Cell. 2019; 18:e13014. https://doi.org/10.1111/acel.13014 PMID:31373126

142. Hansen M, Rubinsztein DC, Walker DW. Autophagy as a promoter of longevity: insights from model organisms. Nat Rev Mol Cell Biol. 2018; 19:579–93. https://doi.org/10.1038/s41580-018-0033-y PMID:30006559

143. Nieto-Torres JL, Hansen M. Macroautophagy and aging: The impact of cellular recycling on health and longevity. Mol Aspects Med. 2021; 82:101020. https://doi.org/10.1016/j.mam.2021.101020 PMID:34507801

144. Romero Y, Bueno M, Ramirez R, Álvarez D, Sembrat JC, Goncharova EA, Rojas M, Selman M, Mora AL, Pardo A. mTORC1 activation decreases autophagy in aging and idiopathic pulmonary fibrosis and contributes to apoptosis resistance in IPF fibroblasts. Aging Cell. 2016; 15:1103–12. https://doi.org/10.1111/acel.12514 PMID:27566137

145. Bareja A, Lee DE, White JP. Maximizing Longevity and Healthspan: Multiple Approaches All Converging on Autophagy. Front Cell Dev Biol. 2019; 7:183. https://doi.org/10.3389/fcell.2019.00183 PMID:31555646

146. Ballesteros-Álvarez J, Andersen JK. mTORC2: The other mTOR in autophagy regulation. Aging Cell. 2021; 20:e13431. https://doi.org/10.1111/acel.13431 PMID:34250734

147. Chowdhury O, Bammidi S, Gautam P, Babu VS, Liu H, Shang P, Xin Y, Mahally E, Nemani M, Koontz V, Lathrop K, Kedziora KM, Franks J, et al. Activated mTOR Signaling in the RPE Drives EMT, Autophagy, and Metabolic Disruption, Resulting in AMD-Like Pathology in Mice. Aging Cell. 2025; 24:e70018. https://doi.org/10.1111/acel.70018 PMID:39957408

148. Dorling JL, Martin CK, Redman LM. Calorie restriction for enhanced longevity: The role of novel dietary strategies in the present obesogenic environment. Ageing Res Rev. 2020; 64:101038. https://doi.org/10.1016/j.arr.2020.101038 PMID:32109603

149. Tulsian R, Velingkaar N, Kondratov R. Caloric restriction effects on liver mTOR signaling are time-of-day dependent. Aging (Albany NY). 2018; 10:1640–8. https://doi.org/10.18632/aging.101498 PMID:30018180

150. Ham DJ, Börsch A, Chojnowska K, Lin S, Leuchtmann AB, Ham AS, Thürkauf M, Delezie J, Furrer R, Burri D, Sinnreich M, Handschin C, Tintignac LA, et al. Distinct and additive effects of calorie restriction and rapamycin in aging skeletal muscle. Nat Commun. 2022; 13:2025. https://doi.org/10.1038/s41467-022-29714-6 PMID:35440545

151. Ching TT, Hsu AL. The impacts of different dietary restriction regimens on aging and longevity: from yeast to humans. J Biomed Sci. 2025; 32:91. https://doi.org/10.1186/s12929-025-01188-w PMID:41039401

152. Ataman M, Mittal N, Tintignac L, Schmidt A, Ham DJ, González A, Ruegg MA, Zavolan M. Calorie restriction and rapamycin distinctly mitigate aging-associated protein phosphorylation changes in mouse muscles. Commun Biol. 2024; 7:974. https://doi.org/10.1038/s42003-024-06679-4 PMID:39127848

153. Derous D, Mitchell SE, Wang L, Green CL, Wang Y, Chen L, Han JJ, Promislow DE, Lusseau D, Douglas A, Speakman JR. The effects of graded levels of calorie restriction: XI. Evaluation of the main hypotheses underpinning the life extension effects of CR using the hepatic transcriptome. Aging (Albany NY). 2017; 9:1770–824. https://doi.org/10.18632/aging.101269 PMID:28768896

154. Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and metabolic health. EBioMedicine. 2019; 43:632–40. https://doi.org/10.1016/j.ebiom.2019.04.005 PMID:30975545

155. Trautman ME, Richardson NE, Lamming DW. Protein restriction and branched-chain amino acid restriction promote geroprotective shifts in metabolism. Aging Cell. 2022; 21:e13626. https://doi.org/10.1111/acel.13626 PMID:35526271

156. Dobroslavska P, Silva ML, Vicente F, Pereira P. Mediterranean Dietary Pattern for Healthy and Active Aging: A Narrative Review of an Integrative and Sustainable Approach. Nutrients. 2024; 16:1725. https://doi.org/10.3390/nu16111725 PMID:38892658

157. Srambikkal Vinesh D, Syed Altaf RR, Mohan A, Palani N, Mendonce KC, Selvan S, Surya P, Rajadesingu S. The Mediterranean diet as a metabolic strategy for healthy aging and non-communicable disease prevention. The Journal of Nutritional Physiology. 2026; 5:100015. https://doi.org/10.1016/j.jnphys.2026.100015

158. Surugiu R, Iancu MA, Vintilescu ȘB, Stepan MD, Burdusel D, Genunche-Dumitrescu AV, Dogaru CA, Dumitra GG. Molecular Mechanisms of Healthy Aging: The Role of Caloric Restriction, Intermittent Fasting, Mediterranean Diet, and Ketogenic Diet-A Scoping Review. Nutrients. 2024; 16:2878. https://doi.org/10.3390/nu16172878 PMID:39275194

159. Pazoki-Toroudi H, Amani H, Ajami M, Nabavi SF, Braidy N, Kasi PD, Nabavi SM. Targeting mTOR signaling by polyphenols: A new therapeutic target for ageing. Ageing Res Rev. 2016; 31:55–66. https://doi.org/10.1016/j.arr.2016.07.004 PMID:27453478

160. Tosti V, Bertozzi B, Fontana L. Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. J Gerontol A Biol Sci Med Sci. 2018; 73:318–26. https://doi.org/10.1093/gerona/glx227 PMID:29244059

161. Xu L, Wang J, Li X, Li Y, Chen C, Xu Z, Xia Y, Lu Z, Zhou J, Zhang M, Wei Y, Wu B, Zhang Z, et al. Physical activities, longevity gene, and all-cause mortality among older adults: a prospective community-based cohort study. BMC Med. 2025; 23:361. https://doi.org/10.1186/s12916-025-04176-x PMID:40598362

162. Kaczorowska A, Kołodziej M, Sebastjan A, Ignasiak Z. Association between lifelong physical activity, physical fitness, and quality of life in older adults in Poland. Sci Rep. 2026; 16:5934. https://doi.org/10.1038/s41598-026-36742-5 PMID:41565753

163. Zaccardi F, Rowlands AV, Dempsey PC, Razieh C, Henson J, Goldney J, Maylor BD, Bhattacharjee A, Chudasama Y, Edwardson C, Laukkanen JA, Ekelund U, Davies MJ, et al. Interplay between physical activity volume and intensity with modeled life expectancy in women and men: A prospective cohort analysis. J Sport Health Sci. 2025; 14:100970. https://doi.org/10.1016/j.jshs.2024.100970 PMID:39181446

164. Fuentes-Barría H, Aguilera-Eguía R, Alarcón-Rivera M, López-Soto O, Aristizabal-Hoyos JA, Roco-Videla Á, Caviedes-Olmos M, Rojas-Gómez D. Exercise-Induced Molecular Adaptations in Chronic Non-Communicable Diseases-Narrative Review. Int J Mol Sci. 2025; 26:12096. https://doi.org/10.3390/ijms262412096 PMID:41465520

165. Mănescu DC, Plăstoi CD, Petre RL, Mărgărit IR, Mănescu AM, Pîrvan A. Metabolic Overdrive in Elite Sport: A Systems Model of AMPK-mTOR Oscillation, NAD^+ Economy, and Epigenetic Drift. Int J Mol Sci. 2026; 27:1817. https://doi.org/10.3390/ijms27041817 PMID:41751953

166. Garcia D, Shaw RJ. AMPK: Mechanisms of Cellular Energy Sensing and Restoration of Metabolic Balance. Mol Cell. 2017; 66:789–800. https://doi.org/10.1016/j.molcel.2017.05.032 PMID:28622524

167. Kjøbsted R, Hingst JR, Fentz J, Foretz M, Sanz MN, Pehmøller C, Shum M, Marette A, Mounier R, Treebak JT, Wojtaszewski JF, Viollet B, Lantier L. AMPK in skeletal muscle function and metabolism. FASEB J. 2018; 32:1741–77. https://doi.org/10.1096/fj.201700442R PMID:29242278

168. Zhou X, Zhu S, Li J, Mateus A, Williams C, Gilthorpe J, Backman LJ. Mechanical Loading Modulates AMPK and mTOR Signaling in Muscle Cells. J Proteome Res. 2024; 23:4286–95. https://doi.org/10.1021/acs.jproteome.4c00242 PMID:39213513

169. Tero-Vescan A, Degens H, Matsakas A, Ștefănescu R, Ősz BE, Slevin M. Exercise-Induced Muscle-Fat Crosstalk: Molecular Mediators and Their Pharmacological Modulation for the Maintenance of Metabolic Flexibility in Aging. Pharmaceuticals (Basel). 2025; 18:1222. https://doi.org/10.3390/ph18081222 PMID:40872612

170. Li J, Madsen AB, Knudsen JR, Henriquez-Olguin C, Persson KW, Li Z, Raun SH, Li T, Kiens B, Wojtaszewski JF, Richter EA, Nogara L, Blaauw B, et al. mTOR Ser1261 is an AMPK-dependent phosphosite in mouse and human skeletal muscle not required for mTORC2 activity. FASEB J. 2025; 39:e70277. https://doi.org/10.1096/fj.202402064R PMID:39835637

171. Knudsen JR, Persson KW, Meister J, Carl CS, Raun SH, Andersen NR, Sylow L, Kiens B, Jensen TE, Richter EA, Kleinert M. Exercise increases phosphorylation of the putative mTORC2 activity readout NDRG1 in human skeletal muscle. Am J Physiol Endocrinol Metab. 2022; 322:E63–73. https://doi.org/10.1152/ajpendo.00389.2021 PMID:34866401

172. Lelarge V, Capelle R, Oger F, Mathieu T, Le Calvé B. Senolytics: from pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. NPJ Aging. 2024; 10:12. https://doi.org/10.1038/s41514-024-00138-4 PMID:38321020

173. Saliev T, Singh PB. Targeting Senescence: A Review of Senolytics and Senomorphics in Anti-Aging Interventions. Biomolecules. 2025; 15:860. https://doi.org/10.3390/biom15060860 PMID:40563501

174. Alum EU, Izah SC, Uti DE, Ugwu OP, Betiang PA, Basajja M, Ejemot-Nwadiaro RI. Targeting Cellular Senescence for Healthy Aging: Advances in Senolytics and Senomorphics. Drug Des Devel Ther. 2025; 19:8489–522. https://doi.org/10.2147/DDDT.S543211 PMID:40994903

175. Cayo A, Segovia R, Venturini W, Moore-Carrasco R, Valenzuela C, Brown N. mTOR Activity and Autophagy in Senescent Cells, a Complex Partnership. Int J Mol Sci. 2021; 22:8149. https://doi.org/10.3390/ijms22158149 PMID:34360912

176. van Vliet T, Varela-Eirin M, Wang B, Borghesan M, Brandenburg SM, Franzin R, Evangelou K, Seelen M, Gorgoulis V, Demaria M. Physiological hypoxia

restrains the senescence-associated secretory phenotype via AMPK-mediated mTOR suppression. Mol Cell. 2021; 81:2041–52.e6. https://doi.org/10.1016/j.molcel.2021.03.018 PMID:33823141

177. Fan Z, Tong Y, Yang Z, Wang S, Huang T, Yang D, Ni Q, Zhang M, Li D, Yang M, Fan X. Inhibitor PF-04691502 works as a senolytic to regulate cellular senescence. Exp Gerontol. 2024; 186:112359. https://doi.org/10.1016/j.exger.2024.112359 PMID:38184267 Erratum in: Exp Gerontol. 2026; 214:113021. https://doi.org/10.1016/j.exger.2025.113021 PMID:41565548

178. Syed DN, Adhami VM, Khan MI, Mukhtar H. Inhibition of Akt/mTOR signaling by the dietary flavonoid fisetin. Anticancer Agents Med Chem. 2013; 13:995–1001. https://doi.org/10.2174/18715206113139990129 PMID:23293889

179. Reyes-Farias M, Carrasco-Pozo C. The Anti-Cancer Effect of Quercetin: Molecular Implications in Cancer Metabolism. Int J Mol Sci. 2019; 20:3177. https://doi.org/10.3390/ijms20133177 PMID:31261749

180. Hasan AMW, Al Hasan MS, Mizan M, Miah MS, Uddin MB, Mia E, Yana NT, Islam MT, Hossain MA, Islam MT. Quercetin promises anticancer activity through PI3K-AKT-mTOR pathway: a literature review. Pharmacol Res Nat Prod. 2025; 7:100206. https://doi.org/10.1016/j.prenap.2025.100206

181. Dai G, Li Y, Zhang M, Lu P, Zhang Y, Wang H, Shi L, Cao M, Shen R, Rui Y. The Regulation of the AMPK/mTOR Axis Mitigates Tendon Stem/Progenitor Cell Senescence and Delays Tendon Aging. Stem Cell Rev Rep. 2023; 19:1492–506. https://doi.org/10.1007/s12015-023-10526-0 PMID:36917311

182. Piskovatska V, Stefanyshyn N, Storey KB, Vaiserman AM, Lushchak O. Metformin as a geroprotector: experimental and clinical evidence. Biogerontology. 2019; 20:33–48. https://doi.org/10.1007/s10522-018-9773-5 PMID:30255224

183. Ni S, Qu H, Liu D, Yuan L, Li M, Zhao W. Recent advances of the mechanistic target of rapamycin (mTOR) inhibitors for drug discovery. Eur J Med Chem. 2025; 298:118046. https://doi.org/10.1016/j.ejmech.2025.118046 PMID:40784306

184. Lee DJ, Hodzic Kuerec A, Maier AB. Targeting ageing with rapamycin and its derivatives in humans: a systematic review. Lancet Healthy Longev. 2024; 5:e152–62. https://doi.org/10.1016/S2666-7568(23)00258-1 PMID:38310895

185. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009; 460:392–5. https://doi.org/10.1038/nature08221 PMID:19587680

186. Wang R, Yu Z, Sunchu B, Shoaf J, Dang I, Zhao S, Caples K, Bradley L, Beaver LM, Ho E, Löhr CV, Perez VI. Rapamycin inhibits the secretory phenotype of senescent cells by a Nrf2-independent mechanism. Aging Cell. 2017; 16:564–74. https://doi.org/10.1111/acel.12587 PMID:28371119

187. Kell L, Jones EJ, Gharahdaghi N, Wilkinson DJ, Smith K, Atherton PJ, Simon AK, Cox LS, Alsaleh G. Rapamycin Exerts Its Geroprotective Effects in the Ageing Human Immune System by Enhancing Resilience Against DNA Damage. Aging Cell. 2026; 25:e70364. https://doi.org/10.1111/acel.70364 PMID:41524558

188. Moel M, Harinath G, Lee V, Nyquist A, Morgan SL, Isman A, Zalzala S. Influence of rapamycin on safety and healthspan metrics after one year: PEARL trial results. Aging (Albany NY). 2025; 17:908–36. https://doi.org/10.18632/aging.206235 PMID:40188830

189. Tu M, Yu H, Chen L, Huang X, He L, Chen R, Tang X, Wu J, Zhang H. Arresting idiopathic pulmonary fibrosis progression: EZY-1 targets mTORC2 to inhibit senescence-associated secretory phenotype. Food Sci Hum Wellness. 2026; 15:9250722. https://doi.org/10.26599/FSHW.2025.9250722

190. Jhanwar-Uniyal M, Amin AG, Cooper JB, Das K, Schmidt MH, Murali R. Discrete signaling mechanisms of mTORC1 and mTORC2: Connected yet apart in cellular and molecular aspects. Adv Biol Regul. 2017; 64:39–48. https://doi.org/10.1016/j.jbior.2016.12.001 PMID:28189457

191. Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. Nat Aging. 2023; 3:642–60. https://doi.org/10.1038/s43587-023-00416-y PMID:37142830

192. Mannick JB, Morris M, Hockey HP, Roma G, Beibel M, Kulmatycki K, Watkins M, Shavlakadze T, Zhou W, Quinn D, Glass DJ, Klickstein LB. TORC1 inhibition enhances immune function and reduces infections in the elderly. Sci Transl Med. 2018; 10:eaaq1564. https://doi.org/10.1126/scitranslmed.aaq1564 PMID:29997249

193. Dai DF, Kang P, Bai H. The mTOR signaling pathway in cardiac aging. J Cardiovasc Aging. 2023; 3:24. https://doi.org/10.20517/jca.2023.10 PMID:37274127

194. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020; 21:183–203. https://doi.org/10.1038/s41580-019-0199-y PMID:31937935

195. Kezic A, Popovic L, Lalic K. mTOR Inhibitor Therapy and Metabolic Consequences: Where Do We Stand? Oxid Med Cell Longev. 2018; 2018:2640342. https://doi.org/10.1155/2018/2640342 PMID:30034573

196. Kaeberlein TL, Green AS, Haddad G, Hudson J, Isman A, Nyquist A, Rosen BS, Suh Y, Zalzala S, Zhang X, Blagosklonny MV, An JY, Kaeberlein M. Evaluation of off-label rapamycin use to promote healthspan in 333 adults. Geroscience. 2023; 45:2757–68. https://doi.org/10.1007/s11357-023-00818-1 PMID:37191826

197. Kraig E, Linehan LA, Liang H, Romo TQ, Liu Q, Wu Y, Benavides AD, Curiel TJ, Javors MA, Musi N, Chiodo L, Koek W, Gelfond JA, Kellogg DL Jr. A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects. Exp Gerontol. 2018; 105:53–69. https://doi.org/10.1016/j.exger.2017.12.026 PMID:29408453

198. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023; 186:243–78. https://doi.org/10.1016/j.cell.2022.11.001 PMID:36599349

199. Chrienova Z, Nepovimova E, Kuca K. The role of mTOR in age-related diseases. J Enzyme Inhib Med Chem. 2021; 36:1679–93. https://doi.org/10.1080/14756366.2021.1955873 PMID:34309456

200. Xu X, Pang Y, Fan X. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. Signal Transduct Target Ther. 2025; 10:190. https://doi.org/10.1038/s41392-025-02253-4 PMID:40500258

201. Wei P, Zhang X, Yan C, Sun S, Chen Z, Lin F. Mitochondrial dysfunction and aging: multidimensional mechanisms and therapeutic strategies. Biogerontology. 2025; 26:142. https://doi.org/10.1007/s10522-025-10273-4 PMID:40634825

202. Bubb K, Etich J, Probst K, Parashar T, Schuetter M, Dethloff F, Reincke S, Nolte JL, Krüger M, Schlötzer-Schrehard U, Nüchel J, Demetriades C, Giavalisco P, et al. Metabolic rewiring caused by mitochondrial dysfunction promotes mTORC1-dependent skeletal aging. Sci Adv. 2025; 11:eads1842. https://doi.org/10.1126/sciadv.ads1842 PMID:40249823

203. Wang J, Yang X, Zhang J. Bridges between mitochondrial oxidative stress, ER stress and mTOR signaling in pancreatic β cells. Cell Signal. 2016; 28:1099–104. https://doi.org/10.1016/j.cellsig.2016.05.007 PMID:27185188

204. Kim HE, Lee JY, Son GY, Park JY, Kim KB, Choi CM, Moon YJ, Choi JK. Nitazoxanide Modulates Mitochondrial Function and Inflammatory Metabolism in Chondrocytes from Patients with Osteoarthritis via AMPK/mTORC1 Signaling. Antioxidants (Basel). 2025; 14:512. https://doi.org/10.3390/antiox14050512 PMID:40427394

205. Ashraf R, Kumar S. Mfn2-mediated mitochondrial fusion promotes autophagy and suppresses ovarian cancer progression by reducing ROS through AMPK/mTOR/ERK signaling. Cell Mol Life Sci. 2022; 79:573. https://doi.org/10.1007/s00018-022-04595-6 PMID:36308626

206. Mito T, Vincent AE, Faitg J, Taylor RW, Khan NA, McWilliams TG, Suomalainen A. Mosaic dysfunction of mitophagy in mitochondrial muscle disease. Cell Metab. 2022; 34:197–208.e5. https://doi.org/10.1016/j.cmet.2021.12.017 PMID:35030325

207. Zhang H, Gu W, Wu G, Yu Y. Aging and Autophagy: Roles in Musculoskeletal System Injury. Aging Dis. 2024; 16:1438–51. https://doi.org/10.14336/AD.2024.0362 PMID:38913046

208. Verdejo HE, Parra V, Del Campo A, Vasquez-Trincado C, Gatica D, Lopez-Crisosto C, Kuzmicic J, Venegas-Zamora L, Zuñiga-Cuevas U, Troncoso MF, Troncoso R, Rothermel BA, Chiong M, et al. mTOR inhibition triggers mitochondrial fragmentation in cardiomyocytes through proteosome-dependent prohibitin degradation and OPA-1 cleavage. Cell Commun Signal. 2025; 23:256. https://doi.org/10.1186/s12964-025-02240-w PMID:40450326

209. Ren R, Ocampo A, Liu GH, Izpisua Belmonte JC. Regulation of Stem Cell Aging by Metabolism and Epigenetics. Cell Metab. 2017; 26:460–74.

https://doi.org/10.1016/j.cmet.2017.07.019
PMID:28826795

210. Rezazadeh S, Ellison-Hughes GM. Editorial: Stem cell exhaustion in aging. Front Aging. 2024; 5:1433702. https://doi.org/10.3389/fragi.2024.1433702 PMID:38881824

211. Panchin AY, Ogmen A, Blagodatski AS, Egorova A, Batin M, Glinin T. Targeting multiple hallmarks of mammalian aging with combinations of interventions. Aging (Albany NY). 2024; 16:12073–100. https://doi.org/10.18632/aging.206078 PMID:39159129

212. Lotfimehr H, Mardi N, Narimani S, Nasrabadi HT, Karimipour M, Sokullu E, Rahbarghazi R. mTOR signalling pathway in stem cell bioactivities and angiogenesis potential. Cell Prolif. 2023; 56:e13499. https://doi.org/10.1111/cpr.13499 PMID:37156724

213. Fauzi A, Wong CZ, Tee PY, Yau AW, Ab Rashid E, Tang YQ, Chia AY. Mechanistic insights into stem cell aging: Pathways and processes. Mech Ageing Dev. 2026; 230:112160. https://doi.org/10.1016/j.mad.2026.112160 PMID:41628864

214. Selman C, Sinclair A, Pedroni SM, Irvine EE, Michie AM, Withers DJ. Evidence that hematopoietic stem cell function is preserved during aging in long-lived S6K1 mutant mice. Oncotarget. 2016; 7:29937–43. https://doi.org/10.18632/oncotarget.8729 PMID:27083004

215. Xu X, Ahmed T, Wang L, Cao X, Zhang Z, Wang M, Lv Y, Kanwal S, Tariq M, Lin R, Zhang H, Huang Y, Peng H, et al. The mTORC1-eIF4F axis controls paused pluripotency. EMBO Rep. 2022; 23:e53081. https://doi.org/10.15252/embr.202153081 PMID:34866316

216. Nanba D, Sakabe JI, Mosig J, Brouard M, Toki F, Shimokawa M, Kamiya M, Braschler T, Azzabi F, Droz-Georget Lathion S, Johnsson K, Roy K, Schmid CD, et al. Low temperature and mTOR inhibition favor stem cell maintenance in human keratinocyte cultures. EMBO Rep. 2023; 24:e55439. https://doi.org/10.15252/embr.202255439 PMID:37139607

217. Mohammad K, Dakik P, Medkour Y, Mitrofanova D, Titorenko VI. Quiescence Entry, Maintenance, and Exit in Adult Stem Cells. Int J Mol Sci. 2019; 20:2158. https://doi.org/10.3390/ijms20092158 PMID:31052375

218. Han YP, Enomoto A, Shiraki Y, Wang SQ, Wang X, Toyokuni S, Asai N, Ushida K, Ara H, Ohka F, Wakabayashi T, Ma J, Natsume A, Takahashi M. Significance of low mTORC1 activity in defining the characteristics of brain tumor stem cells. Neuro Oncol. 2017; 19:636–47. https://doi.org/10.1093/neuonc/now237 PMID:28453744

219. Mattila J, Viitanen A, Fabris G, Strutynska T, Korzelius J, Hietakangas V. Stem cell mTOR signaling directs region-specific cell fate decisions during intestinal nutrient adaptation. Sci Adv. 2024; 10:eadi2671. https://doi.org/10.1126/sciadv.adi2671 PMID:38335286

220. Haller S, Kapuria S, Riley RR, O'Leary MN, Schreiber KH, Andersen JK, Melov S, Que J, Rando TA, Rock J, Kennedy BK, Rodgers JT, Jasper H. mTORC1 Activation during Repeated Regeneration Impairs Somatic Stem Cell Maintenance. Cell Stem Cell. 2017; 21:806–18.e5. https://doi.org/10.1016/j.stem.2017.11.008 PMID:29220665

221. Fedor A, Bryniarski K, Nazimek K. mTOR Signaling in Macrophages: All Depends on the Context. Int J Mol Sci. 2025; 26:7598. https://doi.org/10.3390/ijms26157598 PMID:40806725

222. Ling B, Xu Y, Qian S, Xiang Z, Xuan S, Wu J. Regulation of hematopoietic stem cells differentiation, self-renewal, and quiescence through the mTOR signaling pathway. Front Cell Dev Biol. 2023; 11:1186850. https://doi.org/10.3389/fcell.2023.1186850 PMID:37228652

223. López-Gil L, Pascual-Ahuir A, Proft M. Genomic Instability and Epigenetic Changes during Aging. Int J Mol Sci. 2023; 24:14279. https://doi.org/10.3390/ijms241814279 PMID:37762580

224. Feng JX, Riddle NC. Epigenetics and genome stability. Mamm Genome. 2020; 31:181–95. https://doi.org/10.1007/s00335-020-09836-2 PMID:32296924

225. Ma Y, Vassetzky Y, Dokudovskaya S. mTORC1 pathway in DNA damage response. Biochim Biophys Acta Mol Cell Res. 2018; 1865:1293–311. https://doi.org/10.1016/j.bbamcr.2018.06.011 PMID:29936127

226. Braun F, Mandel AM, Blomberg L, Wong MN, Chatzinikolaou G, Meyer DH, Reinelt A, Nair V, Akbar-Haase R, McCown PJ, Haas F, Chen H, Rahmatollahi M, et al. Loss of genome maintenance is linked to mTOR complex 1 signaling and accelerates podocyte damage. JCI Insight. 2025; 10:e172370. https://doi.org/10.1172/jci.insight.172370 PMID:40392611

227. He Z, Houghton PJ, Williams TM, Shen C. Regulation of DNA duplication by the mTOR signaling pathway. Cell Cycle. 2021; 20:742–51. https://doi.org/10.1080/15384101.2021.1897271 PMID:33691584

228. Xie X, Hu H, Tong X, Li L, Liu X, Chen M, Yuan H, Xie X, Li Q, Zhang Y, Ouyang H, Wei M, Huang J, et al. The mTOR-S6K pathway links growth signalling to DNA damage response by targeting RNF168. Nat Cell Biol. 2018; 20:320–31. https://doi.org/10.1038/s41556-017-0033-8 PMID:29403037

229. Shen C, He Y, Chen Q, Feng H, Williams TM, Lu Y, He Z. Narrative review of emerging roles for AKT-mTOR signaling in cancer radioimmunotherapy. Ann Transl Med. 2021; 9:1596. https://doi.org/10.21037/atm-21-4544 PMID:34790802

230. Silvera D, Ernlund A, Arju R, Connolly E, Volta V, Wang J, Schneider RJ. mTORC1 and -2 Coordinate Transcriptional and Translational Reprogramming in Resistance to DNA Damage and Replicative Stress in Breast Cancer Cells. Mol Cell Biol. 2017; 37:e00577–16. https://doi.org/10.1128/MCB.00577-16 PMID:27956700

231. Moinuddin, Kumar N, Bhadauria S. Nuclear mTORC2 and its emerging role in gene regulation. J Cancer Biol. 2025; 6:34–46. https://doi.org/10.46439/cancerbiology.6.072

232. Wang C, Wang H, Wang Y, Xiao M, Song X, Wang X, Zhang X, Jin K, Zhao D, Chen H, Zhang N, Chen R. mTORC2 Regulates Non-homologous End Joining Through Modulating the Temporal Dynamics of 53BP1. Mol Cell Proteomics. 2025; 24:101035. https://doi.org/10.1016/j.mcpro.2025.101035 PMID:40675556

233. Tian L, Chen C, Guo Y, Zhang F, Mi J, Feng Q, Lin S, Xi N, Tian J, Yu L, Chen Y, Cao M, Lai C, et al. mTORC2 regulates ribonucleotide reductase to promote DNA replication and gemcitabine resistance in non-small cell lung cancer. Neoplasia. 2021; 23:643–52. https://doi.org/10.1016/j.neo.2021.05.007 PMID:34126361

234. Kalpongnukul N, Bootsri R, Wongkongkathep P, Kaewsapsak P, Ariyachet C, Pisitkun T, Chantaravisoot N. Phosphoproteomic Analysis Defines BABAM1 as mTORC2 Downstream Effector Promoting DNA Damage Response in Glioblastoma Cells. J Proteome Res. 2022; 21:2893–904. https://doi.org/10.1021/acs.jproteome.2c00240 PMID:36315652

235. Mukhopadhyay S, Frias MA, Chatterjee A, Yellen P, Foster DA. The Enigma of Rapamycin Dosage. Mol Cancer Ther. 2016; 15:347–53. https://doi.org/10.1158/1535-7163.MCT-15-0720 PMID:26916116

236. Gkioni L, Nespital T, Baghdadi M, Monzó C, Bali J, Nassr T, Cremer AL, Beyer A, Deelen J, Backes H, Grönke S, Partridge L. The geroprotectors trametinib and rapamycin combine additively to extend mouse healthspan and lifespan. Nat Aging. 2025; 5:1249–65. https://doi.org/10.1038/s43587-025-00876-4 PMID:40437307

237. Kakiuchi Y, Yurube T, Kakutani K, Takada T, Ito M, Takeoka Y, Kanda Y, Miyazaki S, Kuroda R, Nishida K. Pharmacological inhibition of mTORC1 but not mTORC2 protects against human disc cellular apoptosis, senescence, and extracellular matrix catabolism through Akt and autophagy induction. Osteoarthritis Cartilage. 2019; 27:965–76. https://doi.org/10.1016/j.joca.2019.01.009 PMID:30716534

238. Stallone G, Infante B, Prisciandaro C, Grandaliano G. mTOR and Aging: An Old Fashioned Dress. Int J Mol Sci. 2019; 20:2774. https://doi.org/10.3390/ijms20112774 PMID:31174250

239. Zheng P, Yan W, Ding Y, Zhang Y, Chen Z, Qian J, Ge J. Cardiovascular ageing: hallmarks, signaling pathways, diseases and therapeutic targets. Signal Transduct Target Ther. 2026; 11:142. https://doi.org/10.1038/s41392-026-02630-7 PMID:42010239

240. Daneshgar N, Rabinovitch PS, Dai DF. TOR Signaling Pathway in Cardiac Aging and Heart Failure. Biomolecules. 2021; 11:168. https://doi.org/10.3390/biom11020168 PMID:33513917

241. Guo J, Wu Y, Wan Z, Zhang Z. Post-translational modifications orchestrate mTOR-driven cell death in cardiovascular disease. Front Cardiovasc Med. 2025; 12:1620669. https://doi.org/10.3389/fcvm.2025.1620669 PMID:40734978

242. Zhang X, Ajam A, Liu Z, Peroumal D, Khan SR, Razani B. Leucine accelerates atherosclerosis through dose-dependent MTOR activation in macrophages. Autophagy. 2025; 21:1618–20. https://doi.org/10.1080/15548627.2025.2474603 PMID:40047228

243. Li G, Wang M, Caulk AW, Cilfone NA, Gujja S, Qin L, Chen PY, Chen Z, Yousef S, Jiao Y, He C, Jiang B, Korneva A, et al. Chronic mTOR activation induces a

degradative smooth muscle cell phenotype. J Clin Invest. 2020; 130:1233–51. https://doi.org/10.1172/JCI131048 PMID:32039915

244. Zhang X, Evans TD, Chen S, Sergin I, Stitham J, Jeong SJ, Rodriguez-Velez A, Yeh YS, Park A, Jung IH, Diwan A, Schilling JD, Rom O, et al. Loss of Macrophage mTORC2 Drives Atherosclerosis via FoxO1 and IL-1β Signaling. Circ Res. 2023; 133:200–19. https://doi.org/10.1161/CIRCRESAHA.122.321542 PMID:37350264

245. Sciarretta S, Zhai P, Maejima Y, Del Re DP, Nagarajan N, Yee D, Liu T, Magnuson MA, Volpe M, Frati G, Li H, Sadoshima J. mTORC2 regulates cardiac response to stress by inhibiting MST1. Cell Rep. 2015; 11:125–36. https://doi.org/10.1016/j.celrep.2015.03.010 PMID:25843706

246. Yang HW, Hong HL, Luo WW, Dai CM, Chen XY, Wang LP, Li Q, Li ZQ, Liu PQ, Li ZM. mTORC2 facilitates endothelial cell senescence by suppressing Nrf2 expression via the Akt/GSK-3β/C/EBPα signaling pathway. Acta Pharmacol Sin. 2018; 39:1837–46. https://doi.org/10.1038/s41401-018-0079-6 PMID:29991711

247. Banerjee D, Sinha A, Saikia S, Gogoi B, Rathore AK, Das AS, Pal D, Buragohain AK, Dasgupta S. Inflammation-induced mTORC2-Akt-mTORC1 signaling promotes macrophage foam cell formation. Biochimie. 2018; 151:139–49. https://doi.org/10.1016/j.biochi.2018.06.001 PMID:29883748

248. Palmer JE, Wilson N, Son SM, Obrocki P, Wrobel L, Rob M, Takla M, Korolchuk VI, Rubinsztein DC. Autophagy, aging, and age-related neurodegeneration. Neuron. 2025; 113:29–48. https://doi.org/10.1016/j.neuron.2024.09.015 PMID:39406236

249. De Gaetano A, Gibellini L, Zanini G, Nasi M, Cossarizza A, Pinti M. Mitophagy and Oxidative Stress: The Role of Aging. Antioxidants (Basel). 2021; 10:794. https://doi.org/10.3390/antiox10050794 PMID:34067882

250. Davoody S, Asgari Taei A, Khodabakhsh P, Dargahi L. mTOR signaling and Alzheimer's disease: What we know and where we are? CNS Neurosci Ther. 2024; 30:e14463. https://doi.org/10.1111/cns.14463 PMID:37721413

251. Jha NK, Chauhan P, Abomughaid MM, Avinash D, Almutary AG, Lakhanpal S, Singh A, Sulaimani GM, Al-Kuraishy HM, Mohammed HA, Misra J, Thakur K, Kumar D. mTOR Signalling in Neurodegenerative Disorders: Unveiling Key Factors, Mechanistic Insights, and Possible Therapeutic Interventions. Cell Physiol Biochem. 2026; 60:136–74. https://doi.org/10.33594/000000858 PMID:42057546

252. Song W, Zhang Y, Xu T, Fan T, Li J, Liu M, Wei W, Pei X, Li R. Metabolic reprogramming in neurodegenerative diseases: New insights into mTOR-mediated microglial polarization. J Transl Int Med. 2025; 13:610–13. https://doi.org/10.1515/jtim-2025-0059 PMID:41438470

253. Tong K, Li S, Chen G, He D, Lin C, Li Y, Chen N. Rictor/mTORC2 signaling pathway protects endogenous neural stem cells to promote recovery after spinal cord injury. Neural Regen Res. 2026; 21:4367–77. https://doi.org/10.4103/NRR.NRR-D-25-00544 PMID:41467432

254. Bar-Tana J. mTORC1 syndrome (TorS): unified paradigm for diabetes/metabolic syndrome. Trends Endocrinol Metab. 2023; 34:135–45. https://doi.org/10.1016/j.tem.2023.01.001 PMID:36717300

255. Amin NG, Rahim AA, Rohoma K, Elwafa RA, Dabees HM, Elrahmany S. The relation of mTOR with diabetic complications and insulin resistance in patients with type 2 diabetes mellitus. Diabetol Metab Syndr. 2024; 16:222. https://doi.org/10.1186/s13098-024-01450-5 PMID:39261960

256. Guillén C, Benito M. mTORC1 Overactivation as a Key Aging Factor in the Progression to Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne). 2018; 9:621. https://doi.org/10.3389/fendo.2018.00621 PMID:30386301

257. Frei IC, Weissenberger D, Müller C, Hall MN, Shimobayashi M. Hepatic mTORC2 compensates for loss of adipose mTORC2 in mediating energy storage and glucose homeostasis. Am J Physiol Endocrinol Metab. 2023; 324:E589–98. https://doi.org/10.1152/ajpendo.00338.2022 PMID:37166264

258. Yuan T, Lupse B, Maedler K, Ardestani A. mTORC2 Signaling: A Path for Pancreatic β Cell's Growth and Function. J Mol Biol. 2018; 430:904–18. https://doi.org/10.1016/j.jmb.2018.02.013 PMID:29481838

259. Dalle Pezze P, Sonntag AG, Thien A, Prentzell MT, Gödel M, Fischer S, Neumann-Haefelin E, Huber TB, Baumeister R, Shanley DP, Thedieck K. A dynamic network model of mTOR signaling reveals TSC-independent mTORC2 regulation. Sci Signal. 2012; 5:ra25. https://doi.org/10.1126/scisignal.2002469 PMID:22457331

260. Joseph GA, Wang SX, Jacobs CE, Zhou W, Kimble GC, Tse HW, Eash JK, Shavlakadze T, Glass DJ. Partial

Inhibition of mTORC1 in Aged Rats Counteracts the Decline in Muscle Mass and Reverses Molecular Signaling Associated with Sarcopenia. Mol Cell Biol. 2019; 39:e00141–19. https://doi.org/10.1128/MCB.00141-19 PMID:31308131

261. Kalenta H, Kilroe SP, Romsdahl TB, Marchant ED, Maroto R, Linares JJ, Russell WK, Rasmussen BB. Constitutively active mTORC1 signaling modifies the skeletal muscle metabolome and lipidome response to exercise. J Appl Physiol (1985). 2025; 138:1173–86. https://doi.org/10.1152/japplphysiol.00987.2024 PMID:40215109

262. Tang H, Inoki K, Brooks SV, Okazawa H, Lee M, Wang J, Kim M, Kennedy CL, Macpherson PC, Ji X, Van Roekel S, Fraga DA, Wang K, et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. Aging Cell. 2019; 18:e12943. https://doi.org/10.1111/acel.12943 PMID:30924297

263. Crombie EM, Kim S, Adamson S, Dong H, Lu TC, Wu Y, Wu Y, Levy Y, Stimple N, Lam WM, Hey HW, Withers DJ, Hsu AL, et al. Activation of eIF4E-binding-protein-1 rescues mTORC1-induced sarcopenia by expanding lysosomal degradation capacity. J Cachexia Sarcopenia Muscle. 2023; 14:198–213. https://doi.org/10.1002/jcsm.13121 PMID:36398408

264. Rion N, Castets P, Lin S, Enderle L, Reinhard JR, Rüegg MA. mTORC2 affects the maintenance of the muscle stem cell pool. Skelet Muscle. 2019; 9:30. https://doi.org/10.1186/s13395-019-0217-y PMID:31791403

265. Ato S, Oya C, Ogasawara R. Rapamycin administration causes a decrease in muscle contractile function and systemic glucose intolerance concomitant with reduced skeletal muscle Rictor, the mTORC2 component, expression independent of energy intake in young rats. PLoS One. 2024; 19:e0312859. https://doi.org/10.1371/journal.pone.0312859 PMID:39637031