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REVIEW

Sestrins as Multifunctional Regulators of Cell Viability on the Pathways from Stress to Aging

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Abstract—The interaction of cells with their environment is crucial for maintaining cellular homeostasis, and disruption of these interactions causes cellular stress and cell death. Thus, cell survival depends on the balance between proteins responsible for cell protection and those inducing cell death. Sestrins are evolutionarily conserved stress-inducible proteins that modulate cell survival under stress conditions. While prokaryotic precursors of Sestrins play a key role in protecting against oxidative stress, eukaryotic Sestrins are critically important for regulating mTORC1 and mTORC2 kinases, as well as for controlling the expression of various proteins responsible for protection against stress, mitochondrial functions, and cell death. Sestrins sustain mitochondrial activity and metabolism, activate autophagy, and limit oxidative damage, thereby promoting cell survival. Conversely, in response to DNA damage and cytokine production, Sestrins promote apoptosis by suppressing the expression of anti-apoptotic proteins, which helps prevent carcinogenesis. As modulators of cellular responses to stress, Sestrins may also serve as markers of various diseases associated with stress responses. In some tissues, expression of all Sestrin genes declines with age, which impairs the regulation of metabolism and cell death and weakens protection against age-related diseases. Thus, maintaining Sestrin activity may contribute to the prevention and treatment of various age-related diseases.

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Keywords: Sestrin, mTOR, cell death, autophagy, metabolism, mitochondria, stress, aging

INTRODUCTION

Sestrins are a family of proteins found in most animal species. They were discovered in the early 2000s as regulators of cell viability under stress conditions. The first member of the family, Sestrin1, previously known as PA26 (p53-activated protein 26), was identified in a screen for novel genes induced in response to the activation of the tumor suppressor and transcription factor p53 [1]. Sestrin2 was discovered several years later in a screen for genes whose expression is induced in response to hypoxia and was therefore initially named Hi95 (hypoxia-inducible 95) [2]. The third member of the family, Sestrin3, was identified *in silico* by searching genomic databases for sequences homologous to Sestrins [2, 3].

Detailed analysis of genomic sequences in various organisms demonstrated that genes encoding Sestrins are present in most animals and in protozoa but are absent from plants and fungi [4]. Vertebrate genomes contain three genes encoding Sestrins, while invertebrates and protozoa have only one Sestrin gene [2]. All Sestrins are highly homologous and share a common architecture: a globular protein composed of 16 α-helices that can interact with many proteins involved in cellular stress responses, signaling pathways, and metabolic regulation [2, 5]. Another common feature of the Sestrin genes is their activation in response to stress, which helps protect the organism from the consequences of stress through the regulation of metabolism and cell death [6].

This review examines the role of Sestrins in regulating cell viability in various cell models and model organisms under stresses that accompany various

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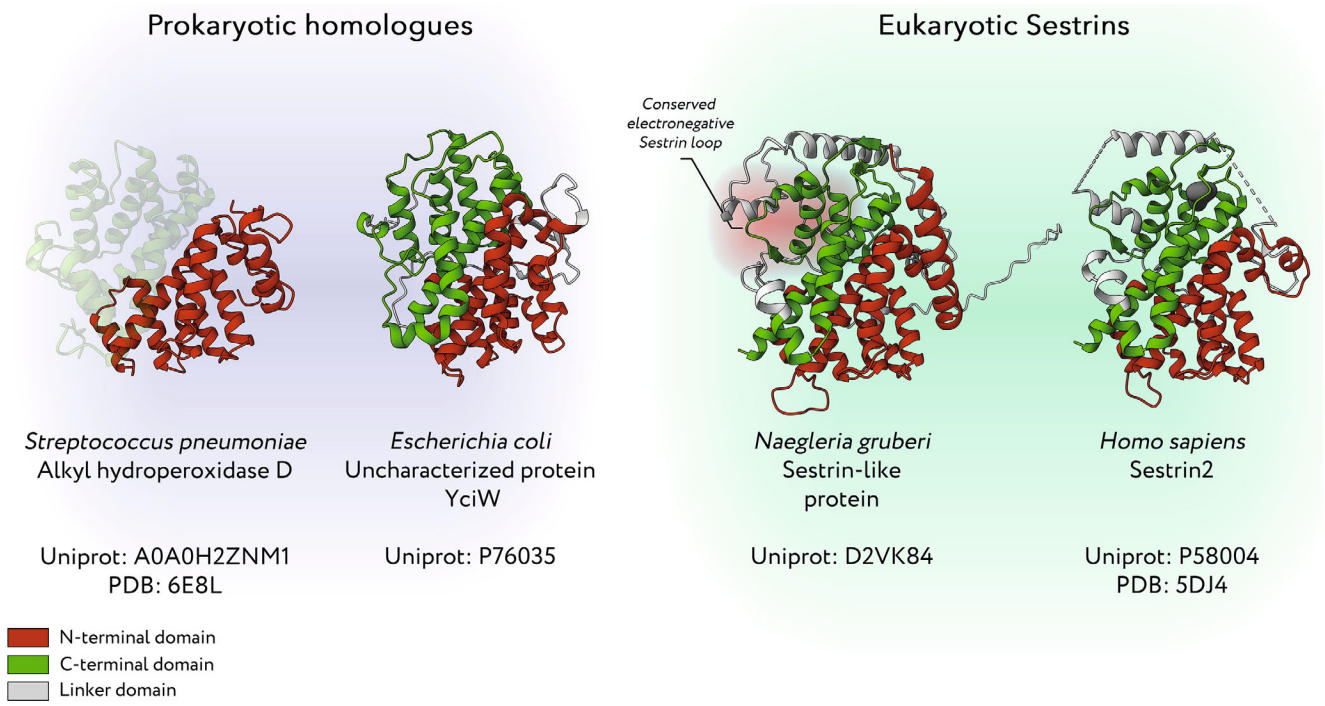

Fig. 1. Eukaryotic Sestrins are homologous to prokaryotic antioxidant proteins. Structural analysis of the Sestrin structure using the AlphaFold program. Regions homologous to bacterial proteins in the primary structure are highlighted in red, and those homologous in secondary and tertiary structures, in green (adapted from [5] and reproduced under the CC BY 4.0 license).

diseases. We take an evolutionary perspective, tracing the structural and functional changes in ancestral Sestrin-like proteins that have given rise to new activities in proteins of this family and connected their antioxidant function to the regulation of metabolism, autophagy, and several forms of cell death. Although individual aspects of Sestrin biology have been reviewed previously, we provide a detailed analysis of Sestrin structure and function in the context of cell death regulation, as well as the association of these proteins with aging and age-related diseases.

ORIGIN AND STRUCTURAL FEATURES OF SESTRINS

Early structural studies of Sestrins led to an important observation regarding their evolutionary origin and potential function. These studies demonstrated that the N-terminal region of Sestrins exhibits weak but statistically significant sequence homology with several bacterial proteins involved in cellular protection against reactive oxygen species (ROS), including AhpD (alkyl hydroperoxide reductase D) from *Mycobacterium tuberculosis* [7]. AhpD is a critical mediator of electron transfer from lipoic acid and thioredoxin to peroxiredoxin AhpC, responsible for the reduction of peroxides [8]. Proteins belonging to the AhpD family contain two highly conserved cysteines required for the complete cycle of peroxiredoxin regeneration, in which one of the cysteines (catalytic) directly catalyzes the reduction of oxidized cysteine of peroxiredoxins, and the second (reducing) cysteine is responsible for the regeneration of the oxidized catalytic cysteine [9]. Sestrins contain a highly homologous reducing cysteine, indicating the likely involvement of these proteins in redox-dependent processes [10]. Interestingly, *in silico* analysis of tertiary structures demonstrated a high degree of structural similarity between the N-terminal region of Sestrins and AhpD-like proteins [7]. Subsequent crystallization studies of Sestrins demonstrated that, despite the absence of homology in the amino acid sequences, the spatial structures of the N-terminal and C-terminal regions of Sestrins are highly similar to each other and to those of AhpD-like proteins [11, 12]. This observation led to the suggestion that Sestrins could have originated through the duplication of an AhpD-like gene followed by the separation of the functions of the N- and C-terminal domains. In our recent work, we demonstrated that some microorganisms encode proteins consisting of two highly homologous AhpD-like sequences that probably possess identical functions; furthermore, we found proteins homologous to Sestrins in which one half has mutated extensively and presumably acquired

new functions, while the other half contains highly homologous cysteines. As a result of the evolutionary process, the amoeba *Naegleria gruberi*, a representative of unicellular eukaryotes, possesses a Sestrin-like protein with the typical structural features of eukaryotic Sestrins [5] (Fig. 1).

While a single protein product has been detected for the Sestrin genes in invertebrates such as *Caenorhabditis elegans* and *Drosophila melanogaster*, mammalian Sestrin genes encode multiple protein products. The *SESN1* gene coding for Sestrin1 gives rise to three proteins with molecular masses of 68, 55, and 48 kDa [1], which are generated through the use of alternative transcription start sites and alternative splicing. A single 60-kDa protein has been demonstrated for *SESN2*, which encodes Sestrin2 [2], although several alternative transcripts have been identified in skeletal muscle, pancreas, and testes [13]. Two Sestrin3 isoforms of 53 and 44 kDa have been demonstrated for *SESN3*, resulting from alternative transcription initiation and splicing [14]. Each mammalian Sestrin gene produces a "canonical" protein of approximately 53-60 kDa that resembles invertebrate Sestrins and is likely to mediate many of the conserved functions of Sestrin family proteins. In contrast, alternative Sestrin isoforms may have distinct biological functions or contribute to the regulation of the canonical forms. For example, they could compete for shared binding sites or modulate additional signaling pathways.

REGULATION OF SESTRIN EXPRESSION IN RESPONSE TO STRESS

The expression of all studied members of the Sestrin family is induced in response to cellular stress, although distinct types of stress preferentially activate different Sestrins. DNA damage, for example, induces the expression of genes encoding Sestrin1 and Sestrin2; their induction in response to genotoxic stress is entirely dependent on the tumor suppressor protein p53 [2]. p53 is a key regulator of the cellular response to stress and is mutated in more than 50% of human tumors [15]. It induces *SESN1* and *SESN2* expression through direct interactions with the promoter and enhancer regions of these genes, respectively [16]. The importance of Sestrins in mediating p53-dependent cellular responses is demonstrated by the evolutionary conservation of their p53-dependent regulation, which is also observed in invertebrate organisms such as *D. melanogaster* and *C. elegans* [17]. p53 promotes cell survival under moderately stressful conditions but can trigger apoptosis or cellular senescence when the damage is severe [10, 18]. In addition to p53, transcription factors of the FOXO (forkhead box O) family are important regulators of Sestrin expression. FOXO1 and FOXO3A induce *SESN3* expression in response to oxidative stress and serum starvation [14, 19, 20]. Oxidative stress also stimulates *SESN2* expression through the activation of several transcription factors, including NRF2 (nuclear factor erythroid 2-related factor), a key regulator of the antioxidant defense, as well as C/EBP1 (CCAAT/enhancer-binding protein), c-Jun, and p53 [7, 21-24].

In addition to genotoxic and oxidative stresses, Sestrin2 expression is induced in response to endoplasmic reticulum stress (ERS) and the associated unfolded protein response (UPR) [25, 26]. ERS can arise from various disturbances in protein homeostasis, including impaired protein folding during synthesis (for example, as a result of defective glycosylation), structural alterations caused by elevated temperature or oxidative damage, and protein aggregation under pathological conditions [27]. Notably, all three major ERS-induced transcriptional pathways, mediated by ATF4 (activating transcription factor 4), XBP1 (X-box-binding protein 1), and ATF6 (activating transcription factor 6), respectively, have been implicated in the induction of Sestrin expression [25].

Under certain conditions (e.g., glucose starvation), ATF4 cooperates with NRF2 to achieve full activation of Sestrin2 transcription [28], whereas following treatment with thapsigargin, an inhibitor of the sarco/endoplasmic reticulum Ca^{2+}-ATPase, or methotrexate, an inhibitor of dihydrofolate reductase, Sestrin2 transcription is regulated through an ATF4- and XBP1-dependent mechanism [26]. Amino acid starvation induces Sestrin2 via an ATF4-dependent mechanism mediated by the GCN2 (general

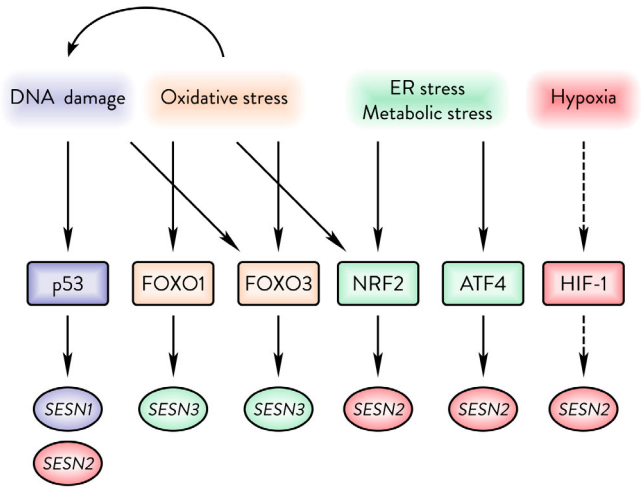

Fig. 2. Transcriptional regulation of the Sestrin family. Sestrins are induced in response to diverse cellular stresses through the activation of key transcription factors involved in metabolic regulation, stress adaptation, and the control of cell viability (adapted from [87] and is reproduced under the CC BY 4.0 license).

control nonderepressible 2) kinase. GCN2 is activated in response to the accumulation of uncharged tRNAs during amino acid deprivation and phosphorylates eIF2α (eukaryotic translation initiation factor 2α), which suppresses global cap-dependent translation while selectively promoting the translation of stress-responsive proteins, including ATF4 [29].

Hypoxia induces Sestrin2 expression through a mechanism that is not yet fully understood and may involve HIF-1 (hypoxia-inducible factor 1) and ERS-related proteins [2, 30]. Sestrin2 expression is also induced by nutrient excess such as elevated glucose and lipid levels, which is associated with hyperactivation of the mTOR (mammalian/mechanistic target of rapamycin) kinase pathway and ERS [16]. Collectively, these findings highlight the important role of Sestrins in coordinating cellular stress responses and maintaining cell viability under stress conditions (Fig. 2).

REGULATION OF THE mTOR KINASE BY SESTRINS

An important milestone in elucidating the functions of Sestrins was the discovery of their role in regulating the mTOR [31]. mTOR belongs to the PIKK (phosphatidylinositol 3-kinase-related kinase) family, which includes ATM (ataxia telangiectasia mutated)-like kinases, and serves as a central regulator of cellular metabolism and cell growth [32]. mTOR exists in two structurally and functionally distinct complexes, mTORC1 (mTOR complex 1) and mTORC2 (mTOR complex 2), which exhibit both distinct and overlapping biological activities. mTORC1 consists of mTOR, RAPTOR (regulatory-associated protein of mTOR), and mLST8 (mammalian lethal with Sec13 protein 8), together with the regulatory subunits PRAS40 (proline-rich AKT substrate of 40 kDa) and DEPTOR (DEP domain-containing mTOR-interacting protein). The core components of mTORC2 are mTOR, RICTOR (rapamycin-insensitive companion of mTOR), mLST8, mSIN1 (mammalian stress-activated protein kinase-interacting protein 1), PROTOR1/2 (protein observed with RICTOR 1/2), and DEPTOR [33]. A defining feature of the two mTOR complexes is their substrate specificity, which is largely determined by the presence of RAPTOR in mTORC1 and RICTOR in mTORC2. The best-characterized substrates of mTORC1 include p70S6K (70-kDa ribosomal protein S6 kinase) and 4EBP1 (eukaryotic translation initiation factor 4E-binding protein 1), both of which promote translational processes and protein synthesis. In contrast, major substrates of mTORC2 include AKT (serine/threonine protein kinase B), SGK1 (serum and glucocorticoid-regulated kinase 1), and PKC (protein kinase C) [32, 33].

mTORC1 is critically important for the regulation of cell growth by promoting anabolic processes, including the synthesis of proteins, lipids, and nucleotides. Another key function of mTORC1 is the negative regulation of macroautophagy (hereafter, autophagy). Autophagy is a cellular degradation process in which cytoplasmic components are sequestered into intracellular vesicles and subsequently delivered to lysosomes for degradation [34]. Although autophagy can contribute to (type II) cell death under certain conditions, its predominant role is protecting cells by supplying them with nutrients, facilitating the removal of damaged organelles, and limiting oxidative stress [35]. mTORC1 suppresses autophagy through several mechanisms. First, it directly phosphorylates and inhibits key autophagy-initiating proteins, including the serine/threonine kinase ULK1 (Unc-51-like kinase 1), which is essential for the initiation of autophagosome formation [36]. Second, mTORC1 phosphorylates and inhibits TFEB (transcription factor EB), a master transcriptional regulator of coordinated lysosomal expression and regulation (CLEAR) genes involved in autophagy and lysosomal degradation [37]. Consequently, high mTORC1 activity, which is characteristic of cell growth under favorable nutrient and growth factor conditions and is also observed in certain pathological states, including metabolic syndrome, is associated with the suppression of autophagy. Conversely, inhibition of mTORC1, for example, by rapamycin or under conditions of nutrient or growth factor deprivation, promotes autophagy [33, 38]. mTORC1 activity is regulated by two major classes of small GTPases: RHEB (Ras homolog enriched in brain) and the heterodimeric RAG GTPases composed of RAGA/B and RAGC/D (Ras-related GTP-binding proteins A-D). RHEB directly activates mTORC1 by inducing conformational changes in the complex, whereas the RAG GTPases mediate the recruitment of mTORC1 to lysosomal membranes, where RHEB is localized. RHEB is active in its GTP-bound state, while GTP hydrolysis converts it to the inactive state. RHEB activity is negatively regulated by the TSC (tuberous sclerosis complex), which functions as a GTPase-activating protein (GAP) toward RHEB. TSC activity is regulated by phosphorylation mediated by multiple signaling kinases. For example, AKT phosphorylates and inhibits TSC in response to the activation of receptor tyrosine kinases and the PI3K (phosphoinositide 3-kinase) pathway, thereby promoting RHEB activation and subsequent mTORC1 signaling. In contrast, phosphorylation of TSC by AMPK (AMP-activated protein kinase) promotes its GAP activity toward RHEB and consequently suppresses mTORC1 activation. The RAG proteins are active when the RAGA/B is GTP-bound and RAGC/D is GDP-bound. Two major protein complexes regulate the nucleotide-binding state of RAGA/B.

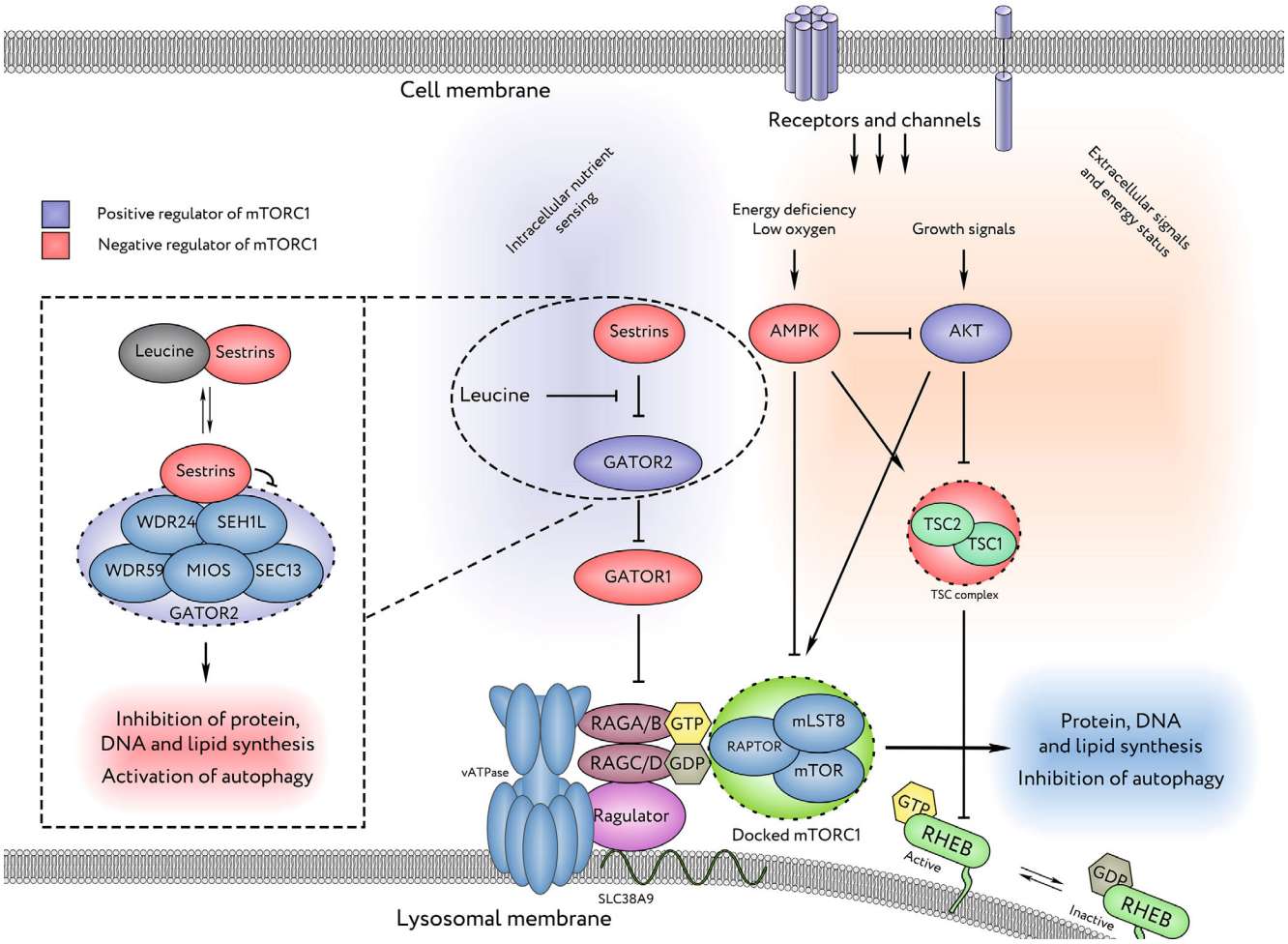

Fig. 3. Regulation of mTORC1 kinase activity. mTORC1 is activated by the small GTPases RAGA-D and RHEB, which are themselves regulated by multiple intracellular and extracellular stimuli, including growth factors, nutrients, and stress (adapted from [5] and published under the CC BY 4.0 license).

The Ragulator complex, which is anchored to the lysosomal membrane, functions as a guanine nucleotide exchange factor (GEF) for RAGA/B and promotes their GTP loading and activity. In contrast, the GATOR1 (GTPase-activating proteins toward RAGs) protein complex acts as a GAP and stimulates GTP hydrolysis, thereby suppressing mTORC1 recruitment to lysosomes. GATOR1 activity is negatively regulated by the GATOR2 protein complex [33] (Fig. 3).

Sestrins inhibit mTORC1 through two parallel mechanisms. First, these proteins stimulate the activity of AMPK, thereby promoting TSC activation [14, 31]. Second, Sestrins directly interact with GATOR2, inducing conformational changes that prevent the GATOR2 complex from inhibiting GATOR1 [39-41]. An important structural feature of Sestrin1 and 2 is their ability to bind the essential amino acid leucine in a specific leucine-binding pocket. Leucine binding induces a conformational change in Sestrins that weakens their interaction with GATOR2, thereby relieving Sestrin-mediated inhibition of GATOR2 (Fig. 3) [11, 42]. Recently, it was shown that the binding of Sestrin3 to GATOR2 is negatively regulated by the aromatic amino acids tyrosine, phenylalanine, and tryptophan [43]. However, the molecular mechanisms underlying this regulation remain poorly understood. Sestrin-mediated inhibition of mTORC1 suppresses mTORC1-dependent biosynthetic processes and consequently limits cell growth and proliferation. In particular, this effect is associated with reduced expression of cyclin D, a key regulator of cell cycle progression [2]. At the same time, Sestrins promote autophagy, thereby contributing to cellular protection against various forms of damage and oxidative stress [6]. Thus, Sestrin-dependent regulation of mTORC1 is two-tiered, as Sestrin activity is determined by both the level of Sestrin expression and the intracellular concentration of leucine. Under stress conditions, Sestrin expression is upregulated, making mTORC1 more sensitive even to a moderate decrease in intracellular leucine levels. Accordingly, tissues with elevated Sestrin expression exhibit increased sensitivity to leucine (Fig. 7).

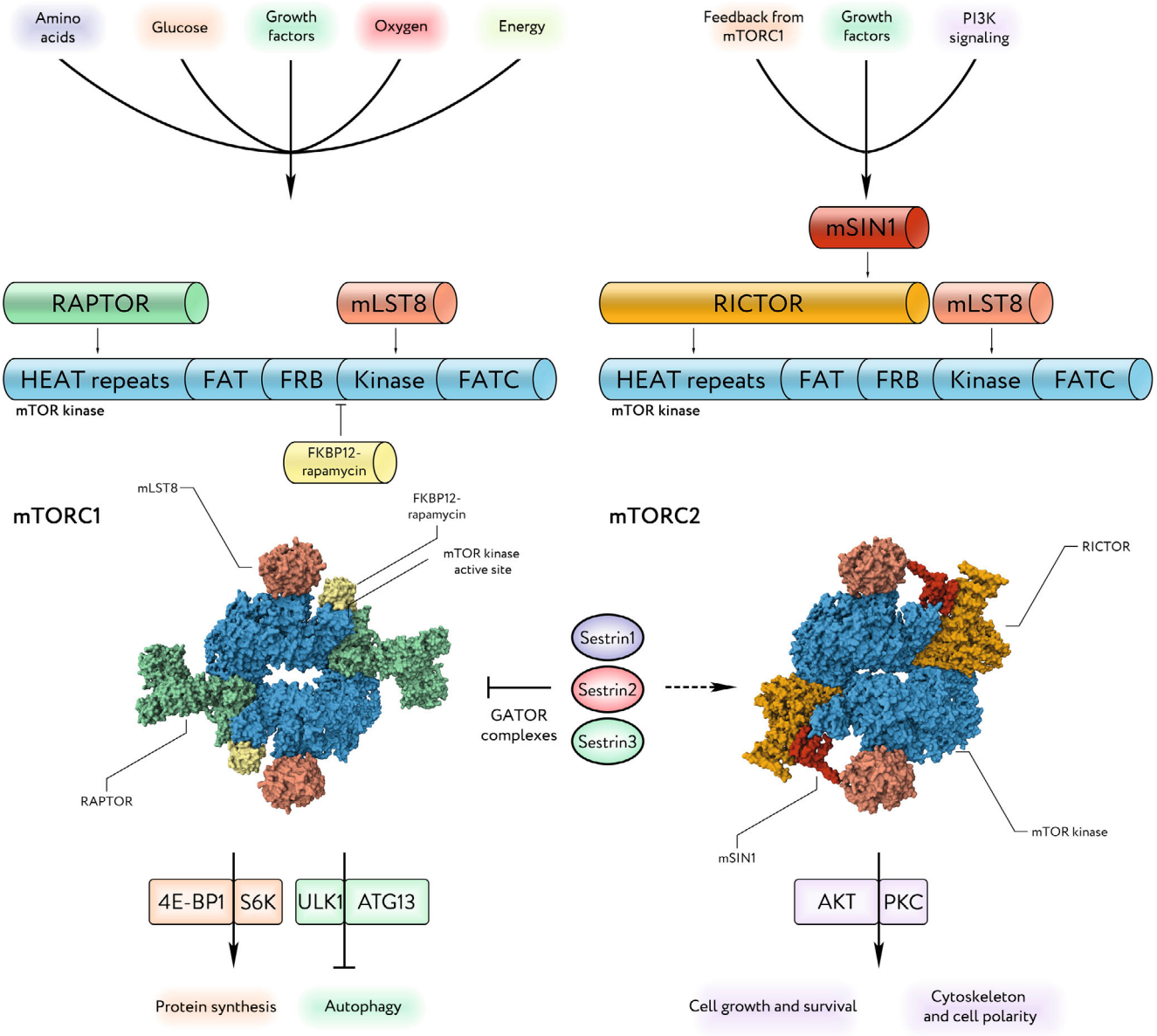

Fig. 4. The role of Sestrins in the regulation of mTORC1 and mTORC2. Sestrins regulate the activity of mTORC1 and mTORC2, thereby modulating cellular responses to various internal and external signals, including nutrient availability, growth factors, and cellular stress.

Organs, such as the liver, can communicate their metabolic state to other organs and tissues through the synthesis of FGF21 (fibroblast growth factor 21) [44]. Studies in *D. melanogaster* further demonstrated a key role for Sestrin in adaptation to leucine deprivation. In Sestrin-deficient flies, leucine deprivation led to metabolic disturbances and reductions in both mean and maximum lifespan, which are associated with elevated mTORC1 activity and impaired autophagy. Interestingly, Sestrin expression in glial cells also influenced feeding behavior, promoting the selection of leucine-containing food [45].

Sestrins are also involved in the activation of mTORC2 and the subsequent induction of AKT [46]. Sestrins may stimulate AKT through at least two mechanisms. The first involves the negative regulation of mTORC1 by Sestrins. In turn, mTORC1 negatively regulates mTORC2 through a feedback loop involving phosphorylation of p70S6K, which subsequently phosphorylates and promotes the degradation of IRS1 (insulin receptor substrate 1), a key mediator of insulin receptor signaling to mTORC2 and AKT [47]. In parallel, mTORC1 phosphorylates GRB10 (growth factor receptor-bound protein 10), which binds to IRS1 and promotes its degradation [48]. Thus, inhibition of mTORC1 by Sestrins may relieve these negative feedback mechanisms and enhance downstream AKT signaling. A second potential mechanism involves

the direct activation of mTORC2 by Sestrins through their interaction with RICTOR, a key component of the mTORC2 complex [49]. However, the details of this mechanism remain incompletely understood and require further investigation.

AKT is a central regulator of cellular metabolism. In particular, it mediates signaling in response to insulin and growth factors and contributes to the maintenance of insulin sensitivity in major insulin-responsive tissues, including the liver, skeletal muscle, and adipose tissue [46]. AKT also plays an essential role in glucose uptake and metabolism and promotes cell survival by phosphorylating and inhibiting pro-apoptotic proteins, such as BAD (BCL2-associated agonist of cell death), as well as members of the FOXO family of transcription factors [50]. Through the stimulation of AKT signaling, Sestrins may therefore contribute to the maintenance of insulin sensitivity and prevent the development of metabolic syndrome [51]. At the same time, Sestrin-mediated activation of AKT can promote cell survival under stress and, in certain cell types, may contribute to carcinogenesis [52, 53] (Fig. 4).

SESTRINS IN THE REGULATION OF MITOCHONDRIAL FUNCTIONS

In addition to regulating mTORC1/2 signaling, Sestrins play a key role in the control of mitochondrial function independently of these kinases [54]. Analysis of mitochondrial respiration demonstrated that Sestrin2 inactivation in mouse embryonic fibroblasts (MEFs) significantly reduced mitochondrial respiratory activity under both basal conditions and glucose deprivation. Sestrin2 was also found to support ATP production during metabolic stress and markedly reduce necrotic cell death induced by glucose starvation [28]. These effects were attributed to the preservation of ATP production under stress, which may facilitate cellular adaptation to unfavorable metabolic conditions. Consistent with these findings, Sestrin2 is required to maintain ATP levels in prostate cancer LNCaP cells under conditions of glycolytic inhibition induced by 2-deoxyglucose treatment [55]. The role of Sestrins in sustaining mitochondrial respiration has also been demonstrated in several other experimental models. Simultaneous knockout of Sestrin1 and Sestrin2 markedly suppressed mitochondrial respiration in human A549 adenocarcinoma cells [56], while Sestrin2 knockdown in mouse C2C12 myoblasts significantly decreased both basal mitochondrial respiration and maximal respiratory capacity [57]. In mouse cardiomyocytes, Sestrin2 similarly maintained mitochondrial respiration under both basal conditions and ischemia-reperfusion stress. A potential mechanism underlying this effect involves the interaction of Sestrin2 with components of the mitochondrial respiratory chain, as well as the preservation of pyruvate dehydrogenase and isocitrate dehydrogenase activities during ischemia-reperfusion [58]. Comparable reductions in mitochondrial respiratory function following Sestrin inactivation have been observed in *C. elegans* and mouse skeletal muscle cells [56, 59].

Sestrins regulate mitochondrial function through several complementary mechanisms. First, they promote mitochondrial biogenesis by stimulating the expression of key regulators of this process, such as PGC1α/β (peroxisome proliferator-activated receptor gamma coactivator 1 alpha/beta), by maintaining elevated AMPK activity [59, 60]. In C2C12 cells, the knockdown of Sestrin2 resulted in reduced expression of PGC1α and its coactivator, the NAD^+-dependent deacetylase SIRT1 (Sirtuin1); however, these effects were not accompanied by changes in AMPK activity. Furthermore, Sestrin2 knockdown significantly suppressed the expression of TFAM (transcription factor A, mitochondrial), as well as COX4 (cytochrome *c* oxidase subunit 4) and MTCO1 (mitochondrially encoded cytochrome *c* oxidase I). Second, Sestrins contribute to the regulation of mitochondrial dynamics, motility, and mitophagy. In C2C12 cells, Sestrin2 knockdown resulted in increased mitochondrial fragmentation and a less organized mitochondrial network compared with control cells. Sestrin2 suppression was also associated with a reduced ratio of the long to short forms of OPA1 (optic atrophy 1). Because the long form of OPA1 is essential for the architecture of mitochondrial cristae, its reduction may impair the organization and efficiency of the respiratory chain [54, 57]. In addition, several studies have demonstrated an important role of Sestrin2 in promoting mitophagy [61, 62]. This function is likely mediated, at least in part, through its interaction with p62/SQSTM1 (Sequestosome-1) [62, 63], an autophagy receptor involved in the delivery of damaged mitochondria to autophagosomes for subsequent degradation in autolysosomes. In macrophages stimulated with lipopolysaccharide and ATP, Sestrin2 interacted with both p62 and mitochondria, promoting the ubiquitination of mitochondrial proteins and the formation of perinuclear mitochondrial clusters, which were subsequently subjected to mitophagy [62]. The colocalization of Sestrin2 with mitochondria has also been demonstrated in other studies [56, 64]. In particular, Sestrin2 has been shown to associate with the outer mitochondrial membrane, where it may contribute to mitochondrial quality control and, upon detection of mitochondrial damage, promote the recruitment of proteins involved in initiating mitophagy [56]. Among these proteins is the E3 ubiquitin ligase Parkin, whose recruitment to damaged mitochondria is promoted by Sestrin2.

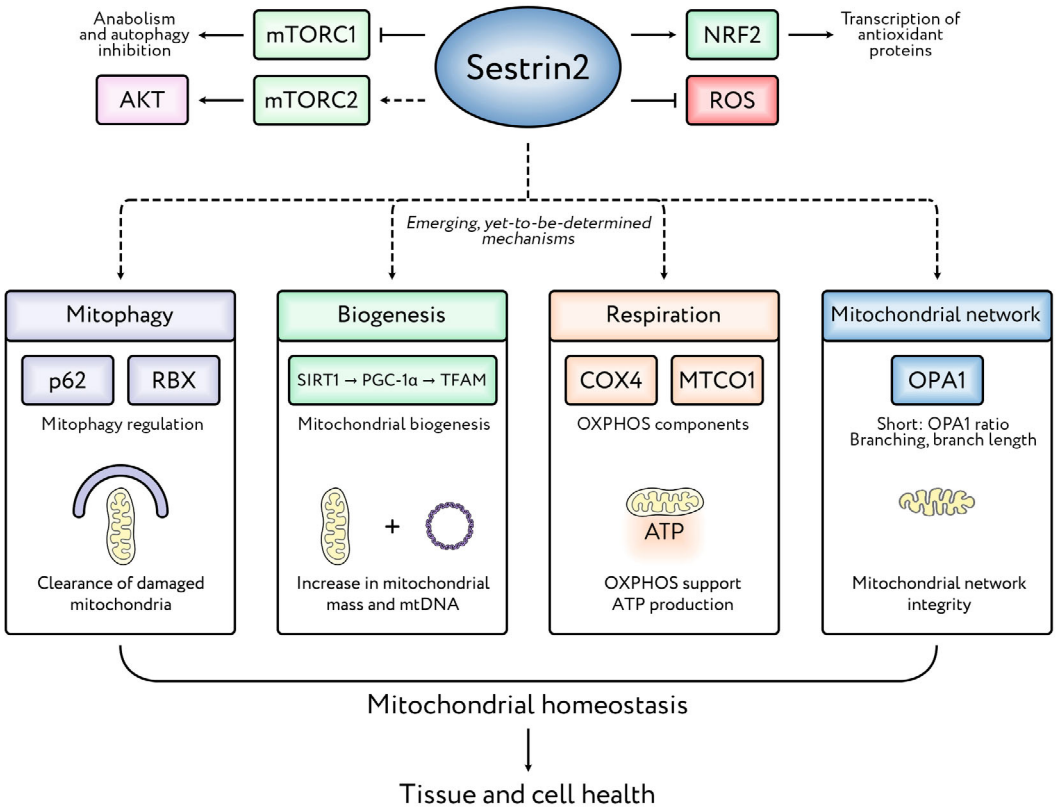

Fig. 5. Regulation of mitochondrial processes by Sestrins. Sestrins regulate mitochondrial functions both indirectly, through signaling pathways involving mTORC1/2 and NRF2, and directly, by interacting with mitochondria and regulating the activity of mitochondrial proteins (adapted from [54] with permission from Wiley).

Parkin subsequently ubiquitinates proteins on the mitochondrial surface, providing a signal for the initiation of mitophagy [65]. Thus, Sestrin2 acts as an important regulator of mitochondrial homeostasis under stress conditions by promoting rapid repair and restoration of mitochondrial functions and preventing cell death.

The role of Sestrin in mitochondrial protection is particularly evident in invertebrate models. In *D. melanogaster*, Sestrin inactivation causes pronounced alterations in mitochondrial morphology in thoracic muscle cells, including disruption of the structure of cristae and increased ROS production. These mitochondrial abnormalities are closely associated with the disruption of muscle fiber architecture, characterized by irregular sarcomere organization and disorganized Z-discs and M-lines, ultimately resulting in impaired muscle function. Cardiac dysfunction has also been observed in this model, manifested by arrhythmia and alterations in the duration of cardiac contractions [17, 59]. Similarly, Sestrin inactivation in *C. elegans* results in a marked reduction in muscle activity, as evidenced by decreased pharyngeal pumping and locomotor activity, accompanied by substantial damage to muscle fibers [66, 67]. Consistent with these findings, Sestrin-deficient adult worms exhibit significantly reduced myocyte density compared with control animals. This phenotype is likely associated with impaired mitochondrial function, increased oxidative stress, and muscle cell death resulting from defective mitophagy (Fig. 5) [68].

SESTRINS IN THE CONTROL OF CELL DEATH

Sestrins as positive regulators of cell death. Our early studies demonstrated that Sestrin2 modulates cell viability in a stress-dependent manner [2]. Thus, ectopic expression of Sestrin2 in breast carcinoma MCF7 cells promoted cell death in response to the genotoxic drug doxorubicin or ultraviolet irradiation, while protecting cells from death induced by hypoxia or oxidative stress [2, 7]. Subsequent studies revealed a diversity of mechanisms through which Sestrins regulate cell death. To elucidate the role of Sestrins in the response to genotoxic drugs such as cisplatin and etoposide, we generated lung adenocarcinoma A549 cells deficient in both Sestrin1 and Sestrin2. Inactivation of Sestrins reduced apoptotic cell death by more than twofold [69]. This phenotype was associated with the increased activity of the key anti-apoptotic transcription factor STAT3 (signal

transducer and activator of transcription 3) and accumulation of MCL1 (myeloid cell leukemia 1), a mitochondrial inhibitor of apoptosis whose expression is regulated by STAT3. Sestrin-mediated inhibition of STAT3 is achieved through maintenance of the transcriptional activity of PTPRD (protein tyrosine phosphatase receptor type D), which promotes STAT3 dephosphorylation and thereby suppresses its activity [69]. Sestrin2 also promotes apoptotic cell death in response to the activation of death receptors, including TNFR (tumor necrosis factor receptor), FAS, and TRAILR (TNF-related apoptosis-inducing ligand receptor), by facilitating the degradation of IAP (inhibitor of apoptosis protein) family members [70]. Sestrin1 appears to play an important role in suppressing the development of follicular lymphoma. Deletion of the 6q21 locus containing the *SESN1* gene, as well as the Y641X mutation in the gene encoding the transcriptional regulator EZH2 (enhancer of zeste homolog 2), which suppresses *SESN1* expression, are frequently observed in follicular lymphomas. Pharmacological inhibition of the $EZH2^{Y641X}$ mutant with the specific inhibitor GSK126 activates Sestrin1 and induces cell death through suppression of mTORC1 activity [71]. This treatment markedly reduces tumor growth and may represent a potential therapeutic strategy for follicular lymphoma.

Sestrins as negative regulators of cell death. Although Sestrins promote cell death under conditions of genotoxic stress in some types of cancer cells, in skin cells (keratinocytes and melanocytes), and cells derived from cutaneous squamous carcinoma and melanoma, Sestrin2 is induced in response to ultraviolet irradiation and protects cells from apoptotic cell death caused by UV exposure. The activation of Sestrin2 in skin cells leads to the activation of AKT by preventing the translocation of the lipid phosphatase PTEN (phosphatase and tensin homolog) to the membrane, where PTEN dephosphorylates phosphatidylinositol 3-phosphates required for AKT activation on the inner surface of the cytoplasmic membrane [52, 72].

Sestrin2 also protects cells against apoptosis under conditions of energy stress induced by treatment with the glycolysis inhibitor 2-deoxyglucose [55]. Notably, Sestrin2 induction in this context depended on AKT activation, consistent with the established role of AKT as a key suppressor of apoptosis. Similarly, Sestrin2 protected MEFs from necrotic cell death induced by glucose deprivation. However, this cytoprotective effect is not universal. For example, in A549 cells, simultaneous knockout of Sestrin1 and Sestrin2 has been reported to decrease cell death under conditions of glucose starvation [53].

Sestrin2 also protected lung adenocarcinoma cells from cell death induced by glutamine starvation. Glutamine is critically important for the survival of transformed cells, as it is converted to glutamate and subsequently to α-ketoglutarate, a key intermediate of the Krebs cycle. Beyond its role in energy metabolism, glutamine serves as a nitrogen donor for nucleotide biosynthesis, which is essential for DNA and RNA synthesis, and contributes to the synthesis of glutathione, a major component of the cellular antioxidant defense system [73]. Glutamine deprivation induces Sestrin2 transcription, which promotes cell survival and protects against apoptosis triggered by this metabolic stress. In the absence of glutamine, Sestrin2 inhibits mTORC1, thereby suppressing biosynthetic processes and promoting autophagy, while simultaneously stimulating mTORC2 and AKT signaling [74]. Under glutamine starvation conditions, Sestrin2 associates with key components of mTORC2, including RICTOR, mTOR, and mSIN1, and prevents the inhibitory action of 14-3-3 proteins on mTORC2. In turn, mTORC2 promotes Sestrin2 stabilization and establishes a regulatory loop that reinforces Sestrin2-mediated inhibition of mTORC1. Collectively, these mechanisms contribute to metabolic adaptation, mitigate oxidative stress induced by glutamine deprivation, and suppress cell death [74].

Sestrins play a key role in protecting cells from oxidative stress-induced death through their intrinsic antioxidant activity [7]. They have been shown to directly reduce alkyl peroxides, with a conserved cysteine residue playing a critical role in this process [12]. In addition, Sestrins promote ROS detoxification by activating NRF2, a key transcription factor that regulates the cellular antioxidant response. In the absence of stress, NRF2 interacts with KEAP1 (Kelch-like ECH-associated protein 1), which inhibits NRF2, thereby preventing its translocation to the nucleus. Under oxidative stress conditions, ROS-mediated degradation of KEAP1 leads to NRF2 release [75]. Sestrin2 further promotes NRF2 activation by interacting with p62 and the RBX1 (RING-box protein 1) ubiquitin ligase complex, thereby facilitating KEAP1 degradation. Activated NRF2 induces the expression of numerous antioxidant genes, including those for GSTA1 (glutathione S-transferase alpha 1) and Srx (Sulfiredoxin), which is responsible for the reactivation of overoxidized peroxiredoxins [63]. Through these mechanisms, Sestrins contribute to the attenuation of oxidative stress and the maintenance of cell viability. An important protective role of Sestrins has been demonstrated in the livers of mice subjected to 16 h of fasting followed by refeeding. Fasting induced the accumulation of Sestrin2, whereas its absence resulted in elevated levels of ROS and ERS, ultimately leading to hepatocyte death [63]. These findings indicate that Sestrins play an important protective role during the reactivation of biosynthetic processes in tissues with high metabolic demands, such as the liver and skeletal muscle.

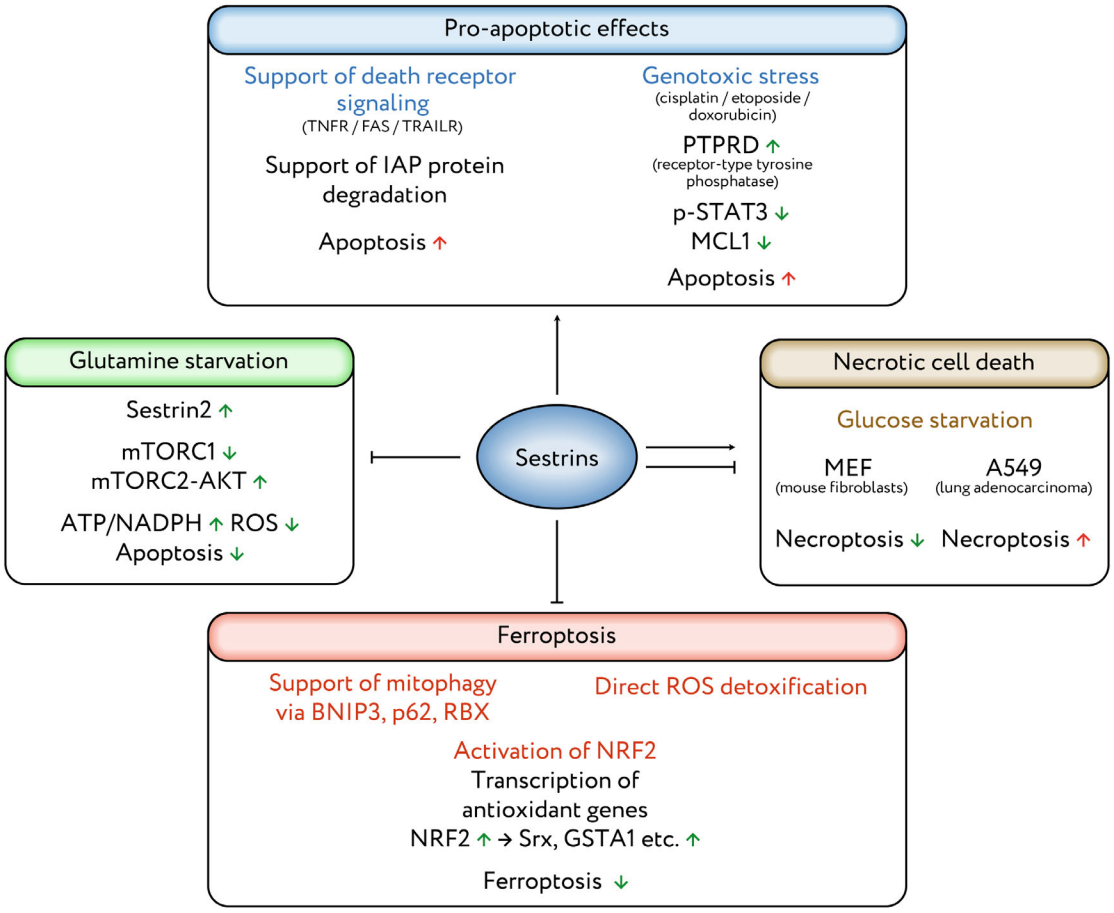

Fig. 6. Regulation of cell death by Sestrins. Sestrins regulate multiple forms of cell death through various mechanisms that involve modulation of anti-apoptotic signaling pathways and proteins, including IAPs, STAT3, and AKT, whereas suppression of ferroptosis is associated with activation of antioxidant defenses and maintenance of mitochondrial quality control through mitophagy.

Sestrins also protect cells from necrotic death under ischemic conditions. For example, in a mouse model of myocardial infarction, Sestrin2 knockout resulted in a significant increase in the necrotic area of the cardiac muscle. This protective effect was mediated by Sestrin2-dependent activation of AMPK through its upstream regulator LKB1 (liver kinase B1) [76].

Oxidative stress can also induce ferroptosis, a form of regulated cell death driven by the iron-dependent oxidation of polyunsaturated fatty acids through the Fenton reaction [77]. Sestrins inhibit ferroptosis in various cell types through at least two potential mechanisms: activation of NRF2, as demonstrated in models of osteoarthritis and intestinal ischemia-reperfusion injury [78, 79], and suppression of the ATF4–CHOP (C/EBP homologous protein)–CHAC1 (cation transport regulator homolog 1) pathway in dendritic cells during sepsis [80]. CHAC1 promotes glutathione degradation, thereby increasing intracellular ROS levels. Sestrin1 suppresses ferroptosis in endothelial cells in a mouse model of atherosclerosis and in human umbilical vein endothelial cells (HUVECs) exposed to oxidized low-density lipoproteins [81]. This activity is closely associated with the suppression of oxidative stress and vascular inflammation. Sestrin2 likewise suppressed ferroptosis induced by erastin treatment in hepatocyte cultures and in a mouse model of hepatic iron overload [82]. This study also demonstrated that induction of ferroptosis increased Sestrin2 expression through an NRF2-dependent mechanism.

Many forms of cellular stress induce ERS, which can ultimately lead to cell death through activation of the transcription factor CHOP. Sestrin2 protects cells from ERS-induced death [26] by inhibiting mTORC1, thereby suppressing protein synthesis, limiting the accumulation of misfolded proteins, and preventing activation of the pro-apoptotic arm of the ERS response. This function of Sestrin2 is particularly important for protecting liver cells from ERS associated with hepatic lipid accumulation [83].

Thus, Sestrins act as modulators of cell death, and their effects on cell viability depend on a combi-

nation of factors, including cell type, the nature and intensity of stress, and the activity of other regulators of cellular homeostasis (Fig. 6).

SESTRINS AS MARKERS OF AGING AND DISEASES

Sestrins and cellular senescence. The process of organismal aging is closely associated with cellular stress, which contributes to the accumulation of senescent cells. Cellular senescence was first described in human fibroblasts maintained in long-term culture, where progressive telomere shortening and the resulting genotoxic stress ultimately led to irreversible cell cycle arrest. Subsequent studies demonstrated that senescence occurs in a broad range of cell types, both *in vitro* and *in vivo*. Senescent cells are characterized by several hallmarks, including increased oxidative stress, accumulation of DNA damage, elevated activity of acidic β-galactosidase, and the development of the senescence-associated secretory phenotype (SASP), which involves a diverse array of cytokines, growth factors, proteases, and extracellular matrix-modifying proteins. In addition, senescent cells accumulate dysfunctional mitochondria, damaged or misfolded proteins, and cytoplasmic DNA, which can activate innate immune signaling. The progressive accumulation of senescent cells in tissues is therefore thought to contribute substantially to age-related tissue dysfunction and organismal aging [84]. A key role of Sestrins in aging may be their ability to protect cells against the development of senescence. Suppression of Sestrin2 expression in human embryonic fibroblasts (HEF) promoted the accumulation of senescent cells at earlier passages compared with control cells during prolonged culturing [7]. Sestrin2 suppression also increased the accumulation of ROS and markers of DNA damage in HEF, supporting an important role for Sestrins in limiting oxidative stress and maintaining cellular homeostasis. As excessive mTORC1 activity can promote cellular senescence, the anti-senescent effects of Sestrins may also be mediated through their ability to inhibit the mTORC1 pathway [31]. Furthermore, preservation of mitochondrial function, including the stimulation of mitophagy by Sestrins, may counteract the development of senescence by promoting the removal of damaged mitochondria and maintaining cellular metabolic homeostasis. Paradoxically, genetic inactivation of Sestrins in T cells was reported to delay cellular aging in a mouse model, potentially through reduced MAPK (mitogen-activated protein kinase) activity. Apparently, the pro-senescent activity of Sestrins is cell type-specific, although the role of senescent T cells in overall organismal aging requires further study [13].

Sestrins and organismal aging. Aging is closely associated with the development of numerous age-related diseases, including myocardial infarction, stroke, diabetes, neurodegenerative disorders, and cancer. As stress-inducible proteins, Sestrins play an essential role in protecting against aging and associated diseases. In skeletal muscle, Sestrins are particularly important for protecting against the accumulation of cellular damage and oxidative stress and for preventing muscle atrophy, as demonstrated in *D. melanogaster*, *C. elegans*, and mouse models [17, 59, 85]. Sestrins also protect tissues from the damage associated with myocardial infarction and stroke [76]. In metabolic disorders, Sestrins protect against the development of type 2 diabetes by contributing to the maintenance of insulin sensitivity and glucose tolerance, as well as against fatty liver disease [46]. Furthermore, Sestrins exhibit neuroprotective functions in ischemia and neurodegenerative disorders, including Alzheimer's and Parkinson's diseases [86]. Sestrins may also suppress the development of certain malignancies, such as follicular lymphoma, colon cancer, and lung cancer [53, 87]. Consistent with these protective functions, several studies have shown that the expression of Sestrin family members declined significantly with age in tissues such as cartilage and skeletal muscle in both humans and rodents. This age-associated reduction in Sestrin expression may diminish the capacity of tissues to respond to cellular damage and stress [88]. The mechanisms underlying the suppression of Sestrin expression during aging remain poorly understood. However, they are believed to involve age-related alterations in the levels of cytokines and/or hormones that regulate Sestrin expression and trigger the aging process. Sestrin expression also changes in response to various pathological conditions. For example, patients with lung adenocarcinoma exhibit elevated circulating levels of Sestrin2, which may reflect its release from cells undergoing stress or death [89]. In contrast, reduced Sestrin levels have been reported in type 2 diabetes and may have potential utility for monitoring disease progression. Elevated circulating Sestrin levels have also been observed in sepsis, neurodegenerative diseases, and cardiovascular diseases [88]. Many pathological conditions are characterized by intracellular stress. Ischemia, for example, is associated with increased ROS production, disruption of proteostasis, and damage to cellular organelles. Severe or persistent stress can ultimately lead to cell death, resulting in the release of Sestrins and other cell components into the extracellular space and circulation. Thus, as stress-inducible proteins, Sestrins may serve as indicators of cellular and tissue stress. In combination with other disease-associated biomarkers, circulating Sestrins may be used for the detection and monitoring of diverse pathological conditions (Fig. 7) [88].

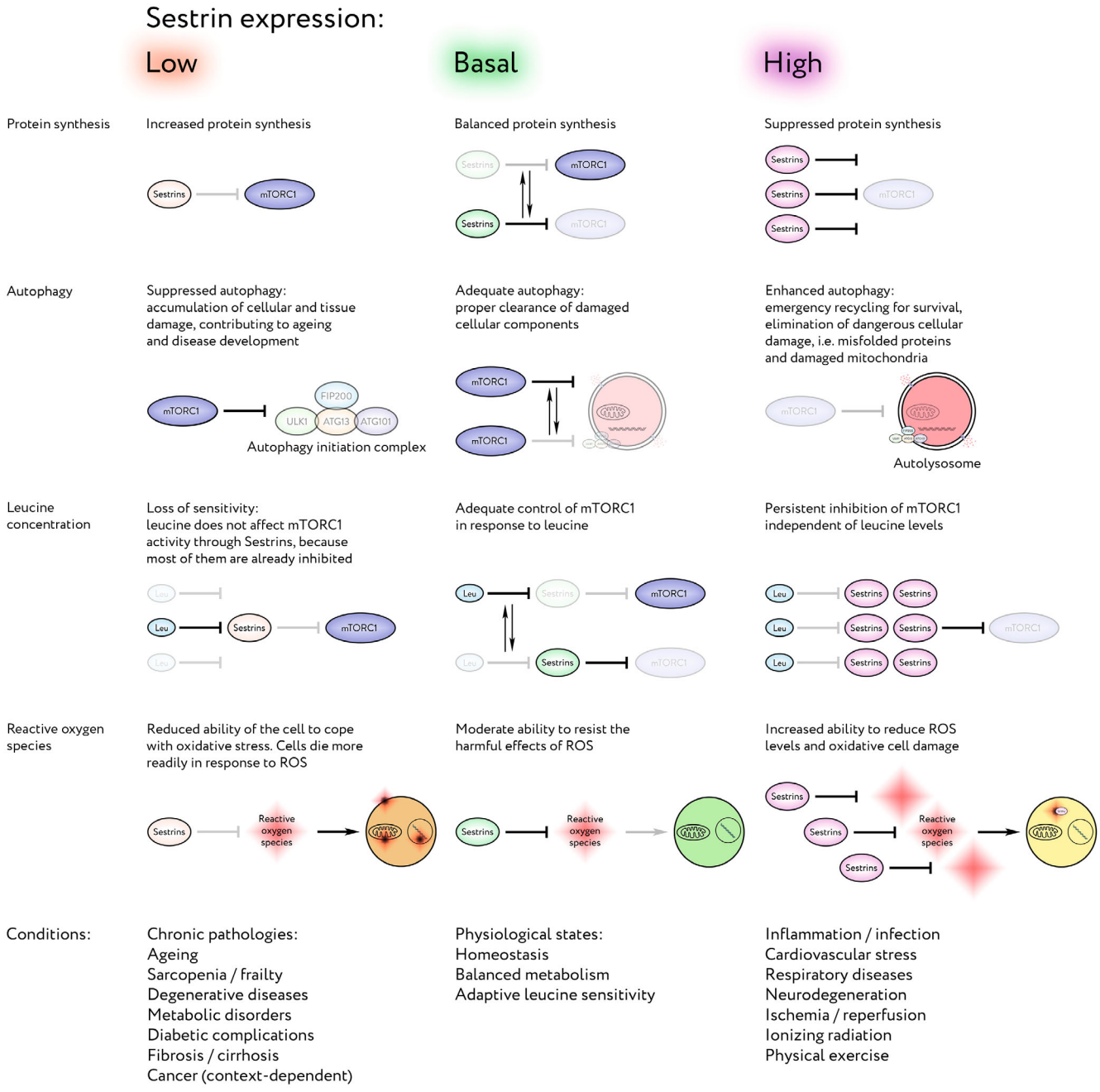

Fig. 7. Modulation of Sestrin activity and its association with various diseases. Sestrin activity in various tissues is regulated through both gene expression and leucine binding. These regulatory mechanisms contribute to the maintenance of cellular homeostasis and protection against stress. The development of pathological processes leads to changes in Sestrin activity, resulting in the accumulation of tissue damage and aging.

CONCLUSION

Sestrins contribute to cellular homeostasis and play important roles as modulators of stress-induced cell death. Depending on the cellular and physiological context, Sestrin activation can either promote cell death, as observed in response to chemotherapeutic agents or pro-apoptotic cytokines in certain types of cancer cells, or enhance cell survival under conditions such as ischemia and oxidative stress, as demonstrated in numerous tissues. Of particular interest is the role of Sestrins in cellular senescence and its effects on the organism, as this process has a dual impact: it suppresses carcinogenesis while contributing to organismal aging. Accordingly, Sestrins may produce context-dependent effects on both carcinogenesis and aging. Age-related decline in Sestrin expression may contribute to the development

of various pathologies by promoting degenerative processes, reducing responsiveness to anticancer therapies, or altering the duration and intensity of immune responses. Therefore, tissue-specific Sestrin expression may serve as a potential biomarker of biological aging and age-related diseases. At the same time, interventions such as physical exercise and certain pharmacological treatments (e.g., metformin) have been reported to increase Sestrin production and may thereby delay the development of age-related pathologies [88]. Thus, strategies aimed at maintaining or enhancing Sestrin activity through lifestyle interventions or pharmacological approaches represent a promising avenue for promoting healthy aging and extending lifespan.

Abbreviations

AhpD	alkyl hydroperoxide reductase D
AKT	protein kinase B
AMPK	AMP-activated protein kinase
ATF4	activating transcription factor 4
ERS	endoplasmic reticulum stress
FOXO	forkhead box O
GAP	GTPase-activating protein
GATOR1/2	GTPase-activating proteins toward RAGs1/2
mTOR	mammalian target of rapamycin
mTORC1/2	mTOR complex 1/2
NRF2	nuclear factor erythroid 2-related factor
RAGA-D	Ras-related GTP-binding protein A-D
RICTOR	rapamycin-insensitive companion of mTOR
ROS	reactive oxygen species
STAT3	signal transducer and activator of transcription 3
TSC	tuberous sclerosis complex

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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