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THE PROTECTIVE ROLE OF SESTRINS AGAINST CHRONIC TOR ACTIVATION AND OXIDATIVE STRESS

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24.1 INTRODUCTION

Oxidative stress is an undesirable consequence of oxidative respiration, which our cells utilize to produce the required levels of energy for life processes. Reactive oxygen species (ROS), a side product of mitochondrial respiration, can damage many important macromolecules, including DNA, lipids, and proteins. Therefore, complex mechanisms have evolved to defend cellular architecture and genomic information against damage produced by ROS. One well-characterized defense mechanism is performed by redox regulating enzymes, including catalase, peroxidase, and superoxide dismutase, which can directly scavenge or eliminate ROS [1]. Another defense mechanism is the stress-induced signal transduction pathway, which can block cell growth and promote repair of damaged macromolecules such as DNA under conditions of oxidative stress [2, 3]. During oxidative stress, ROS-induced damage of mitochondrial DNA, lipids, and proteins can decrease respiration efficiency, provoking mitochondria to compensate and produce more ROS. To avoid this destructive cycle, cells eliminate their damaged mitochondria through a mechanism called mitophagy—mitochondria-specific autophagy [4, 5].

In this chapter, we discuss a unique family of proteins, the Sestrins, that is critically involved in the cellular defense system against ROS (Fig. 24.1) [6, 7]. Sestrins are induced by oxidative stress-induced signaling pathways, and they protect cells and organisms from the detrimental consequences from oxidative stress by several means [8]. One activity of Sestrins is promotion of recycling of peroxiredoxins, which are important ROS-scavenging small proteins [1]. This effect of Sestrins contributes to elimination of ROS during oxidative stress [9]. A separate activity of Sestrins is inhibition of signaling mediated by the target of rapamycin complex 1 (TORC1). This activity of Sestrins can stop cell growth and funnel the saved energy expenditure into macromolecular repair machinery [10]. In addition, by inducing autophagy that eliminates damaged mitochondria, Sestrins contribute to mitochondrial quality control [11]. Sestrin deficiency therefore leads to cellular ROS accumulation, which can cause diverse ROS-associated pathologies such as muscle degeneration and cardiac dysfunction [12].

24.2 SESTRIN—A UNIQUE GENE FAMILY

The first discovered Sestrin family protein was Sestrin 1 (Sesn1), which was identified as a p53 target gene in a differential display screen using a cell line expressing a temperature-sensitive mutant of p53 [13] and was originally named PA26 (p53-activated gene 26). The *cis*-regulatory sequences in the *Sesn1* genomic locus contain p53 binding sites, and Sesn1 is induced by virtually every p53-activating stimulus. However, the function of

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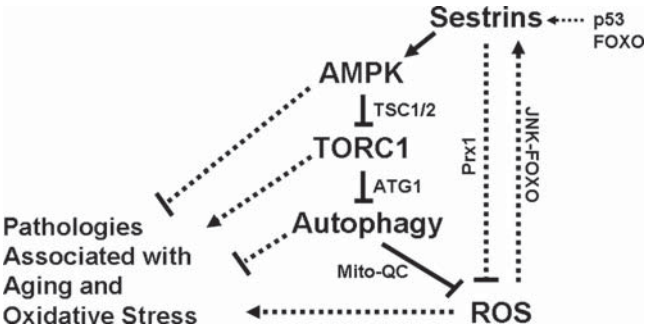

Fig. 24.1 Role of Sestrins against oxidative stress and aging. Sestrin has two independent biochemical roles against oxidative stress: (i) Sestrins can reduce ROS by promoting peroxiredoxin recycling, and (ii) Sestrins inhibit chronic TORC1 that suppresses autophagy, which is critical for eliminating ROS-producing dysfunctional mitochondria. Through these activities Sestrins can prevent diverse age-associated pathologies such as fat accumulation and cardiac and skeletal muscle degeneration.

TABLE 24.1 Conservation of genetic components of Sestrin-related signaling pathways. Currently known homologs of Sestrin, p53, and catalytic subunits of AMPK, TOR, and ATG1 in yeast (*S. cerevisiae*), worm (*C. elegans*), fly (*D. melanogaster*), and mouse (*M. musculus*) are listed

S. cerevisae	*C. elegans*	*D. melanogaster*	*M. musculus*
	cSesn	dSesn	Sesn1
			Sesn2
			Sesn3
	Cep53	dp53	p53
			p63
			p73
SNF1	AAK-1	dAMPK	AMPKα1
	AAK-2		AMPKα2
Tor1	CeTOR	dTOR	mTOR
Tor2			
ATG1	Unc-51	dATG1	ULK1
			ULK2

Sesn1 remained elusive because it does not contain any known domains or motifs that can be used to infer its molecular functions. Three years later, the second member of the Sestrin family, Sestrin 2 (Sesn2), was isolated in a microarray analysis designed to identify novel hypoxia-inducible genes [14] and, consequently, was originally named Hi95 (hypoxia-inducible gene 95). Sesn2 shares a high degree of amino acid sequence similarity with Sesn1. Finally, bioinformatic analyses identified the third member of Sestrin family, Sesn3, which is also closely related to the other two Sestrins. Sesn1, Sesn2, and Sesn3 constitute a unique protein family that does not share any obvious sequence homologies to other proteins.

Sestrins are found throughout the animal kingdom, as well as some protistan species [6]. Sestrin genes are found in a single copy in most invertebrate protostome species as well as hemichordates of the deuterostome lineage. However, in the vertebrate lineage, the Sestrin locus was triplicated and diverged into Sesn1, Sesn2, and Sesn3 (Table 24.1). Interestingly, similar triplication and divergence were also found for the p53 gene [15]. However, there are no currently known immediate homologs of Sestrin or p53 in the genome of yeast, plant, or bacteria, suggesting that these genes arose selectively during evolution of the animal kingdom.

24.3 REGULATION OF SESTRIN EXPRESSION BY STRESSES

24.3.1 Genotoxic Damage

As p53 transcriptional targets, Sesn1 and Sesn2 can be activated by most of the genotoxic stresses that induce p53 expression, including doxorubicin and UV and gamma-irradiation [13, 14]. The *Sesn1* genomic locus contains functional p53 binding sites, which may mediate the p53 induciblity of Sesn1 [13], although functional p53 sites in *Sesn2* locus have yet to be identified. Sesn1/2 induction after genotoxic damage requires p53, since p53-knockout cells have defects in the Sesn1/2 induction [13, 14]. Genomic instability caused by deficiency of the mitotic regulator Securin can also cause Sesn1 upregulation [16].

24.3.2 Hypoxia

Sesn1 and Sesn2 are inducible upon hypoxic insult, which is accomplished in a p53-independent fashion [14]. It has been proposed that hypoxia-inducible factor 1 (HIF-1) may be involved in the regulation of Sesn1/2 [17]. Cells in the mouse brain strongly expresses Sesn2 in response to hypoxia induced in an experimental model of acute stroke [14], suggesting that Sesn2 may have a neuroprotective role against ischemic injury. In macrophages, Sesn2 was also among the top 14 genes significantly induced by hypoxia and nitric oxide [18]. The induction of Sesn2 in macrophages is believed to be important in the regulation of peroxide signaling [17].

24.3.3 Oxidative Stress

Oxidative stress by H_2O_2 treatment also induced Sesn1/2 in cultured cell lines [9, 14]. The induction of Sesn2 upon oxidative stress is p53 independent in most cell lines [9, 14], although in some cell lines it is dependent on p53 and its downstream target p53-induced nuclear protein 1 (Inp1) [19]. The FoxO signaling pathway, which can be

activated by oxidative stress [20], may mediate the induction of Sesn1/2/3 during oxidative stress [20, 21].

24.3.4 Developmental and Environmental Ques

In *Xenopus*, Sesn1 was reported to be developmentally expressed in the notochord [22], while in mice, Sesn1 is mostly expressed in skeletal muscle [13, 23]. *Drosophila* Sestrin is also enriched in skeletal muscle (indirect flight muscle) [12]. In *Drosophila*, dSesn expression increases upon maturation and aging [12]. In short-lived mice recuperated from maternal protein restriction, Sesn1 expression in kidney was significantly downregulated [24]. In mouse lung, restraint in nose-only exposure tubes by itself can induce expression of Sesn1, as well as other stress-inducible genes [25]. In humans, Sesn1 is upregulated in peripheral blood mononuclear cells of chronic fatigue syndrome patients [26].

24.3.5 Chronic TORC1 Activation

In *Drosophila* cells, genotoxic damage-, hypoxia- or oxidative stress-dependent induction of *Drosophila* Sestrin (dSesn) were not observed, in contrast to mammalian cells, although gamma-irradiation-dependent induction of dSesn can be observable in first instar larvae [8]. Nevertheless, dSesn did accumulate in tissues in response to chronic TORC1 activation, which is associated with elevation of oxidative stress [12]. Accumulation of ROS and activation of JNK-FoxO signaling pathways are both required for this induction of dSesn [12]. In mice, Sesn1 expression is significantly increased in PTEN-deleted prostate cancer tissue relative to normal prostate tissue [27]. However, in human fibroblasts, oncogenic activation of Ras or AKT causes downregulation of Sesn1/3, which results in oxidative senescence [21, 28].

24.3.6 Regulation of Sestrins in Nervous System

It has been shown that Sesn1/2 are induced upon the activation of NMDA receptor in neurons [29] through increased histone acetylation [30]. Treatment of neuronal cells with neurotoxin amyloid-β significantly elevated the level of Sesn2 [31]. HIV-1 infection of mouse brains through nasal spray also caused upregulation of Sesn2 [32]. The induced Sestrins may protect neurons against oxidative, proteotoxic, and virus-induced damage [33].

24.3.7 Chemical Induction of Sestrins

Induction of Nur77, an orphan nuclear receptor, by methylene-substituted diindolylmethanes was known to induce Sesn2 [34], and Rosiglitazone, an antidiabetic drug, can induce Sesn1 in retinal cells [35]. Pyrrolidine dithiocarbamate, which can cause oxidative stress in vivo, induces Sesn2 in human fibroblasts [36].

24.4 SESTRIN AS A REDOX REGULATOR

Peroxiredoxins (Prx) are evolutionarily conserved peroxidases found from bacteria to mammals that are major scavengers of endogenously produced ROS [37]. Overoxidation of Prx inactivates its redox activity, which requires reactivation by another oxidoreductase [38]. The bacterial AhpD protein is an oxidoreductase that can regenerate Prx [39] and has distant sequence homology to Sestrins [9], suggesting that Sestrins may have an oxidoreductase function that reduces ROS. Indeed, silencing of Sesn1 or Sesn2 increased cellular oxidative level in both basal and H_2O_2-treated conditions, while overexpression of Sesn1 or Sesn2 can decrease intracellular ROS [9]. Cys130 of Sesn1 and Cys125 of Sesn2 are equivalent to critical redox-active cysteine residues in the AhpD protein. Thus mutation of the cysteine residues can abolish the ROS-reducing activity of Sesn1 and Sesn2 [9]. Sesn1/2 can physically interact with Prx inside the cells and can change the redox state of Prx [9]. However, recombinant Sesn2 does not function as a oxidoreductase for Prx in vitro [40], suggesting that Sesn2-dependent regeneration of Prx may be indirect.

As Sesn1/2 are targets of p53, Sestrins' redox activity contributes to antioxidant function of p53, which is important for its tumor-suppressing activity against certain cancers such as lymphoma [41]. Mice expressing single extra copies of p53 and ARF, which have higher p53 activity, are characterized by cancer resistance, delayed aging, and decreased oxidative damage [42]. These phenotypes are associated with dramatic upregulation of Sesn1/2 [42], which can reduce cellular oxidative stress. Conversely, $p53^{Ser15Ala}$ hypomorphic mutant mice, which exhibit reduced levels of Sesn1/2/3 expression, display metabolic derangements associated with redox deregulation [43]. Therefore, Sesn1/2 contribute to protecting p53-activated cells against oxidative insults, in combination with other antioxidant targets of p53 such as glutathione peroxidase 1, superoxide dismutases, and catalase [44, 45].

Sestrins' antioxidant function is observed in diverse cellular and physiological contexts. In cancer cell lines, Sesn1/2 protect cells from oxidative damage-induced cell death [9, 14]. Sesn3 is also important in reducing oxidative stress, and FoxO-induced Sesn3 expression can suppress premature oncogenic senescence caused by ROS accumulation [21]. In macrophages, Sesn2 plays an important role in peroxide defense [17]. In neurons, Sesn1/2 is induced upon synaptic activity and reduces

neuronal oxidative damage [29, 33]. Since Sesn2 is induced upon ischemic insults in rat brain [14], Sesn2 may also have neuroprotective functions against ischemia-reperfusion injury that induces mitochondrial oxidative burst [8].

24.5 OVERVIEW OF TORC1 SIGNALING

Another important output of Sestrin is target of rapamycin (TOR), which is a critical regulator of cell growth, development, and physiology [46–51]. TOR is a large protein kinase (289 kDa) and participates in two distinct protein complexes, TORC1 and TORC2 [51]. Among the TOR complexes, rapamycin-sensitive TORC1, composed of TOR, Raptor, PRAS40, and GβL, is the nutrient-sensing TOR complex. TORC1 can stimulate cellular anabolism of proteins and lipids while inhibiting autophagy (Fig. 24.2) [51]. TORC1 stimulates protein translation by phosphorylating p70 ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein (4E-BP) [47]. TORC1 facilitates lipid synthesis through lipogenic transcription factor sterol-responsive element binding protein (SREBP) [52]. In addition, TORC1 phosphorylates and inhibits an autophagy-initiating protein kinase complex composed of ATG1 and ATG13 [53]. On the one hand, TORC1 activity is critical for cell growth since TORC1 increases anabolism and decreases autophagic catabolism. On the other hand, when TORC1 activity is misregulated it can cause diverse pathologies associated with aging and obesity [50, 54].

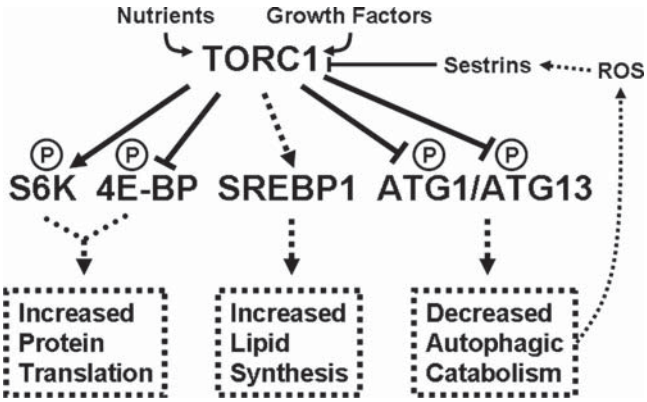

Fig. 24.2 Consequences of chronic TORC1 activation. TORC1, chronically activated by nutrient imbalance, can induce cellular anabolism of proteins and lipids while it can inhibit autophagic catabolism. Chronic TORC1 and diminished autophagy can cause accumulation of lipid droplets, protein aggregates, and damaged mitochondria, which can ultimately lead to diverse age-associated pathologies. Chronic TORC1-induced oxidative stress can induce Sestrin expression, which in turn acts as a negative feedback inhibitor of TORC1.

TORC1 is activated by two small GTPases, RAG and Rheb [51]. RAG mediates amino acid-dependent activation of TOR, while Rheb is negatively regulated by tuberous sclerosis complex 2 (TSC2), a GTPase activating protein. Lack of energy sources such as glucose and lipids that results in energy crisis causes activation of AMP-activated protein kinase (AMPK) [55]. AMPK activates TSC2 by direct phosphorylation, which subsequently silences the TORC1 activity by catalyzing hydrolysis of GTP bound to Rheb, a TORC1-activating small GTPase [56, 57]. Therefore, TORC1 is only active when nutrients are available. Conversely, diverse growth factors can increase TORC1 activity through AKT-mediated inactivation of TSC2 [47, 51].

24.6 CHRONIC TORC1 INDUCES STRESS-ASSOCIATED PATHOLOGIES

Chronic activation of TORC1 can cause various cellular stresses including endoplasmic reticulum (ER) stress, hypoxia, and oxidative stress [58–63]. The best-characterized function of TORC1 is its regulation of protein translation. The p70 S6 kinase (S6K) is activated by TORC1-dependent phosphorylation and subsequently phosphorylates ribosomal protein S6, which induces the translation of cell growth-related mRNAs [64, 65]. S6K also phosphorylates eukaryotic translation initiation factor 4B (eIF4B), which stimulates initiation of protein translation [66, 67]. At the same time, TORC1-dependent phosphorylation of 4E-BP releases eukaryotic translation initiation factor 4E (eIF4E) from 4E-BP-mediated inhibition [68]. In combination, these events cause increased protein synthesis, resulting in accumulation of unfolded proteins in ER and induction of unfolded protein responses [60]. Subsequently, cells having undergone TORC1 hyperactivation are more vulnerable to ER stress-induced cell death [60, 69]. TORC1-dependent increased protein synthesis and energy expenditure also cause a local hypoxic response and changes in the metabolic transcriptional program inside cells [61].

In addition to unfolded protein and hypoxic stresses, chronic TORC1 can result in oxidative stresses. Chronic TORC1 alters mitochondrial protein synthesis, rendering mitochondria inefficient in oxidative respiration and leading to the generation and accumulation of ROS [70–73]. Conversely, persistent reduction in TORC1 activity increases the efficiency of oxidative phosphorylation, contributing to the expansion of chronological life span. In conjunction with controlling mitochondrial protein synthesis, TORC1 can directly affect the quality of mitochondrial function, through removal of damaged mitochondria by a mitochondria-specific form of autophagy (mitophagy [5]). TORC1

phosphorylates the autophagy-initiating protein kinase complex [74–77], composed of ATG1/ULK1, ATG13, and ATG17/FIP200. ATG1 is the catalytic subunit of the complex, which is inhibited by TORC1-mediated phosphorylation [78–83]. ATG1 activity is also critical for mitophagy [84]. Therefore, TORC1 hyperactivation can cause chronic downregulation of ATG1 activity, subsequently reducing mitophagy, which then leads to the accumulation of damaged, ROS-producing mitochondria. Conversely, inhibition of TORC1 by starvation or rapamycin treatment induces autophagy including mitophagy [85, 86] and improves mitochondrial quality and hence energy conservation [4].

Autophagic defects cause mitochondrial dysfunction and oxidative stress in diverse model organisms. Depletion of ATG1, as well as ATG6, ATG8, or ATG12, causes accumulation of dysfunctional mitochondria and oxidative stress in the yeast *Saccharomyces cerevisiae* [87]. Depletion of ATG5 or ATG7 in mouse cardiac cells, skeletal muscle, and insulin-producing pancreatic beta cells induces accumulation of damaged mitochondria, which ultimately leads to oxidative stress and then organ dysfunction [88–92]. In *Drosophila*, ATG1 ablation causes severe degeneration of cardiac and skeletal muscles, which is associated with accumulation of damaged mitochondria and oxidative stress [12]. The neurodegenerative phenotypes observed in mice with autophagy-deficient neurons [93, 94] may be also associated with mitochondrial dysfunction and oxidative stress commonly observed in brains of Alzheimer and Parkinson disease patients [95]. Such chronic TORC1 activation and reduced autophagy can result in degenerative phenotypes [4]. Indeed, obesity, which is associated with chronic TORC1 activation, is also associated with cardiac dysfunction and neurodegeneration [50, 96–99]. Conversely, inhibition of TORC1 by caloric restriction or rapamycin reduced the incidence and severity of cardiac and neuronal dysfunction upon aging and stresses in various model organisms [100–103].

24.7 SESTRIN AS A SUPPRESSOR OF TORC1

Sestrins were identified as an inhibitor of TORC1, which can suppress TORC1-dependent cell growth [10] and anabolic processes [12]. Upon induction, Sesn1/2 completely blocked the TORC1-dependent phosphorylation of S6K and 4E-BP in cells and caused cell size reduction [10]. Sesn1/2 is a part of large protein complex that contains AMPK and TSC2. In the complex, Sesn1/2 induces activating phosphorylation of AMPK and potentiates AMPK-induced phosphorylation of TSC2, which in combination silence TORC1 activity [10]. Sesn2-mediated inhibition of TORC1 can also induce autophagy [11]. Given that Sestrins are induced upon diverse stresses, including genotoxic and oxidative stresses as well as hypoxia, they may mediate the stress-dependent silencing of TORC1 activity, which eventuates in inhibiting cell growth and induction of autophagy under more extreme conditions [8, 12, 104].

There is ample documentation of the TORC1-suppressing role of Sestrins in diverse cell lines, as well as in animal models [6]. Both in cells and in *Drosophila* tissues, overexpression of Sestrins caused cell size reduction mediated via inhibition of TORC1 [10, 12]. Since Sestrin is induced upon chronic TORC1 activation, Sestrin acts as a feedback inhibitor of TORC1 signaling. Indeed, loss of Sestrins enhanced clonogenic growth of cancer cells [10] or hyperplastic growth of *Drosophila* wing tissue caused by TORC1 hyperactivation [12]. Sesn2-dependent TORC1 silencing was also observed in the mouse lung [105], while in the liver it mediated DNA damage-induced silencing of TORC1 [10]. Similarly, in fibroblasts, Sesn3 mediated oxidative stress-induced silencing of TORC1 [106]. Collectively, Sestrins can mediate stress-induced silencing of TORC1, ultimately attenuating cell growth and funneling the saved energy into cellular repair and protecting cells from damage-induced apoptotic or necrotic cell death.

24.8 SESTRIN DEFICIENCY RESULTS IN AGE-ASSOCIATED PATHOLOGIES

Although TORC1 is a critical regulator of cell growth [47] and Sestrin potently inhibits TORC1 activity when overexpressed [10, 12], we were unable to detect any gross developmental defects in cell size and growth regulation in *Sestrin*-null mutant flies [12], implying that Sestrin-dependent control of TORC1 is not critical for normal development and cell growth under standard laboratory conditions. Therefore, the role of Sestrins may only be important in the context of homeostatic regulation rather than developmental cell growth, although there may combinations of circumstances in nature in which developmental events are also dependent on Sestrin regulation. Supporting a primarily homeostatic role for Sestrins, expression of *Drosophila* Sestrin increases with maturation and aging [12].

Sestrin-null mutant adult flies showed significant elevation of triglyceride level in the fat body [12], which provides functions similar to the mammalian liver [107]. In the fat body, Sestrin deficiency reduced AMPK activity while increasing that of TORC1 [12]. Fat accumulation was found to be dependent on AMPK-TORC1 regulation, since pharmacological activation of AMPK or inhibition of TORC1 relieved the accumulation

of triglycerides. Increased lipogenic gene transcription, which is associated with TORC1-dependent triglyceride accumulation [108], was also observed in *Sestrin*-null animals.

More striking phenotypes were discovered when we analyzed the heart physiology of the *Sestrin*-null mutant flies. That the heart is exquisitely sensitive to Sestrin function is consistent with the stringent metabolic and energy requirements in this tissue. In accordance with aging, *Drosophila* hearts spontaneously develop cardiac arrhythmia [109–111], and this age-associated cardiac degeneration is facilitated by TORC1 activation and suppressed by TORC1 silencing [96, 108, 112, 113]. Hearts from *Sestrin*-null mutant flies showed cardiac hypertrophy, increased heart period, and arrhythmicity, most of which were suppressed by pharmacological reduction of TORC1 activation [12]. It is very likely that cardiac arrhythmicity is associated with oxidative stress, as administration of antioxidant vitamin E as well as expression of catalase ameliorated the arrhythmic phenotypes. The cardiac degeneration is not a simple consequence of fat accumulation, because heart-specific downregulation of Sestrin expression, which does not cause fat accumulation in the fat body, can also induce cardiac degeneration [12].

In addition to the cardiac degeneration, *Sestrin*-null mutant flies exhibited skeletal muscle degeneration [12], which is also associated with aging [114]. The degeneration is preceded by mitochondrial dysfunction and ROS accumulation and is attenuated by antioxidant feeding [12]. The degenerative muscle phenotype as well as mitochondrial dysfunction were rescued by administration of the TORC1 inhibitors AICAR and rapamycin. Therefore, the AMPK-TORC1-controlling function of Sestrin seems to be important for regulating redox homeostasis in skeletal muscles. Furthermore, human Sestrin 1 is most highly expressed in skeletal muscle like its *Drosophila* counterpart [13], suggesting that Sestrin's role in muscle physiology may be conserved in mammals, which again highlights the importance of Sestrins in tissues with a high metabolic demand.

24.9 CONCLUSION AND PERSPECTIVES

As outlined in this review, biochemical and physiological functions of Sestrins revealed by mammalian cell culture and *Drosophila* genetics suggest that Sestrins protect cells and organisms against oxidative stress and age-associated pathologies as a feedback regulator. Upon acute oxidative stress, Sestrins function as a direct redox regulator to ensure cell survival. During chronic oxidative stress caused by TORC1 hyperactivation, Sestrins function as feedback inhibitors of TORC1, which reduces TORC1-induced cellular anabolism and oxidative stress. Thus it is very likely that Sestrin homologs in mammalian organisms can also exert a protective function against oxidative stress and aging. Understanding the precise role of Sestrins in diverse pathological contexts may provide a novel way to attenuate metabolic derangement and tissue injury that are caused by oxidative stresses. Diversification of the Sestrin gene family in the mammalian genome suggests that each of them may have unique specialized functions. Although the biochemical and cell biological roles of Sestrins are indistinguishable between Sestrin members, the detailed mechanism for transcriptional regulation varies. Therefore, there is an obvious need for continued rigorous study of the specific roles of each mammalian Sestrin homolog in various tissues and physiological contexts.

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