Review

Recent Insights into the Biological Functions of Sestrins in Health and Disease

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Key Words

Sestrin • Oxidative stress • AMPK • mTOR • Biomarker

Abstract

Sestrins (Sesns) have been identified as a family of highly conserved stress-inducible proteins that are strongly up-regulated by various stresses, including DNA damage, oxidative stress, and hypoxia. The Sesns play protective roles in most physiological and pathological conditions mainly through the regulation of oxidative stress, inflammation, autophagy, endoplasmic reticulum stress, and metabolic homeostasis. In this review, we discussed the possible regulators of Sesns expression, such as p53, forkhead box O, nuclear factor erythroid 2 like 2 (Nrf2), NH (2)-terminal kinase (JNK)/c-Jun pathway and hypoxia-inducible factor-1 α (Hif-1 α), and the downstream pathways regulated by the Sesns including AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling, mitogen-activated protein kinases (MAPKs) signaling, Nrf2 signaling, NADPH oxidase signaling and transforming growth factor β (TGF- β) signaling in heart diseases, lung diseases, gastrointestinal tract diseases, liver and metabolism diseases, neurological diseases, kidney diseases and immunological diseases. This review aims to provide a comprehensive understanding the protective effects of Sesns.

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Introduction

Sestrins (Sesns) have molecular masses that range from 52-57 kDa and have been identified as a family of highly conserved stress-inducible proteins. There are three isoforms, including Sestrin1 (Sesn1 or PA26), Sestrin2 (Sesn2 or Hi95) and Sestrin3 (Sesn3). Most vertebrates express all isoforms, while only one is expressed in most invertebrate species [1-3]. The crystal structure of human Sesn2 (hSesn2) is revealed to contain twofold pseudo-symmetric with two globular subdomains, which contributes to its physiological functions [4]. Due to the helix-turn-helix oxidoreductase motif of N-terminal domain, hSesn2 has the function of reducing alkylhydroperoxide radicals [4]. However, investigations into the

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structures of Sesn1 and Sesn3 are limited. As a family of stress-inducible proteins, Sesns have been reported to be upregulated and activated upon exposure to DNA damage, oxidative stress, and hypoxia [2, 3, 5]. Originally, the expression of Sesn1 and Sesn2 was found to be regulated by p53, while the expression of Sesn3 was regulated by forkhead box O. As the research moves along, other regulators responsible for the expression of Sesns were found, including nuclear factor erythroid 2 like 2 (Nrf2), NH (2)-terminal kinase (JNK)/c-Jun pathway and hypoxia-inducible factor-1 α (Hif-1 α). The activated Sesns act as antioxidants to protect cells against reactive oxygen species (ROS) and diminish the production of ROS through promoting the recycling of peroxiredoxin with sulfinic acid reductase activity [2, 3, 6]. Furthermore, it is well documented that Sesns are involved in regulation of the mammalian target of rapamycin complex 1 (mTORC1) signaling through the activation of AMP-activated protein kinase (AMPK) [5, 7]. In addition, Sesns have been found to suppress mTOR lysosomal localization in a Rag-dependent manner by interacting with GATOR2 and inhibiting mTORC1 via an AMPK-independent mechanism [8]. The C-terminal domain of Sesn2 accommodates physical interaction with GATOR2 and subsequent inhibition of mTORC1 [4]. Intriguingly, the interaction of Sesns and GATOR2 has been demonstrated to be amino acid-sensitive [9]. More detailed, the leucine binds Sesn2 through a single pocket that coordinates its charged functional groups and confers specificity for the hydrophobic side chain. A loop encloses leucine and forms a lid-latch mechanism required for the binding [10]. Further investigations have revealed that Sesn2 binds to GATOR2 and liberates GATOR1 from GATOR2-mediated inhibition. The released GATOR1 subsequently binds to and inactivates RagB and then ultimately suppresses mTORC1 [11]. Numerous studies have demonstrated that Sesns play important roles in the defense against different pathologies, including aging, metabolic homeostasis, lipid accumulation, and insulin resistance [12, 13]. In this review, we summarize the expression, regulation and function of Sesns in health and different diseases.

Sesns in heart

Sesns have been reported to regulate the production of ROS, which play highly important roles in various cardiovascular diseases. The original evidence of the function of Sesns in the regulation of heart function was reported by Lee et al. [13]. They demonstrated that, loss of dSesn resulted in age-associated pathologies including triglyceride accumulation, mitochondrial dysfunction, muscle degeneration, and cardiac malfunction. The cardiac dysfunction appeared as decreased heart function and slower heart rate. All the effects induced by dSesn deficiency were mostly prevented by the AMPK activator AICAR and the mTORC1 inhibitor rapamycin [13]. Since then, many studies are done to investigate the function of Sesns in heart [14].

Cardiac hypertrophy is one of the most important risk factors for the development of heart failure. Studies have demonstrated the Sesn1 and Sesn2 could regulate the progression of cardiac hypertrophy. The expression of Sesn1 was declined in pressure overload- and phenylephrine (PE)-induced cardiac hypertrophy [15, 16]. Knockdown of Sesn1 deteriorated PE-induced cardiac hypertrophy, whereas the overexpression of Sesn1 blunted hypertrophy through the regulation of autophagy function via AMPK/mTORC1 pathways [15]. Meanwhile, the same group has demonstrated that the Sesn2 was down-regulated after PE stimulation in cardiomyocytes and overexpression of Sesn2 protected cardiomyocytes from PE induced hypertrophy through the ERK1/2 cascade [16]. In addition to cardiac hypertrophy, the Sesn2 was demonstrated to be involved in cardiac ischemia injuries. When Sesn2-knockout (Sesn2 KO) mice was subjected to ischemia and reperfusion (I/R) injury, higher myocardial infarct size and worse cardiac function were found in Sesn2 KO hearts compared with wild type mice [17]. The decreased LKB1-AMPK association may contributed to the deteriorate effect of Sesn2 KO on infarct size. Besides, the Sesn2 KO aggravated the irradiation induced cardiac dysfunction through up-regulating the severity of cardiac fibrosis and down-regulating the capillary density [18].

In addition, the Sesns has been demonstrated to display important function in cardiac fibroblasts and endothelial cells. Down-regulation of Sesn1 aggravated AngII-induced proliferation of fibroblasts and up-regulated the expressions of collagen type I and connective tissue growth factor by activating ERK1/2 and mTOR pathways [19]. However, the overexpression of Sesn1 and Sesn2 significantly reduced the proliferation of fibroblasts, as well as decreased the protein expression of collagen and fibronectin1 in AngII-stimulated cardiac fibroblasts [20]. In human umbilical vein endothelial cells, the expression of Sesn2 was induced after AngII stimulation with a time-dependent and dose-dependent manner. Also, knockdown of Sesn2 using small RNA interference promoted cellular toxicity of AngII, as demonstrated by the reduced cell viability, exacerbated oxidative stress, and increased apoptosis [21].

Even though the studies described above have validated the function of Sesns in heart, the dynamic changes of three Sesn isoforms in different stages of the same disease remain unclear. Recently, we demonstrated that the expression of Sesn2, but not Sesn1 or Sesn3 was significantly up-regulated in human failing hearts due to ischemic cardiomyopathy and dilated cardiomyopathy [22]. In addition, the increased expression of Sesn2 in human hearts was verified in mouse I/R and myocardial infarction models, and rat doxorubicin-induced heart failure model [22]. Dong et al. have demonstrated that all the expression of Sesn1, Sesn2, and Sesn3 were significantly higher in patients with permanent atrial fibrillation than that in sinus rhythm patients. And they demonstrated that all Sesn isoforms contributed to the survival of paced HL-1 cells through regulating the levels of ROS and Ca^{2+} in HL-1 cells [20]. Further studies are needed to investigate the dynamic changes of different Sesn isoforms in the different stages of the same disease model and to investigate whether there is a compensate effect among different Sesn isoforms.

Sesns in lung

Growing evidence indicates that Sesns play a key role in lung diseases such as emphysema, chronic obstructive pulmonary disease (COPD) and lung cancers. It has been demonstrated that the lack of and excessive degradation of elastin promote the progress of emphysema [23]. Using the pulmonary emphysema model induced by inactivating mutation of the small splice variant of the *Ltbp4* gene (*Ltbp4S^{-/-}*), Frank et al. found that the Sesn2 null alleles (*Ltbp4S^{-/-}Sesn2^{-/-}*) partially rescued the pulmonary emphysema of *Ltbp4S^{-/-}* mice, as evidenced by the decreased parenchymal lesions and lung compliance in *Ltbp4S^{-/-}Sesn2^{-/-}* mice [24]. In addition, they found that the inactivation of Sesn2 in *Ltbp4S^{-/-}* mice selectively up-regulated the TGF- β signaling that partly encodes elastin but not the characteristic profibrotic genes, such as collagen I and collagen III through an ROS independent pathway. Other studies found that Sesn2 may inhibit platelet-derived growth factor receptor β (PDGFR β) expression through regulating the levels of the intracellular superoxide anions and through activation of Nrf2 and the proteasome, which contribute to the negative regulation of the transcriptional inducer of PDGFR β and promote the degradation of PDGFR β [25, 26]. In addition, they found that the mutational inactivation of Sesn2 prevents the development of cigarette-smoke-induced pulmonary emphysema by upregulating PDGFR β expression. These studies indicated that Sesn2 was an important contributor to the emphysema and that patients with COPD may benefit from antagonists of Sesn2. Considering the anti-fibrosis role of Sesn2 in heart, these studies indicated that the Sesns may execute different functions depending on the tissue type and cell context.

In addition, the Sesns have been demonstrated to be involved in the development of lung cancers. Tsilioni et al., found the levels of Sesn2 in malignant pleural effusions were significantly higher than that in benign pleural effusions [27]. In human adenocarcinoma cells, Sesn2 silencing strongly inhibited cytokine-induced cell death through mechanisms independent of the regulation on ROS and mTORC1. They determined that the X-linked inhibitor of apoptosis protein plays a critical role in the attenuation of cytokine-induced cell

death by Sesn2 [28]. Xu et al. found that the low expression level of Sesn2 was associated with the poor survival in lung cancer patients [29]. In addition, in BEAS-2B cells (lung bronchial epithelial cell), knockdown of Sesn2 potently stimulated the proliferation and malignant transformation of cells via activation of mTOR signaling, whereas ectopic expression of Sesn2 re-suppressed the malignant transformation. Moreover, knockdown of Sesn2 in BEAS-2B cells promoted the BEAS-2B cell-transplanted xenograft tumor growth in nude mice [29]. Recently, Sesn3 was found to be essential for the anti-cancer effect of cucurbitacin B. Cucurbitacin B caused specific increase in the expression of Sesn3 in EGFR-mutant lung cancer cells, but not in EGFR-wild type cells. Knockdown Sesn3 amplified the decrease in cell-viability and caused more sustained G2-phase cell cycle arrest after cucurbitacin B treatment. Researchers also found that Sesn3 contributed to the induction of apoptosis by cucurbitacin B in both EGFR-wild type and EGFR-mutant lung cancer cells [30].

Sesns in gastrointestinal tract

In gastrointestinal tract, the research regarding the function of Sesns has mainly concentrated on colorectal diseases, including colitis and colorectal cancer. Kim et al., found that Sesn2 has an important role in regulating the apoptosis process induced by quercetin in HCT116 colon cancer cells [31]. Further reports from the same group demonstrated that not only the Sesn2/AMPK/mTOR pathway but also the Sesn2/AMPK/p38 mitogen-activated protein kinase (MAPK) signaling pathway were involved in the pro-apoptosis effect of quercetin on colon cancer [31, 32]. Then, researchers found that the overexpression of Sesn2 could inhibit the migration and invasion of HCT116 cells and suppress the tumor growth in a mouse xenograft model through degrading of HIF-1 α via AMPK-prolyl hydroxylase pathways [33]. Evidence from Ro et al. revealed that the expression of Sesn2 and Sesn3, but not Sesn1 were elevated in the colon of ulcerative colitis patients than that in controls. However, the increased Sesn2 was lost upon p53 inactivation during colon carcinogenesis [34]. Then, *in vivo* data revealed that endogenous Sesn2 was critical for the suppression of colon endoplasmic reticulum (ER) stress after colitis insults. And the Sesn2 deficiency promoted colon cancer growth through mTORC1 signaling during colitis-promoted tumorigenesis [34]. These results were consistent with a previous study, which showed that the expression of Sesn2 was decreased in both human colorectal cancer tissues and cell lines [35]. Furthermore, a low expression of Sesn2 was significantly correlated with advanced tumor stage, lymphatic invasion, lymph node metastasis, vascular invasion and liver metastasis and also decreased survival rate [35]. More importantly, the Sesn2 deficiency cells showed less susceptible to the chemotherapeutic drug treatments [34]. Together with the function of Sesn2 in lung cancers, Sesn2 may function as a novel tumor suppressor and the expression of Sesn2 may be a prognostic biomarker for cancer patients.

Sesns in liver and metabolism

The liver is sensitive to oxidative stress due to its metabolic activities. Much attention has been paid to investigate the function of Sesns in diverse liver injuries and metabolism disorders [12, 36, 37]. The results about the expression of Sesns in high-fat diet induced disease models were inconsistent. Kimball et al. demonstrated that both Sesn2 and Sesn3 levels were increased in the livers of rats fed with the high-fat diet [38]. Similarly, Park et al. demonstrated that the Sesn2 was induced in the mice livers after high-fat diet fed [39]. However, Jin et al. showed that the expression of Sesn2 was reduced in the livers of high-fat diet fed mice, whereas the expression of Sesn1 was not changed [40]. Even though, the protective function of different Sesns against high-fat diet related diseases were consistent. Bae et al. suggested that Sesn2 acts as an antioxidant to prevent oxidative liver damage via the activation of Nrf2 by promoting the p62-dependent autophagic degradation of

Keap1 [41]. Further study demonstrated that Sesn2, which was induced by the ER stress pathway, protected against the hepatic steatosis by maintaining hepatic ER homeostasis via suppressing AMPK-mTORC1 dependent pathway [39, 42]. Correspondingly, loss of Sesn2 allows for persistent protein synthesis in hepatocytes even under chronic ER stress, which further exacerbates the level of ER stress and subsequently results in extensive liver damage, inflammation and fibrosis [39].

In addition, Sesns were demonstrated to protect against insulin resistance and diabetes [43]. Studies showed that the expression of Sesn1 or Sesn2 mRNA was unaltered in skeletal muscle biopsies between the normal glucose tolerance and type 2 diabetes (T2D) participants. Conversely, Sesn3 mRNA and protein were increased in T2D patients and the expression levels were correlated with the fasting plasma glucose, 2-h postprandial plasma glucose and HbA1c levels [44]. Then, *in vivo* experiments showed that Sesn3 knockout mice exhibited insulin resistance and glucose intolerance, while Sesn3 transgenic mice were protected against insulin resistance [45]. The Sesn2 levels in HepG2 cells could be regulated by insulin via inhibiting its proteasomal degradation. Moreover, the Sesn2 levels played a negative feedback role in insulin signaling via modulating phosphatase and tensin homolog content [46]. Further, the expression of Sesn2 was decreased in palmitate-induced C2C12 cells (a mouse myoblast cell line). Overexpression of Sesn2 could effectively restore the impaired insulin signaling through reversing the palmitate-suppressed autophagic signaling via AMPK-mTORC1 pathway [47]. Meanwhile, Sesn2 overexpression in brown adipocytes could interfere with normal metabolism and thermogenesis by reducing mitochondrial respiration via the suppression of uncoupling 1 expression [48, 49].

Despite the regulation of energy homeostasis and metabolism, Sesns were demonstrated to protect the livers against chemical-induced injuries. Using a model of ethanol-induced liver injury, researchers revealed that overexpression of Sesn3 ameliorates the hepatic steatosis through suppression of lipid synthesis [50]. Moreover, recent data showed that Sesn2 was downregulated in acetaminophen-induced acute liver injury and overexpression of Sesn2 attenuated hepatocyte degeneration, inflammatory cell infiltration and ROS generation [51].

Sesns in the nervous system

Sesns in the peripheral nervous system

Neuropathic pain is a debilitating and hampering condition that heavily impacts the quality of life. ROS are required for the development and maintenance of neuropathic pain, which indicated that the Sesns may protect against the neuropathic pain. In spared nerve injury model, a well characterized model of neuropathic pain, researchers found that the expression of Sesn2, but not Sesn1 or Sesn3, was up-regulated in sciatic nerves [52]. Then, they found that Sesn2 knockout (*Sesn2*^{-/-}) mice exhibited considerably increased latephase neuropathic pain behavior. The increased ROS levels and increased expression of activating transcription factor 3 may contribute to the exacerbated neuropathic pain behavior in *Sesn2*^{-/-} mice [52]. In PC12 cells, a widely used neuron-like cell model for studying neurotoxicity and neuroprotection, researchers found that the expression of Sesn2 was induced by H₂O₂ in a time-dependent and dose-dependent manner through the c-Jun NH (2)-terminal kinase (JNK)/c-Jun pathway [53]. The H₂O₂ induced apoptosis of PC12 cells was further aggravated after Sesn2 knockdown. Regrettably, they did not evaluate the expression changes and functions of Sesn1 and Sesn3 in PC12 cells after H₂O₂ stress.

Sesns in the central nervous system

Growing evidence indicates that Sesns can relieve central nervous injuries through diverse signaling pathways. In rat hippocampal CA1 subfield, the expression of Sesn2 was progressively increased in the 1–48 h after transient global ischemia, reaching the maximal level at 24 h, and declined thereafter. They found that downregulation of Sesn2 with siRNA enhanced neuron apoptosis induced by transient global ischemia with reperfusion for 48 h

[54]. The protective function of Sesn2 against ischemia stroke was further validated in the rat middle cerebral artery occlusion/reperfusion model. At 24 h after reperfusion, exacerbated neurological deficits, enlarged infarct volume and increased mitochondria-related neuron apoptosis were found in the Sesn2 siRNA group than that in the scramble siRNA group. In contrast, activation of AMPK with AICAR attenuated the deteriorated effects of Sesn2 siRNA, which indicated that the AMPK mediated mitochondria pathway contributed to the protective function of Sesn2 in ischemia stroke [55].

Hypoxic ischemic encephalopathy is still the leading cause of perinatal brain injury resulting in long term disabilities. In rats subjects to severe hypoxic-ischemic (carotid artery ligation for 150 min), researchers found that the expression of Sesn2 and the infarct area were higher than that in sham rats and moderate hypoxic-ischemic group (carotid artery ligation for 100 min) [56]. Recombinant human Sesn2 attenuated brain infarct and edema, while silencing Sesn2 reversed these protective effects after severe hypoxic-ischemic. Mechanically, Sesn2 protected against severe hypoxic-ischemic encephalopathy through attenuating the blood-brain barrier permeability via inhibiting the expression vascular endothelial growth factor and promoting the expression of junction proteins [56]. In addition, the studies from the same group revealed that Sesn2 improved the infarct volume and neurological function through activating the AMPK pathway which in turn inhibits mTOR signaling and attenuates neuron apoptosis in rat hypoxic-ischemic encephalopathy model [57].

Meanwhile, Sesns were demonstrated to be involved in many other central nervous diseases. Chen et al. demonstrated that Sesn2 is induced by amyloid β -peptide, which is a biomarker of Alzheimer's disease, and protects cortical neurons against amyloid β -peptide by regulating autophagy [58]. In addition, clinical study showed that the serum levels of Sesn2 were significantly increased in the Alzheimer's disease group compared to mild cognitive impairment, and elderly controls [59]. Another study indicated that Sesn2 is upregulated in the midbrains from Parkinson's disease patients [60]. Using the Parkinson's disease model induced by the drug 1-methyl-4-phenylpyridinium, researchers found that deficiency of Sesn2 promoted 1-methyl-4-phenylpyridinium-related neurotoxicity by increasing oxidative stress, mitochondrial dysfunction, and apoptosis [60]. Intriguingly, in cell model of Parkinson's disease that is induced by rotenone toxicity, Sesn2 expression was induced by rotenone. And the upregulation of Sesn2 protected the dopaminergic cells against rotenone toxicity through AMPK-dependent autophagy activation [61]. What's more, Sesn3 was found to be the transcriptional module that encoded proconvulsive cytokines and Toll-like receptor signaling genes in macrophages, microglia and neurons. The knockdown of Sesn3 in zebrafish attenuated chemically induced behavioral seizures [62]. This study suggested the potential pro-epilepsy effect of Sesn3 and further indicated the different function of Sesns in different central nervous diseases.

Sesns in kidney

Studies have demonstrated that the Sesns play important roles in different kidney cell types. In renal tubular cells, the expression of Sesn2 was significantly increased after renal I/R injuries. Overexpression of Sesn2 in renal tubular cells could protect the cells against acute renal injuries through activating autophagy process [63]. In addition, silencing Sesn2 in renal proximal tubule cells increased hyperoxidized peroxiredoxins and ROS production, which may contributed to the increased renal oxidative stress and blood pressure [64]. Another study found that Sesn2 was mainly expressed in parietal epithelial cells in glomerular in normal rats [65]. In adriamycin-induced focal segmental glomerulosclerosis model and puromycin aminonucleoside-induced minimal-change nephrotic syndrome model, the expression of Sesn2 in parietal epithelial cells was decreased, which may associated with the occurrence of proteinuria and increased periglomerular fibrosis. Further, in cultured parietal epithelial cells, downregulation of Sesn2 resulted in increased cell apoptosis through regulating the activity of mTOR pathway [65, 66]. Besides, the Sesn2 was found to

be expressed in the glomerular mesangial cells and the levels of Sesn2 and activity of AMPK was negatively regulated by high glucose [67]. More importantly, the Sesn2-dependent AMPK activation attenuated high glucose-induced fibronectin synthesis in mesangial cells through blockade of Nox4-dependent ROS and peroxynitrite generation, with subsequent eNOS uncoupling. However, investigation about the function of Sesn1 and Sesn3 in kidney was limited. Only one study show that the expression of Sesn1 was decreased in kidney in low birthweight mice resulting from maternal protein restriction during pregnancy followed by accelerated growth in rodents, which may contributed to the shortened lifespan [68].

Sesns in immune system

The immune cells, which consists of innate immunity cells and acquired immunity cells, is involved in various pathophysiological process. Therefore, the function of Sesns in different immune cells including macrophage, T cells has received much attention. In RAW 264.7 cells, a widely used model of mouse macrophages, the expression of Sesn2 was up-regulated upon different stresses, such as hypoxia, nitric oxide, oxidized low-density lipoprotein (oxLDL) and lipopolysaccharide (LPS) [69-73]. The upstream regulators responsible for the Sesn2 expression in macrophages could be different. In hypoxia and nitric oxide stressed cells, it seems that mainly hypoxia-inducible factor-1-dependent mechanism contributed to the expression of Sesn2 [71]. In LPS stressed cells, the activation of AP-1, Nrf2, and the ubiquitin-proteasome system contributed to the increased expression of Sesn2 [73]. In addition, it has shown that the JNK/c-Jun pathway also contribute to the Sesn2 expression [70]. More importantly, the post-transcriptional regulation mediated by the NOS2-generated NO could also up-regulate the protein expression of Sesn2 in macrophages and this increased Sesn2 induced mitophagy activation, which contributed to the suppression of prolonged NLRP3 inflammasome activation [72]. Despite the different upstream regulators, studies have demonstrated that the increased expression of Sesn2 could promote the survival of macrophages against apoptosis and attenuate the expression of proinflammatory cytokines, which may contribute to the improvement of inflammatory diseases.

In addition to macrophages, the Sesns were demonstrated to regulate the function of T lymphocytes. The expression of Sesn1, Sesn2 and Sesn3 were all higher in human senescent CD4⁺ T cells from young donors than that in nonsenescent and intermediate CD4⁺ T cells. Besides, inhibition of Sesn1, Sesn2 and Sesn3 in senescent T cells showed broad functional reversal of senescence, apparent as enhancement of cell proliferation [74]. Mechanically, they demonstrated that the MAPKs including ERK, JNK and p38, but not mTOR pathway, mediated the pro-senescent function of Sesns in CD4⁺ T cells through the formation of a new immune-inhibitory complex (Sesn-MAPK activation complex (sMAC)). These results were opposite to the well-documented anti-aging properties of Sesns [13, 75, 76], which indicated that the Sesns may exert different functions in T cells. Moreover, they found that T cells from old humans (>65 years old) or mice (16-20 months old) were more likely to form the sMAC, and disruption of this complex restored antigen-specific functional responses in these cells [74].

Conclusion

The Sesns are regarded as stress-responsive and have been found to have a variety of functions in health and disease in different organs due to their responses to DNA damage, oxidative stress, hypoxia, metabolic stresses etc. However, some questions remain unanswered. Despite the relatively more understanding of Sesn2, little is known about the function of Sesn1 and Sesn3 in different diseases. In addition, the dynamic expressions and compensate functions of different Sesn isoforms during the same disease remain to be determined. More importantly, to what extent these findings about the functions of Sesns

in different diseases are applicable to humans is still unclear. A better understanding of the upstream regulators and downstream pathways of Sestrins would further facilitate the development of therapeutics that modulate Sestrins signaling to treat human diseases.

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Disclosure Statement

None.

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