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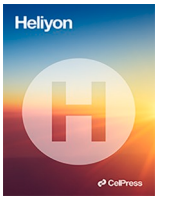

Review article

Interventions of sestrin proteins: Insights to clinical therapy

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ABSTRACT

Sestrin proteins, conserved family proteins which mainly induced by ROS, DNA damage, inflammation, and other injuries. Growing evidences proved sestrin proteins exert protective functions in cardiovascular diseases, chronic degenerative osteoarthritis, musculoskeletal diseases, aging and others, sestrin proteins exhibit an anti-inflammatory response, improving metabolism and other valuable character. However, there is no comprehensive and detailed summary and literature research on the intervention methods of sestrin proteins at present. As the advance of research during last several years, exercise training and other interventions are considered to be the potential methods to up-regulate expression level of protein. In view of the physiological function of this protein, a review of the main studies on regulating the expression level of this protein can provide a novel approach for the clinical treatment and scientific research. In present study, all related researches about interventions and potential mechanisms were reviewed and the mainstream methodologies were described.

1. Introduction

Sestrins (SESNs) are highly conserved proteins induced by stress, DNA damage, inflammation and other circumstances in cells [1]. Expression levels of SESNs are low in healthy human cells and upregulated when cells suffer from injury, stress and other disorders, resulted in exerting different functions [2]. SESNs were first described in 2003 [3], according to study in journal Science 2004, SESNs were considered as the peroxiredoxins [4]. Since then, it has been comprehensively and deeply studied by more scholars. In 2010, Science magazine published another article showed that SESNs had anti-aging function [5]. In the past ten years, studies published in Nature and Science journal have proved that SESNs have crucial positive physiological functions in pathology of inflammation, cell damage, fibrosis, metabolism and others [6,7]. SESNs own three functional sites: mechanistic target of rapamycin complex (mTORC) regulation, reactive oxygen species (ROS) suppression and leucine binding [8]. SESNs are expressed through activating several transcription factors including p53, forkhead box O (FoxO), CCAAT-enhancer-binding protein (c/EBP), activating transcription factor 4 (ATF4) and activator protein 1 (AP-1) [9]. Sestrin-AMPK-mTORC pathway regulates the related biological functions under most circumstances. SESNs promote phosphorylation of threonine (Thr172) resulting in activation of AMP-activated protein kinase (AMPK) and tuberous sclerosis complex-2 (TSC2). TSC2 negatively regulates mTORC signalling by converting Rheb-GTP into RhebGDP [10].

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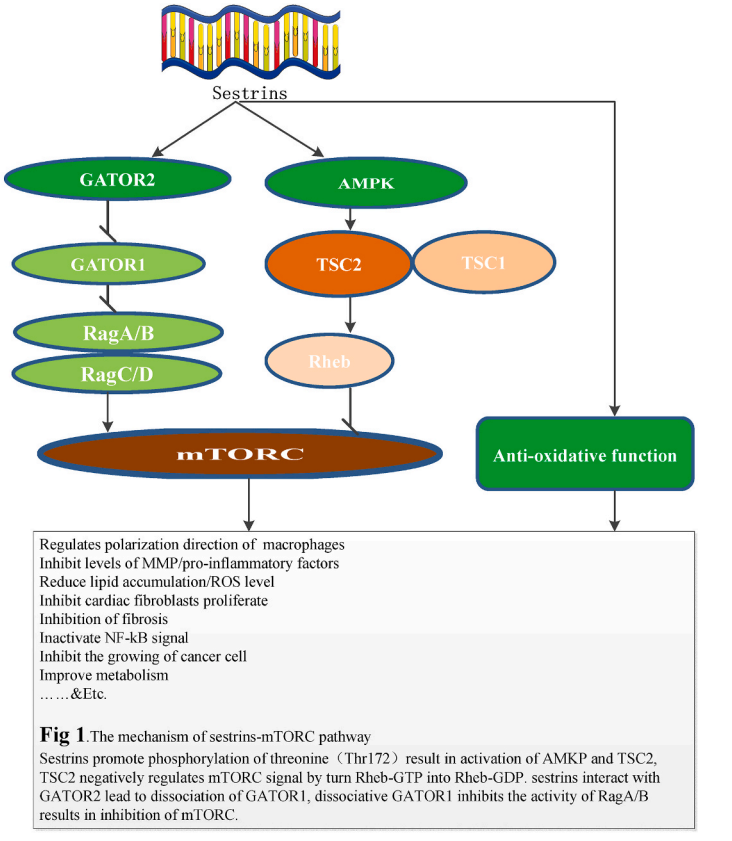

Fig 1.The mechanism of sestrins-mTORC pathway
Sestrins promote phosphorylation of threonine（Thr172）result in activation of AMKP and TSC2, TSC2 negatively regulates mTORC signal by turn Rheb-GTP into Rheb-GDP. sestrins interact with GATOR2 lead to dissociation of GATOR1, dissociative GATOR1 inhibits the activity of RagA/B results in inhibition of mTORC.

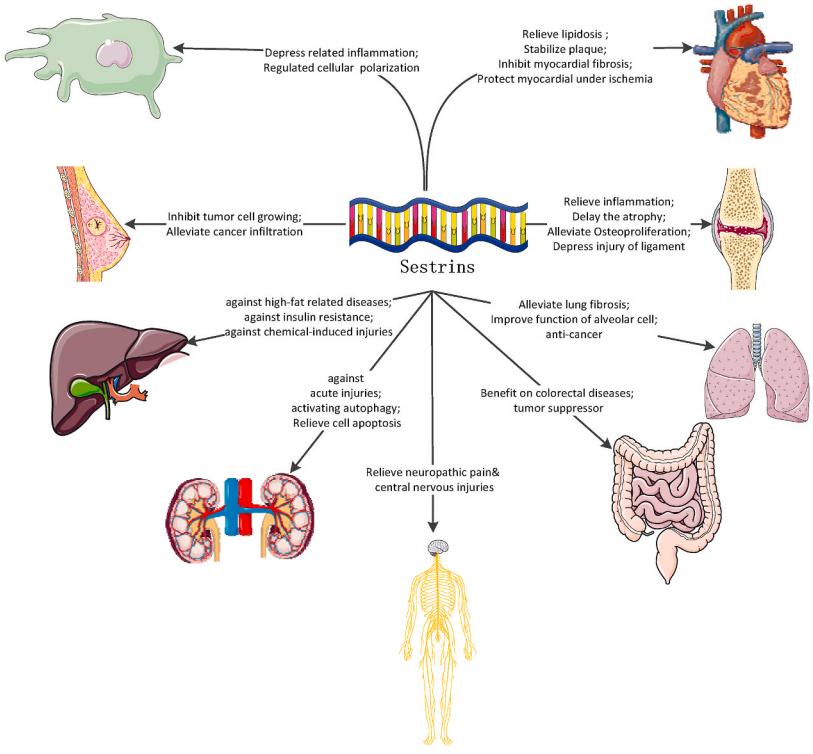

Fig. 1. The mechanism of sestrins-mTORC pathway Sestrins promote phosphorylation of threonine (Thr172) result in activation of AMKP and TSC2, TSC2 negatively regulates mTORC signal by turn Rheb-GTP into Rheb-GDP. sestrins interact with GATOR2 lead to dissociation of GATOR1, dissociative GATOR1 inhibits the activity of RagA/B results in inhibition of mTORC.

Other studies proposed that SESNs can bind with GATOR2 and result in the release of GATOR1 from GATOR, leading to the dissociated GATOR1 depressing the activity of RagA/B and resulting in the inhibition of mTORC [11]. According to the studies in last decade, SESNs exert different critical functions in the heart, lung, immune system, gastrointestinal tract, liver, nerve system and kidney (see Fig. 1) [12–15]. Abundant studies had demonstrated that lesion in diversity diseases can be relieved by regulating the expressive level of SESNs, inflammation and pathological process were alleviated by up-regulating SESNs [16], ROS level and cellular oxidative damage were inhibited in situation of SESNs expressed [17], high expressive level of sestrin2 protein exerted protect function in acute lung damage by regulating macrophages [18], other researchers suggested that SESNs may play as the potential treatment kid in stroke [19], similar conclusion has been proved by abundant studies in different kinds of disorders. Hence, exploring the intervention method of SESNs will contribute to promoting the development of new treatment techniques in diagnosis and treatment.

In view of such important physiological functions of SESNs, it was of great significance to explore a set of effective intervention methods, especially intervention programs that can guide clinical diagnosis and treatment. However, there was no available intervention to up-regulate the expression level in clinical practice since SESNs were discovered. The intervention methods of proteins were mainly laboratory cell technology or molecular technology until in-vitro techniques had become popular in last 5 years, growing evidences have pointed out those kinds of method to regulate SESNs which were much more meaningful to clinical application and scientific researching. There was no related article to introduce the interventions on SESNs until now, for a better understand and integrity comprehension of SESNs, a review article was urgent need in order to let more researchers quickly understand the knowledge and frontier trends related to SESNs regulation. This review presented the whole details of the methods and the mechanisms were discussed meanwhile, quickly and comprehensively let researchers realize the important role and prospect of SESNs in diseases, provided new theoretical support for clinical rehabilitation and treatment of diseases also a new scientific research direction meanwhile.

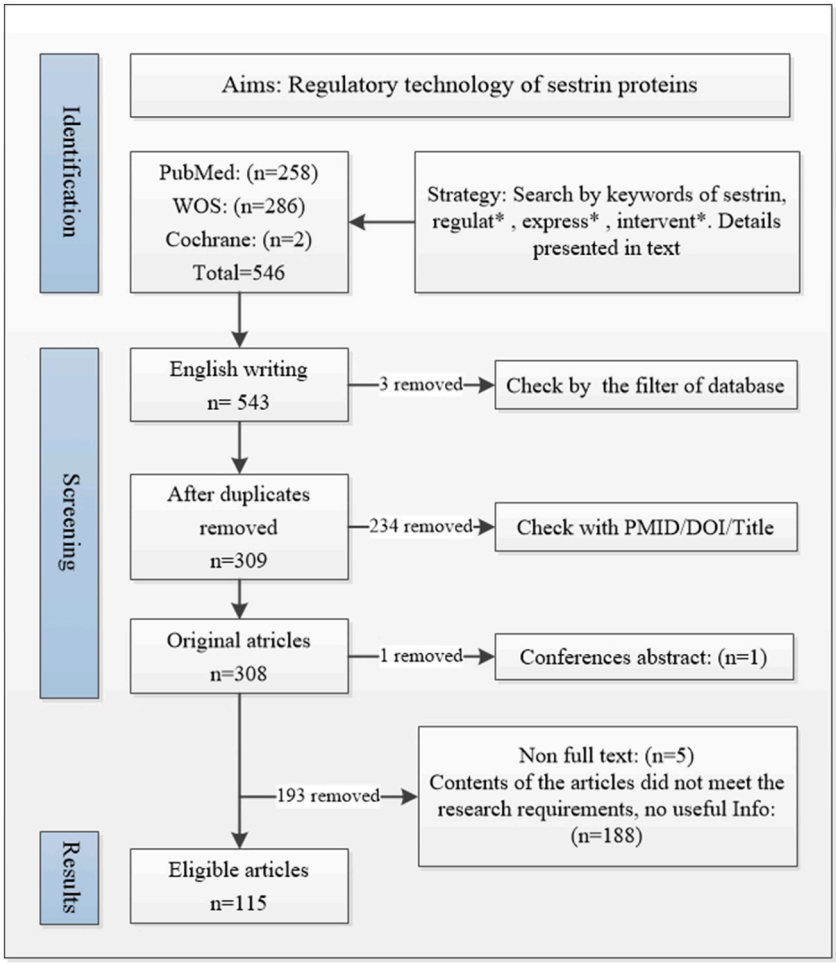

Fig. 2.

2. Searching strategy

2.1. Databases and terms

The whole searching steps followed the standard of PRISMA. Databases include web of science (WOS), PubMed, Cochrane with keywords of sestrin, regulat*, express*, intervent* and followed the term: PubMed: Pubmed: (sestrin[Title/Abstract]) AND (regulat* or express* or intervent*[Title/Abstract]); WOS: sestrin(topic) and regulat* or express* or intervent*(topic); Cochrane: sestrin(title/abstract keyword) and regulat* or express* or intervent*(title/abstract keyword).

Two authors (Yawei Wu and Yunfeng Sun) were pointed to exert searching in database and identified the articles were eligible for inclusion respectively, a third author (Ronghua Jing) joined the identify work when opinions of those two authors were contrary.

2.2. Including and excluding criteria

Articles published until May 2nd, 2024 were included, excluding criteria: Non-English writing; non original research article; repetitive articles. Total 546 (PubMed: 258, WOS: 286, Cochrane: 2) articles were included, 543 articles were written in English and 309 articles were left after tests for repeatability. Among those 309 articles, 1 abstract of conference was excluded. 308s were qualified for the following double examination eventually.

Among those 308s, 5 articles failed to access the full text. 115 articles were eligible for the study of extracting the related information after reading the abstract and the full text (details in the following flowchart Fig. 2).

3. Results

Two authors (Caterina Fede and Xiaoxiao Zhao) were pointed to extract the information which including "Disease/Pathology, Methodology, Experiment type, Species, Results, Treated cells and reference" of those 115 articles, all details were presented in the Supplementary Table 1. Not similar to the studies of other proteins, the species of SESNs studies were very restricted and mainly focused on mice (rat) and drosophila while small size in human. Diversity was presented in the disease/pathology of SESNs, such as inflammation/immune/cancer/cardiovascular disease/fibrosis/aging/stress/neurology was studied in different organs. Consider the outstanding functions of SESNs in kinds of pathology, to understand the interventions about regulating the expressive level of SESNs has become a potential technique which may contribute to the promoting of clinical practice. Medicine, gene technology and in-vitro interventions were the main methods which have been proved to have clear effects on expression of SESNs. Gene technology and medicine were the dominant way of regulating of SESNs. However, gene technology was not able to guide clinical practice in current formation and conditions. Regard as medicine, studies have proved that some special objects such as Oleacein/a-tocopheryl phosphate/angiotensin II/ghrelin/rotenone owned up-regulatory effects on SESNs under the pathology of autoimmune encephalomyelitis, adipocytes metabolism, cardiomyocyte apoptosis, muscle fiber shift and others. But, there still remains a huge gap between these interesting findings and clinical application due to the drugs development requires more complicate steps than simple basic research can solve even though some current conclusions came from the high quality studies in human. Even those methods were unable to be used in clinic, some in-vitro intervention with promising status, application and research prospects were worth describing. The main

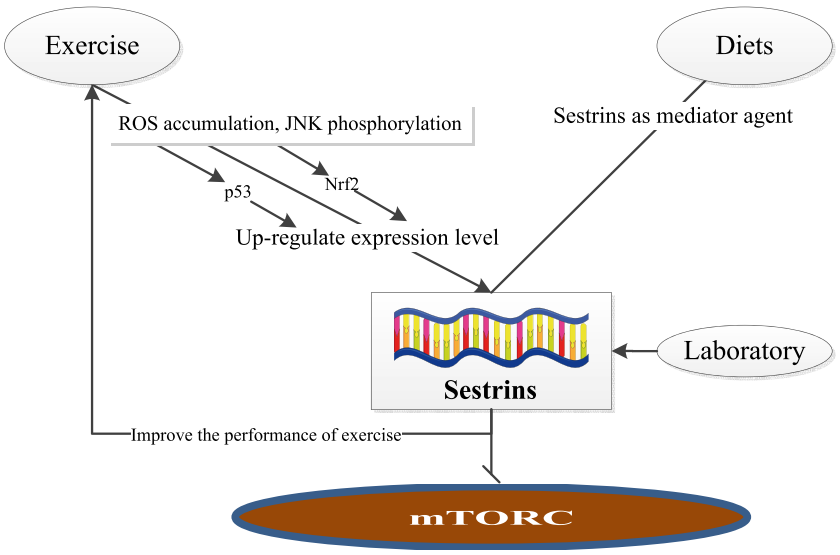

Fig. 3. The potential mechanisms of exercise and dietary restriction in regulating sestrins. Exercise up-regulate sestrins's expression level through p53 or Nrf2 while dietary restrictions use the protein as mediator agent to inhibit the activation of mTORC.

methodologies were discussed in the following text, for details please check the Supplementary Table 1 and Fig. 3.

3.1. Exercise/Physical training

Aerobic exercise or endurance exercise was recommended by clinicians in order to prevent and cure chronic diseases such as atherosclerosis, osteoarthritis, and other aging disorders [20,21], but there was no consistent mechanism interpretation for why exercise exert such an important function. Recent studies had proved that physical exercise and other aerobic-liked training through regulating the SESNs and result in exerting above pathophysiological performance. These exciting outcomes not only made SESNs become promising candidate intervention for preventing or treating disorders, but also elevated the importance of aerobic-liked exercise in clinical practice. As a critical intervention, exercise had been used in various species including fly, murine and human. Our previous study demonstrated 8 weeks of aerobic exercise depressed the macrophage related inflammatory response and relieved the plaque process by regulating the expressive level of sestrin1 protein in atherosclerosis mice [22], expressive level of sestrin was significant up-regulated compared to those control mice while further investigation showed macrophage related inflammatory signal or cytokines such as NF-κB (nuclear factor kappa-B)/MMP (Matrix Metallopeptidase)/IL-1β/IL-18/NLRP3 (NOD-like receptor thermal protein domain associated protein 3) were depressed in exercise mice [22]. Study from Myungjin Kim, etc. in 2022 via mice and drosophila showed SESNs were sufficient to modify exercise outcome and sestrin was required for increased performance after exercise, this finding was consistent to other studies that SESNs were the downstream factors of exercise and the mediator between exercise and pathobiology function [14,23,24]. Another research proved sestrin1 and sestrin2 were significant up-regulated after exercise of 2–4 h but levels were diminished after chronic exercise of 4 weeks in mice [25] , this study had revealed that expressive levels of proteins may positive correlated with training in short term and negative with chronic exercise while the mechanism were not clear, above results were consistent with the research in 2021 which suggested that both sestrin1/2 were up-regulated after wheel running exercise in mice [26]. Similar to Nina Zeng's study which performed in humans, levels of sestrin1 was up-regulated after acute exercise and related inflammation was depressed, meanwhile no effect on sestrin2/3 after the exercise of 12 weeks [27], another study in hemodialysis patients showed that sestrin1 was up-regulated under exercise as well [28]. In contrary, studies showed the level of SESNs in rats were down-regulated under exercise only [29] and study from Luciano demonstrated that rat's sestrin2 were inhibited in different training protocol, but the mechanism was not clear [30]. We supposed several possibilities here: ①Influences of metabolism, there was no accurate evidence about the half-life and metabolic duration of proteins. ②Testing timing of proteins, the timing of protein's peak after exercise were not established. ③The key was not only detecting the concentration of protein but also the functional

Table 1
Exercise-related interventions on SESNs.

Disease/Pathology	Model	Methods	Result	Conclusion	References
Atherosclerosis	Mice	8 weeks of exercise	Level of sestrin was up-regulated; Related inflammation was depressed	Exercise upregulates expression level	[22]
Ageing	Drosophila	3 weeks of exercise	Extended flight endurance and performance; sestrin was up-regulated	Exercise upregulates expression level; Sestrin was necessary to modify exercise outcome	[23]
Ageing	Mice	3 weeks of exercise	Sestrin was up-regulated; extended running capacity and performance	Exercise upregulates expression level; Sestrin-family proteins were essential for obtaining beneficial effects from exercise;	[23]
Muscle biology	Mice	Acute exercise; chronic exercise	Acute: sestrin up-regulated; inflammation depressed/ chronic: negative effects on sestrins	Acute exercise protocol increased sestrins, effects of chronic exercise was unclear	[25]
Sarcopenic	Mice	Voluntary wheel running	Strength improved under physical activity, sestrin1/2 were up-regulated	Physical activity induced high expression of sestrin, as a potential molecule for therapeutic benefits	[26]
Muscle biology	Human	Acute: Single-leg strength exercise; Chronic: a 12-week lower body resistance training	Acute/chronic: Sestrin1 up-regulated/no effects on sestrin2-3	Long-term training induced the protein expression of Sestrin1	[27]
Hemodialysis	Human	24 weeks of training, chest press, squat, knee/hip exercise, ect.	Sestrin2 up-regulated, inflammatory factors down-regulated	Resistance training up-regulated sestrins in chronic kidney patients	[28]
Spatial memory	Rat	Treadmill at a speed of 15 m/ min for 15 min for 2 weeks + MitoQ	Sestrin2 up-regulated under exercise + MitoQ, down-regulated under exercise	Exercise + MitoQ positively regulated sestrins	[29]
Muscle hypertrophy	Rat	Endurance resistance training/ Strength resistance training/ Hypertrophy resistance training	Sestrin2 down-regulated in each exercise condition	Sestrin2 down-regulated, mechanism unclear	[30]
Autophagy/ muscle biology	Mice	Swimming pool for 10 min during 3 consecutive days.	Sestrin2 up-regulated	Exercise induces sestrin2 accumulation in the skeletal muscle of old mice	[32]

advances of tissue/cell/organs which were related to SESNs while the latter was more important in clinical practice.

The following views were clear according to the conclusion of collected articles: first, exercises do have critical effects on regulating expressive level; second, different exercise regimens have different effects on the expression level of SESNs; third, different exercise prescriptions have different effects on SESNs and no effective evidence to clarify it. Regard as the potential mechanism, abundant studies had proved that physical exercise contributes to ROS accumulation, JNK phosphorylation, antioxidant response and other main inducers of SESNs which result in up-regulating the expressive level through p53 or Nrf2 (NF-E2–related factor 2) [25,31]. A series of studies [32] about exercise had summarized in Table 1. All those studies have revealed that proteins were the critical object which regulated by exercise, also a key intermedium to exert important pathobiology reaction. Further investigations need to be performed to solve the remained questions including the exercise prescription and issues ①/②/③ were mentioned above.

3.2. Diets

Dietary restrictions have a positive function in health maintained due to weight loss and metabolic equilibrium [33]. Recent studies have focused on dietary components and caloric restriction in order to clarify the effects on SESNs expressive levels and related biological functions. Amino acids (leucine, valine) in diet own critical relationship with the activation of mTORC which exerting important functions such as autophagy, cellular proliferation [34]. Research of Jiongming Lu [35], in flies by knockout the SESNs showed the life-span and health state were blunted compared to those normal flies, SESNs were the mediator of dietary restrictions and health, dietary restriction prolongs life by inhibiting mTOR signaling pathway via SESNs. Another research exhibited similar result in drosophila [7], but both two studies were failed to elucidate the mechanism of expression level variation of SESNs under dietary restriction. Research from Wrońska A showed that sestrins' expression was not altered by calorie restriction in short-term [36]. Contrary, S. Rafia showed that starvation promoted the expression level of SESNs in dictyostelium discoideum while these researches were failed to interpret the reasons [37].

3.3. Laboratorial technology

Lentiviral techniques were the regular methods in laboratory, common technology in animal research or cellular experiments. First, the gene sequences of those 3 different isoforms of SESNs were achieved from NCBI or published article: human Sesn1 5′-CTTCTGGAGGCAGTTCAAGC-3' (sense) and 5′-TGAATGGCAGCCTGTCTTCAC-3' (antisense); human Sesn2 5′-CAAGCTCGGAATTAATGTGCC-30 (sense) and 5′-CTCACACCATTAAGCATGGAG-3' (antisense); human Sesn3 5′-GTTCACTGTATGTTTGGAATCAGG-3' (sense) and 5′-GGGTGATACTTCAGGTCAAATG-3′(antisense); mouse Sesn2 5′-TAGCCTGCAGCCTCACCTAT-3' (sense) and 5′-TATCTGATGCCAAAGACGCA-3' (antisense) [38]. Two typical lentiviral vectors could be generated through above gene sequence, lentiviral contained target SESNs gene can up-regulate the expressive level while lentiviral contained siRNA or shRNA will result in down-regulating of the expressive level in contrary. Once those lentiviral were generated successfully will be applied to transfect the target cells and result in modifying the protein levels eventually. Lentiviral technology mainly used in cellular experimental or early common in-vivo animal study, but the application prospects were restricted due to the complicate processes and the limitation of reliability also the transfection success rate especially in animal in-vivo research. Regard as animal in vivo study, the gene silencing animal (mice) has become the best way to make the experimental results much more reliable. First step is plasmid construction: a sequence was cloned into the plasmid and then microinjected into the pronuclei of fertilized eggs of anima after resection of fragments, the embryos will be planted into pseudo-pregnant foster female mice and the gene silenced mice were generated [39]. This method were mainly used to breed sestrin genes silencing mice for in vivo study, and its biological characteristics were stable, the experimental results were more scientific and objective compare to others.

4. Discussion and prospect

SESNs are conserved family proteins which contain 3 different isoforms named sestrin1 sestrin2 sestrin3, sestrin1 and sestrin2 are the most widely studied and own the most comprehensive biological function [40]. Abundant studies have proved SESNs can regulate the activation of mTORC and result in exerting physiological functions such as anti-inflammatory, antioxidant, anti-aging and fibrosis inhibition. However, a big gap and challenges between clinical practice and scientific research still remained. First of all, the current intervention techniques are laboratory setting, and these intervention protocols do not provide much guidance for the development of new diagnostic and therapeutic techniques. Second, the majority of current studies are still animal studies, with few related to humans. Third, there is a lack of exploration of the potential risks of SESNs application. For exciting is that studies have showed that exercise therapy is an effective in vitro intervention method to improve the expressive level of SESNs, but the correlation between the elements of exercise therapy such as frequency, intensity, duration time and the expression level of SESNs is not clear, this gap mainly due to the differences of understanding between clinical practice and medical scientific research as well as the differences in research concerns. More researches which cooperated by multi-discipline are urgent to help clinicians utilize exercise therapy through the mediated effects of SESNs in the treatment of related diseases in order to translate the knowledge into clinic. Collaborate together to determine what kind of study is most important for the development of new diagnostic and therapeutic technologies, and to jointly promote the SESNs from the laboratory to the clinical application. Although SESNs are an important regulatory agent of dietary restriction in regulating related pathophysiological processes, the effects of dietary restriction and other interventions on protein's expressive levels still remained unclear and more robust evidences are needed to clarify the above relationship.

5. Conclusions

Above all, the intervention methods of SESNs are limited, but exercise has been proved to be the most promising medical intervention at present. However, the application value is limited by exercise prescription parameters and many other factors, and the application scenario in clinical practice is still questionable. Biological techniques in the laboratory are different from exercise, the application scenarios and prescriptions are highly adjustable, but there is no relevant translational research at present. Combined with current trends, the above issues will be important breakthroughs in future research.

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CRediT authorship contribution statement

Yunfeng Sun: Resources, Funding acquisition, Conceptualization. **Yawei Wu:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization. **Ronghua Jing:** Writing – original draft, Investigation, Data curation, Conceptualization. **Keping Yang:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Xiaoya Wang:** Data curation. **Xiaoxiao Zhao:** Data curation. **Caterina Fede:** Investigation, Data curation. **Carla Stecco:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Yunfeng sun reports administrative support and travel were provided by State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia Fund. Natural Science Foundation of Xinjiang Uygur Autonomous Region. China Scholarship council. None If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34590.

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