REVIEW ARTICLE

Type of Sestrins And Their Functional Role in Type 2 Diabetes Mellitus

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ABSTRACT
Sestrins (SESNs) highly conserved stress-inducible proteins that respond to multiple cellular stressors to protect organisms including DNA damage, oxidative stress, endoplasmic reticulum (ER) stress, starvation, and hypoxia. SESN regulate signaling and metabolism mainly through the AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) complex pathways, highlights their importance in the perspective of glucose metabolism and insulin sensitivity. Insulin resistance and chronic inflammation was observed in type 2 diabetes mellitus (T2DM). SESNs act as to protect and modulate oxidative stress and inflammatory reactions. Also SESNs facilitate the augmentation of insulin sensitivity through the regulation of glucose uptake and lipid metabolism, contributing to enhanced metabolic profiles. This review examines the comprehensive types and functions of SESNs in T2DM, underline their roles in cellular stress response mechanisms, and their therapeutic targets that influence the protective attributes of SESN in the management and prevention of T2DM.

Keywords: *Sestrin, Type 2 Diabetes Mellitus, Insulin Sensitivity, mTOR, DNA damage.*
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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a persistent metabolic disorder categorized by decreased insulin secretion and higher in insulin resistance, leading to increased blood glucose levels. T2DM is a most prevalent metabolic condition continues to rise globally, and due to dietary modifications, sedentary lifestyles, and genetic predisposition[1,2]. Oxidative stress is an imbalance between the reactive oxygen species (ROS) production and the body's antioxidant defenses, is an important provider to the pathophysiology of various chronic diseases including diabetes and its associated complications[3].

There are various molecular mechanisms concerned in the oxidative stress processes and also involved sestrin (SESN), family of proteins, comprising SESN1, SESN2, and SESN3[4]. SESNs encompass an evolutionarily conserved family of proteins and were found in animals and highly expressed in cells exposed to a variety of stresses, including oxidative stress. SESN1 is a member of the growth arrest and DNA damage-inducible gene (GADD) family and ubiquitously expressed in skeletal muscle, heart, liver, and brain of human tissues. SESN2 is also known as hypoxia-inducible gene 95, is over expressed in cells under hypoxic conditions, DNA damage, oxidative stress, endoplasmic reticulum stressors, high-fat diet and starvation[5]. SESN2 is identified as a key leucine sensor for the mTORC1 pathway[6] and highly expressed in leukocytes, kidney, lungs, gastrointestinal tract, liver, and brain. SESN1 and SESN2 are regulated by p53, a tumor suppressor protein. SESN3, the least reported one of the family, is mainly activated by FoxO transcription factors. SESN3 is highly expressed in kidney, colon, brain, small intestine, skeletal muscle and liver[5].

2. SESTRIN FAMILY

There are three highly conserved proteins for SESN (SESN1, SESN2, SESN3), which play crucial roles in metabolisms, cellular homeostasis by regulating oxidative stress, and autophagy (Table 1). These stress inducible proteins are primarily known for stress responses involvement, and recent time, they have been linked to metabolic disorders, including T2DM[7].

Table 1. Structure, and functions of Sestrins

Sestrin	Structure	Functions
SESN1	Mainly composed of α-helical regions	Reduces ROS, senses nutrients (amino acids, glucose, leucine), Suppresses mTORC1 activity and promotes autophagy.
SESN2	Displays two-fold pseudo	Inhibits ROS, DNA damage, ER stress, Senses nutrients

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	symmetry with three sub domains	(amino acids, glucose, leucine) , suppresses cell growth and mTORC1, induces autophagy, maintains homeostasis of glucose and insulin, as well as fat (fatty acid, and triglyceride)
SESN3	Unknown	Suppresses ROS, senses nutrients (amino acids, glucose, and leucine), regulates mTORC1/mTORC2/PKB, induces autophagy, regulates homeostasis of glucose and insulin

ROS: Reactive Oxygen Species, ER: Endoplasmic Reticulum, mTORC1: Mammalian Target of Rapamycin Complex 1, PKB: Protein Kinase B

2.1. SESN1

It is first member of the family was identified, induced by the tumor suppressor p53 and is involved in responses to oxidative stress and DNA damage [5]. SESN1 is transcriptionally regulated by P53 and forkhead transcription factors, exhibits oxidoreductase activity and protects cells from oxidative stress. Rapamycin attenuates stress-induced apoptosis of endothelial cells through mTOR and SESN1-related redox regulation[8,9]. SESN stimulate antioxidant enzymes such as glutathione peroxidise and catalase to neutralize reactive oxygen species (ROS), thereby protecting cells from oxidative damage[10]. SESN1 is studied in less in metabolic contexts, its regulation of lipotoxicity associated oxidative stress in tissues such as the liver[11].

2.2. SESN2

The most studied member is SESN2, mainly in relation to metabolic disorders like T2DM[7]. SESN2 is induced by both p53 and Nrf2, a significant regulator of the cellular response as an antioxidant, and is involved in decreasing oxidative stress and promoting autophagy[10]. SESN2 alter many numbers of key metabolic pathways, including AMPK and mTOR pathways, are essential for energy balance and cellular metabolism[12]. SESN2 plays a protective role by decreasing ROS, enhancing autophagy, and mitigating inflammation. SESN2 activation of AMPK, an energy-sensing enzyme, increases glucose uptake and fatty acid oxidation in muscle and adipose tissues, leading to improved insulin sensitivity[13]. In addition, SESN2 inhibits mTORC1, prevents autophagy dysfunction, common in insulin resistance, and contributes to preserving pancreas β-cell function[14].

2.3. SESN3

Similar to SESN2, SESN3 regulates metabolism and oxidative stress but it's mainly controlled by the transcription factor FoxO through insulin signaling[15]. In T2DM models, SESN3 shown to improve insulin sensitivity by vary insulin receptor substrates (IRS) and promoting lipid metabolism, reducing hepatic glucose production. SESN3 enhances hepatic insulin sensitivity by activation of the mTOR-Akt signaling. SESN3 have multifaceted functions, including activation of AMPK and mTORC2 and inhibition of mTORC1. The endogenous SESN gene expression and function may be useful for the diabetes prevention. SESN can be very useful targets for the nutrient homeostasis and modulation of insulin sensitivity. SESN mimetic might be useful for the management and treatment of diabetes[16].

3. FUNCTIONAL AND MOLECULAR ROLE OF SESNS

SESNs family of proteins involved in the several defence mechanisms of antioxidant, functions stimulated under oxidative stress[17]. Multiple pathways involved and altered for these processes, such as the AMPK/mTORC1 pathway and mTORC2-AKT pathway[5]. Moreover, SESNs regulate cellular metabolism and homeostasis in normal as well as diseased conditions[18]. Despite their overlapping functions, SESN1 is more specialized in stress responses, whereas SESN2 and SESN3 are heavily involved in metabolic regulation and autophagy[12,19]. SESNs have increasing recognition for their critical roles in metabolic regulation, particularly concerning insulin sensitivity and glucose homeostasis in T2DM. SESNs proteins, classified into three isoforms (SESN1, SESN2, and SESN3), are known to mediate cellular responses to various stressors, thereby influencing metabolic pathways crucial for maintaining energy balance. Sestrins exert their effects on T2DM is through the AMPK and the mTOR pathways. Table 2 describes the role of Sestrins in T2DM.

Table. 2. Role of sestrins in T2DM with reference to serum SENS2 levels

Disease	Pathway/Function	Reference
Newly diagnosed drug-naive T2DM	AMPK/mTORC1 signaling and Increased serum levels of SESN2	[20]
T2DM	AMPK/mTORC1 signaling pathway. Significant elevation in mean serum SESN2 levels related to the presence of diabetic nephropathy (DN)	[21]
T2DM patients	AMPK/mTORC1 signaling and decreased serum SESN2 levels	[22]
T2DM individuals with diabetic kidney disease (DKD)	TGF-β/Smad and YAP/TEF1 signaling. Reduced SESN2 expression observed in podocytes from diabetic patients	[23]
T2DM patients with diabetic nephropathy	AMPK or Nrf2 signaling. Enhancement and mTORC1 pathway inhibition and decreased serum SESN2 levels	[24]

T2DM individuals with diabetic peripheral neuropathy	AMPK and mTOR signaling pathways. Serum SESN2 levels are reduced	[25]
Obese children with T2DM	PI3K/AKT signaling and decrease in serum SESN2	[24]
T2DM patients	AMPK/mTORC1 signaling pathway. Serum SESN2 levels are reduced.	[26]
T2DM patients with coronary heart disease (CHD)	Activation of AMPK, inhibition of mTORC1, and activation of autophagic signaling pathways. Decreased serum SESN2 levels in T2DM patients with CHD	[27]
Diabetes	AMPK/mTOR pathway	[7]
T2DM with diabetic nephropathy	JAK/STAT pathway. Serum SESN2 levels significantly decreased	[28]

4. SESTRIN ON AMPK AND mTOR SIGNALING

AMPK functions as a central cellular energy sensor activated under conditions of low energy or metabolic stress. SESN2, have been identified as upstream activators of AMPK, primarily through the mTORC1 inhibition that promotes catabolic processes, such as glucose uptake and lipid oxidation, critical for restoring energy balance[29]. SESNs has crucial role in inhibiting mTORC1, a key regulator of cell growth and metabolism frequently hyper activation in T2DM and thereby is linked to insulin resistance, as it negatively impacts insulin signaling pathways by inhibiting IRS proteins[30]. Experimental studies have demonstrated that the activation of SESN2 results in significantly increased glucose uptake in skeletal muscle and adipose tissue, two primary sites for insulin action thereby ultimately contributing to better metabolic outcomes in diabetic contexts[31].

5. SESTRIN IN OXIDATIVE STRESS, INFLAMMATION AND AUTOPHAGY

Chronic inflammation and oxidative stress are the foremost features of T2DM, contributing to β-cell dysfunction and insulin resistance. SESNs are induced by oxidative stress in various pathological conditions including, diabetes[5] and promoting antioxidant responses by reducing inflammatory actions[32]. Antioxidant properties of SESN2 exert by increasing antioxidant enzymes including catalase and glutathione peroxidase. These enzymes reduce ROS levels, thereby protecting cells from oxidative damage. In T2DM, elevated ROS levels impair insulin signaling by promoting the activation of stress-related kinases, such as c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB), which interfere with insulin receptor activity[33]. SESNs comprise as a novel stress-responsive proteins and have crucial for reducing oxidative damage in stress conditions[34]. During oxidative stress SESNs are activated, mainly SESN2 and potentially has a role in ROS metabolism[13]. Low grade chronic inflammation is a hallmark of T2DM, driven by cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These pro-inflammatory mediators aggravate insulin resistance by interfering with signaling of the insulin receptor actions[35]. SESN2 helps to maintain the balance of oxidative metabolism by apply biological functions directly and reduce the accumulation of ROS[31]. Also SESN2 is activated by transcription factors, including NF-kB, activator protein-1 (AP1), forkhead box O3 (FOXO3), p53, and CCAAT-enhancer-binding protein beta (C/ERPb)[30,36].

Both mTORC1 and mTORC2 has significant function in the regulation of insulin mechanisms. mTORC1/ribosomal protein S6 kinase 1 (S6K1) and mTORC2/protein kinase B (AKT), is essential for the maintenance of insulin sensitivity and their dysfunction leads for the development of T2DM. Apoptosis and autophagy of β -cell is mediated through mTORC1/S6K1 pathway. Also, β-cell proliferation is mediated through mTORC1/4E-BP2-eIF4E pathway. β -cell-specific mTORC1 loss can leads to diabetes and β -cell failure[7,37,38]. mTORC2 is necessary for maintaining a balance between the β-cells proliferation and the cell size[39]. Moreover, mTORC2 contribute in the regulation of glycolysis, lipogenesis and hepatic insulin sensitivity[40,41].

Autophagy, a crucial cellular housekeeping process responsible for degrading damaged organelles and proteins, has an important role in maintaining cellular homeostasis including nutrient deprivation. Deregulated autophagy has been linked to impaired β-cell function, insulin resistance, and the development of complications in T2DM. Involvement and functions of mTORC1 and mTORC2, as a crucial sensor for redox states, energy, thereafter regulates protein synthesis and autophagy. mTOR complexes are now may be used in the clinical trials to treat a various conditions[42]. Autophagy plays an crucial role in pancreatic β-cells viability maintaining and function by preventing oxidative related stress and the toxic proteins accumulation. Deregulation of autophagy in β-cells contributes to decreased insulin secretion, a hallmark of T2DM[43]. Sestrin2 can directly bind to RagA/B regulatory protein complex 2 (GATOR2), and suppress mTORC1. GATOR2-mTORC2 axis is crucial for SESN2-induced AKT activation, which exerts various glucose- and lipid-regulating effects[7].

6. THERAPEUTIC TARGETING OF SESNS

Given the comprehensive roles of SESNs in regulating inflammation, autophagy, oxidative stress, and metabolic homeostasis represent promising therapeutic targets for the management of T2DM. SESNs related pathways have exposed potential strategies for connect these proteins in therapeutic interventions that can improve insulin

sensitivity, β-cell function, and decreasing the complications associated with diabetes. Metabolic disorders of diabetes are one of the altered and principal nutrient sensing mechanisms AMPK and mTOR. To develop drugs by targeting SESN pathways have primarily focused on small molecules that activate AMPK or inhibit mTORC1. Chronic activation of mTORC1 during over nutrition increases lipid and protein synthesis and represses autophagic catabolism. mTORC1 activation is the transcriptional activation of SESN2[17]. The upregulation of SESN2 by insulin and mediated through PI3K/PKB/mTOR pathway. Molecular loop be present between insulin and SESN2 during chronic activation of mTORC1 would give us close to develop novel therapeutic approaches for the management of metabolic disorders[44]. Rapamycin and its analogs that inhibit mTOR, have shown promise in preclinical studies for improving insulin sensitivity and preventing diabetic complications, suggesting that targeting the SESN-mTOR axis may offer a new avenue for T2DM therapy[45]. SESNs and their involvement in metabolic and various physiological progressions considered as a careful approach for the drug developments and ensuring that potential therapies specifically target metabolic pathways. Though, challenges remain in translating with more these findings into clinical applications.

7. CONCLUSION

SESN has important role and the pathophysiology of T2DM by regulating metabolic pathways that linked to oxidative stress, inflammation, autophagy, and insulin sensitivity. SESNs pathways targeting may be an electrifying opening for managing T2DM. SESN has regulatory effects on AMPK and mTOR signalling that can contribute in maintaining cellular homeostasis. Studies evidence and inferred that SESN2 mainly involved in the pathogenesis, and suggesting multiway for the diagnosis and treatment of diabetes and its complications. Furthermore studies need for this confirmation to disclose associated signalling and to explore potential treatment.

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