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The Potential Role of Sfrp5 in the Treatment of Obesity

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Abstract

Obesity is frequently defined as excess body weight for a given height, which has become a central issue for the global health concern. Secreted frizzled-related protein 5 (SFRP5) is an anti-inflammatory adipokine secreted by adipocytes, which has been regarded as a "good" a adipokine that could promotes good health. Researchers believed that SFRP5 could become the therapeutic target for the treatment of obesity, which takes effect through SFRP5/Wnt pathway. The purpose of this review is to summarize the effects of SFRP5, including being the signature of obesity, inhibiting adipogenesis, regulating triglyceride metabolism and alleviating inflammation, which is important for our increased understanding of the potential therapeutic role of SFRP5 in metabolic disease.

Keywords: SFRP5; Obesity; Signature of obesity; Adipogenesis; Triglyceride metabolism; Inflammation

Introduction

Obesity is frequently defined as excess body weight for a given height, which has become a central issue for the global health concern [1]. Current obesogenic environment, favoring high-calorie foods and physical inactivity, is a major reason of the growing obesity. However, the way people respond to environmental factors determined by their genetic predisposition to obesity in part [2]. The pathophysiological features of obesity can be described as the accretion of lipids (mainly triglycerides), adipokines (cell-signaling proteins) and hormones, and the low-grade systemic inflammatory state [3]. Evidence suggests that obesity is among the most important factors for the development of metabolic syndrome (MetS) and comorbidities, including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, cardiovascular disease (CVD) [4]. As a result, obesity has long been a question of great interest in a wide range of medical fields.

Secreted frizzled-related protein 5 (SFRP5) is one of the SFRP family members that contains a cysteine-rich domain homologous to the putative Wnt-binding site of Frizzled proteins. Moreover, SFRP5 has been proved to inhibit the activation of c-Jun N-terminal kinase (JNK) which is the downstream of the Wnt signaling pathway. SFRP5 is an anti-inflammatory adipokine secreted by adipocytes, which has been regarded as a "good" a adipokine that could promotes good health [5]. SFRP5 is highly expressed in white adipose tissue, which could also be detected in the circulating plasma [6]. A couple of researches have established that SFRP5 plays a pivotal role in the development of obesity, so that researchers believed that SFRP5 could become the therapeutic target for the treatment of obesity, which takes effect through SFRP5/Wnt pathway [7].

Whilst some research has been carried out on obesity, further understanding of pathogenesis and treatment of obesity are still needed. Up to now, far too little attention has been paid to SFRP5 as a novel anti-inflammatory adipokine. The aim of this review is to explore the relationship between obesity and SFRP5.

Circulating SFRP5 is a Signature of Obesity

Circulating SFRP5 concentrations could be determined by using ELISA. A number of cross-sectional studies suggested an association between obesity and SFRP5. Previous studies have demonstrated that overweight/obese subjects (BMI ≥ 25 kg/m^2) had apparently lower circulating SFRP5 levels than control groups [8]. This phenomenon can be observed not only in adults, but even earlier. SFRP5 levels were lower in the excessive gestational weight gain (EGWG) mothers and their offspring, when compared with healthy controls, and the umbilical cord SFRP5 levels were positively associated with the maternal serum SFRP5 levels. Furthermore, the umbilical cord SFRP5 depended on its levels in the maternal serum, each 1 ng/mL decrease in the maternal serum SFRP5 concentration was associated with a decrease in the umbilical cord SFRP5 level by 0.33 ng/mL [9]. It has previously been observed that SFRP5 levels would decrease with age in pre-pubertal children [10]. The SFRP5 level was significantly lower in obese children, while Wnt5a level was elevated [11], and could be increased after weight loss by lifestyle intervention [12].

The existing body of research on SFRP5 suggested that dietary is one of the most important influence factors for the circulating levels of SFRP5. The high consumption of vegetables and fruit associated with higher SRFP5, while high sugar-sweetened beverage consumption with lower SRFP5 [13]. This also accorded with Catalan's observations, which showed that SFRP5 concentrations quickly increased after caloric decrease instead of surgery despite, suggesting the use of this molecule as a biomarker of the energy balance by dietary interventions [14]. In addition, a SFRP5 concentration was also influenced by some drugs such as Liraglutide [8] and metformin [15] in humans.

SFRP5 Regulates Triglyceride Metabolism

In mammals, long-term energy storage is based on production of intracellular triglycerides, storing within white adipocytes tissue (WAT) and liberating free fatty acids from triglycerides when energy demand [16]. As a result, the main characteristics of WAT are to stores excess energy as triglycerides. Compare with WAT brown adipose tissue (BAT) has been increasingly recognized as the main site of thermogenesis in mammals [17]. However, WAT expansion triggered by caloric excess was also implicated as a risk factor of MetS.

Previous research has established that there are strong positive correlations between adipocyte size, adipose tissue expansion and mRNA levels of SFRP5, which examined the effects that SFRP5 plays a potential role in adipose tissue differentiation. SFRP5 mRNA displayed a tendency towards higher levels paralleling the increased expression of BAT differentiation-associated genes, while the expression of SFRP5 gradually reduced during differentiation of WAT [18]. The thermo genic processes in BAT are occurred *via* a biochemical property of the mitochondria. The number of mitochondrion increased could be observed in SFRP5^{Q27stop} adipocytes, which suggested that SFRP5 may restrain adipocyte growth under obesogenic environmental conditions due to increased number of mitochondria [19].

Reports have shown that serum Wnt5a concentrations were positively correlated to triglyceride levels, while not related to glucose levels or insulin resistance [20]. SFRP5 initially binded with Wnt5a to prevent JNK activation in the downstream of Wnt signaling pathway in adipose tissues, these results confirmed the association between SFRP5 and lipid metabolism. In addition to interacting with Wnt5a, SFRP5 was also related to secreted lymphocyte antigen-6/urokinase-type plasminogen activator receptor-related peptide (SLURP-1). It has previously been observed that SFRP5 interacted with SLURP-1 decreased triglyceride accumulation by using the immunoprecipitation assay [21]. It not only acted directly on adipocytes, but also played a regulatory role in the central nervous system, SFRP5 activation of the InsR-Akt PI3 kinase-KATP channel pathway in the hypothalamus of rats as a brain–hepatic neuro-circuitry underlying the SFRP5 regulation of hepatic triglyceride-rich very-low-density lipoprotein (VLDL-TG) secretion [22].

SFRP5 Alleviate Inflammation of Obesity

The characterize of obesity-associated inflammation is infiltration of macrophages in adipose tissue, which seems probably a direct response to the abnormal fat metabolism. What is surprising is that SFRP5 regulates the micro-environment of adipose tissue. In obesity, SFRP5 expression is reduced while Wnt5a concentrations are increased because of the higher number of macrophages within adipose tissues, which leads to an imbalance of Wnt5a/SFRP5.

A series of cross-sectional studies of Chinese population suggest that the down regulation of SFRP5 might have a potential role in the pathogenesis of the MetS related metabolic disorders and chronic inflammation [23]. An *in vitro* experiment has shown that SFRP5 could inhibit Wnt5a-induced macrophage chemotaxis and activation, on account of suppressing the induction of cytokines, CCL2, and COX-2/PGE2 by Wnt5a [24]. Sfrp5-/-mice represented aggravated fat inflammation and systemic metabolic dysfunction after fedding a high-calorie diet, while the acute administration of SFRP5 to obese and diabetic mice reduced adipose tissue inflammation and ameliorated metabolic function. These results provided further support that SFRP5 neutralizes JNK activation by Wnt5a pathway in macrophages and adipocytes [25]. The existing body of research suggested that SFRP5 played a positive role in metabolic dysfunction by controlling inflammatory cells in adipose tissue, which could inhibit the apoptosis by resisting wnt5a/caveolin-1/JNK signaling pathway [26].

These studies provided new insights into inflammation of

obesity, thus providing a new strategy for the clinical treatment of MetS. SFRP5 promoted adipocyte differentiation by antagonizing canonical Wnt signalling and can be up-regulated by PPRP-r (phosphoribosylpyrophosphate) activators rosiglitazone and metformin, which suggested that these agents could sequester Wnt ligands and restrain the chronic inflammatory state [15]. Recently investigators have examined that raloxifene ameliorated obesity, adipogenesis, and adipose tissue hypertrophy as well as inflammation by activating non-canonical SFRP5 signaling [27].

Discussion and Conclusion

In this review, we summarized the relationship between obesity and SFRP5, including circulating SFRP5 is a signature of obesity, SFRP5 regulates triglyceride metabolism, and SFRP5 alleviate inflammation of obesity. SFRP5 is decreased in overweight/obese subjects while Wnt5a level is elevated not only in adults, but even earlier, and can be influenced by dietary. On the other hand, there are strong positive correlations between adipocyte tissue and SFRP5, which suggests that SFRP5 plays a potential role in adipocyte size, adipose tissue expansion and adipose tissue differentiation. In addition, SFRP5 regulates the micro-environment of adipose tissue by Wnt5a pathway in macrophages and adipocytes. Taken together, these findings suggest a potential role for SFRP5 in ameliorating MetS. This review will prove useful in expanding our understanding of how to find the therapeutic targets of SFRP5 in metabolic disease.

It is unfortunate that most of the existing mechanism researches concentrated on *in vitro* study, it is difficult to know if there are the same effects of SFRP5 between systemic and local treatment. In spite of its limitations, the study certainly adds to our understanding of the biological functions of SFRP5. Further research is required to establish the therapeutic efficiency of recombinant SFRP5 in MetS.

In summary, most of the current studies in the treatment of MetS with SFRP5 and its related drugs are mostly in the preclinical stage. Most of these studies with indicating the benefits of SFRP5 in the treatment of MetS, although the use of recombinant SFRP5 in clinical treatment remains to be further verified.

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Author Contributions

Author Chunyan Yin, Mengnan Lu, Huangtao Chen, Guo Li and Jingyu Wang designed the study. M Lu and H Chen contributed equally to this work.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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