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Review

The blooming intersection of subfatin and metabolic syndrome

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Metabolic Syndrome (MS) remains the leading cause of mortality and morbidity globally. Adipose tissue releases adipokines that play key roles in metabolic and cardio-cerebro-vascular homeostasis. Subfatin, induced after exercise or upon cold exposure in adipose tissue, is a novel secreted protein homologous to Metrn, a neutrophic factor with angiogenic properties. The protein was proved to be of great significance in the browning of white adipose tissue (BWT) and insulin resistance (IR). It affected insulin sensitivity at least via its local autocrine/paracrine action through AMP-activated protein kinase (AMPK) or peroxisome proliferator-activated receptor δ (PPAR-δ) dependent signaling. Subfatin blocked the release of inflammatory mediators, improved intracellular insulin signal transduction and reversed IR. It also improved glucose tolerance and played a key role in metabolism and cardiovascular and cerebrovascular homeostasis. It was reported that the level of serum subfatin was significantly correlated with the occurrence and severity of coronary heart disease, which might be a new target for the treatment of coronary heart disease. In addition, exercise increased the level of subfatin in circulation and adipose tissue, promoted energy consumption, improved glucose and lipid metabolism, increased the heat production of brown fat, and strengthened the anti-inflammatory mechanism. Given its role in metabolic disorders, subfatin is considered as a candidate biomarker of MS. However, the clinical significance of subfatin remains largely unclear. The purpose of this article is to review the research on the effect of subfatin on MS in recent years.

Keywords

Subfatin; Metrnl; Cometin; Interleukin 39; Metabolic syndrome

1. Introduction

Metabolic dysfunction is a risk factor of cardio-cerebrovascular disease, and key molecules that play pivotal roles in its pathogenesis need to be further investigated. As a common risk factor for a variety of metabolic diseases, obesity promotes the imbalance of expression and secretion of a variety of cytokines and eventually leads to the occurrence of metabolic and cardiovascular diseases [1–4]. Given that improving insulin resistance (IR) represents a critical strategy in the treatment of type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS), novel insulin-sensitizing treatments are needed [5–7]. Recently, a novel adipokine, subfatin, has been found, which may be involved in the pathophysiology of obesity and IR and therefore have comprehensive effects on atherosclerosis [8]. And it may become a potential biomarker or a therapeutic target of MS.

To date, subfatin has been found to play roles in lipid metabolism, tumor and immunity [9–11], which are of great clinical interest. However, the current literature is still limited and some findings are controversial. For instance, in the study of patients with newly diagnosed T2DM, contradictory results of both increasing and decreasing serum levels of subfatin were noted, which requires a larger sample size to reduce bias [12–14].

Given the potential role of subfatin in patients with MS, this article aimed to review the novel findings and profound function of subfatin (Fig. 1).

2. Identification of subfatin

Adipose tissue is the largest endocrine organ [15], which secrets a variety of adipokines. Jorgensen *et al.* firstly reported a novel secreted protein termed subfatin which together with meteorin defines a new evolutionary conserved protein family. Li *et al.* [16] identified subfatin as a novel adipokine. Subfatin is possibly also a neurotrophic factor with therapeutic potential [17].

Subfatin is also named Metrnl (Meteorin-like), cometin [18], or interleukin 39 (IL-39) [19, 20]. The gene of *subfatin* is located in chromosome 11qE2 in mice and chromosome 17q25.3 in humans, respectively [21]. Bioinformatic analysis shows that the subfatin protein is encoded in human genomes contain 311 amino acids, with an NH2-terminal signal pep-

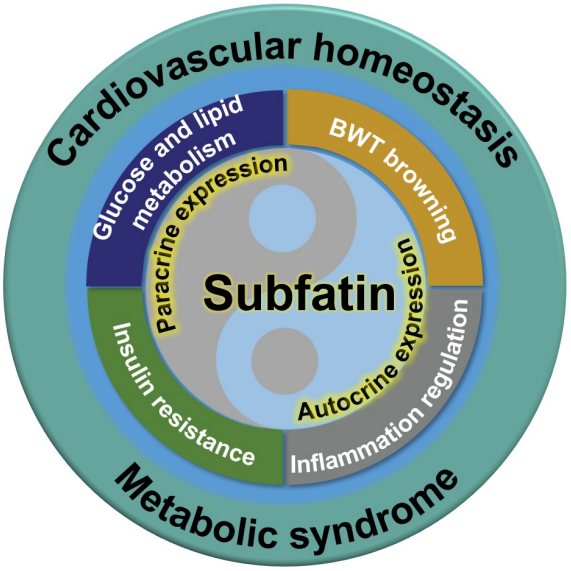

Fig. 1. The schematic illustration of subfatin in metabolic syndrome. This review explains the biological functions of subfatin in cardiovascular homeostasis and metabolic syndrome, especially in the terms of glucose and lipid metabolism, insulin resistance, inflammation regulation, and browning of white adipose tissue (BWT).

tide of 45 amino acids and without any transmembrane region, suggesting a mature protein that contains 266 amino acids when secreted (Fig. 2). Studies have shown that its expression was induced by a chronic high-fat diet, inflammation, exercise, cold exposure and other factors.

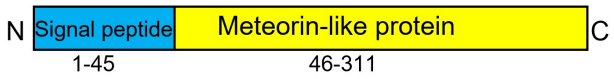

Fig. 2. The schematic illustration of human subfatin gene. The subfatin gene is composed of a signal peptide at the N-terminus and a meteorin-like protein at the C-terminus. The secreted subfatin presents two expression modes of autocrine and paracrine in the body.

It is named meteorin-like protein due to the similar sequence to metrn protein [22, 23]. The initial name of Meteorin (Metrn) was a vivid description of its function in transforming glial cells into cells with an elongated tail that look like meteors [24]. Following studies found that subfatin was mainly distributed in white adipose tissue, different from the homologous Metrn that is majorly expressed in the brain, and ubiquitously throughout the whole body. It plays a pivotal role in the browning of white adipose tissue (BWT), and highly enriched in subcutaneous fat. Therefore, Li *et al.* [16] propose a more appropriate name "subfatin" (refers to subcutaneous fat highly expressed protein) instead of "Meteorin-like".

We searched the literature from the PubMed database and found that although subfatin protein was first mentioned in 2012, there are still only a handful of studies on it in the past 9 years. Given its involvement in lipid metabolism, oncology and immunity, and without a very specific breakthrough point, most studies are still scattered. Zheng *et al.* [21] published four successive articles from 2014 to 2016, and had a more in-depth study on the potential of the protein [16, 21, 25, 26].

3. Physiological function of subfatin

Based on the available literature, subfatin may improve insulin sensitivity, increase systemic energy expenditure, induce white adipose browning, regulating lipid metabolism and promote anti-inflammatory gene programs in obese/diabetic mice [22, 27].

Both aerobic and resistance exercises improve insulin sensitivity [28]. As is known, exercise promotes the release of metabolism-related proteins through repeated muscle contraction and relaxation in skeletal muscle, which leads to a series of phenotypic adaptations of skeletal muscle and helps to alleviate metabolic disorders [29]. Subfatin is induced into circulation after exercise and in the adipose tissue upon cold exposure. Increased subfatin stimulates energy expenditure, improves glucose tolerance and the expression of genes associated with beige fat thermogenesis and anti-inflammatory cytokines [30]. The serum level of subfatin is independently related to insulin resistance. It affects insulin sensitivity at least via its local autocrine/paracrine action through AMP-activated protein kinase (AMPK) or peroxisome proliferator-activated receptor δ (PPAR-δ) dependent signaling. Therefore, subfatin can be regarded as a bridge between exercise and thermogenesis, and participates in the molecular mechanism of energy metabolism, involving in maintaining energy homeostasis [31].

4. Subfatin and metabolic syndrome

Obesity is associated with chronic inflammation and dysregulation of adipokine secretion and may increase the risk of T2DM and CAD (coronary artery diseases) [32–35]. Adipose tissue, as the largest endocrine organ of the body [15], participates in homeostasis regulation by releasing adipokines which function in various signaling pathways [36]. Adipokines are considered as potential candidates for the relation of the adipose tissue with systemic glucose and lipids metabolism [13, 26]. Subfatin is a novel adipomyokine that shows high levels of expression in white adipose tissue and barrier tissues. It ameliorates lipid-induced inflammation and IR via AMPK or PPAR-δ-dependent signaling pathways in the skeletal muscle of mice [37, 38]. Therefore, subfatin might be a potential therapeutic target in inflammation and MS by regulating tissue energy homeostasis [30]. The overall regulation mechanism of subfatin was showed in Fig. 3, and the detailed explanation as followed.

Firstly, subfatin promoted eosinophils to infiltrate adipose tissue, induced the expression of eosinophil-specific chemokines in adipocytes, to induce immune cytokines (IL-

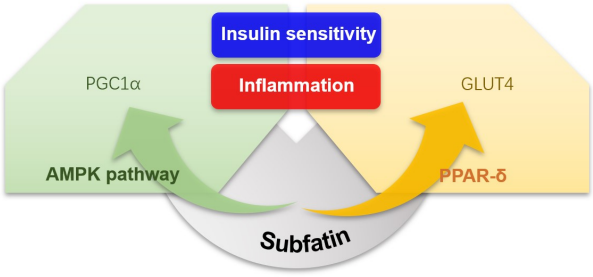

Fig. 3. The signaling mechanism of subfatin in the glucose and lipid metabolism. Subfatin regulates glucose and lipid metabolism through AMPK and PPAR-δ dependent signal pathways, and finally mediates insulin resistance and inflammation progression through PGC1α and GLUT4, respectively.

4/IL-13) to stimulate thermogenesis, and upregulated the expression of pyrogen gene [39–41]. Secondly, in addition to stimulating thermogenesis, subfatin also promotes inflammatory cytokines that inhibit the phenotype of macrophages.

Subfatin exerts effects through AMPK and PPAR-δ-dependent signaling pathways in skeletal muscle. In addition to its role in maintaining intracellular energy balance, AMPK regulates systemic energy metabolism [37]. AMPK activity decreases in adipose tissue of overweight individuals with IR, which is related to increased oxidative stress and changes in gene expression. PPARs are members of the superfamily of nuclear hormone receptors, including PPAR-α, PPAR-β/δ and PPAR-γ [42–45]. PPARs control the expression of a large number of genes involved in metabolic homeostasis, lipid, glucose and energy metabolism, adipogenesis and inflammation. PPARs regulate a large number of metabolic pathways that are implicated in the pathogenesis of MS such as T2DM, nonalcoholic fatty liver disease and cardiovascular disease [46].

IR represents a core culprit of MS. Molecular and phenotypic changes in adipose tissue, skeletal muscle, and the liver are involved in the development of IR and eventually T2DM [47]. At present, it has been mentioned in the literature that the level of subfatin is related to IR and endothelial dysfunction and ultimately affects the occurrence of MS such as obesity, diabetes, coronary artery disease, and acute ST-segment elevation myocardial infarction.

4.1 Subfatin and obesity and IR

Human adipose tissue includes brown adipose and white adipose tissues, mainly distributed subcutaneously and viscerally [48]. White adipocytes are the excess energy stored by the body in the form of fat, and its volume varies greatly with energy storage and release [49]. Brown adipose tissue is functionally a thermogenic organ [50]. Brown adipocytes contain a large number of neutral fat droplets and are rich in mitochondria [51]. There are rich capillaries and a large number of sympathetic nerve endings between the cells, forming a complete thermogenic system [52, 53]. Obesity is caused by the imbalance of energy metabolism, calorie intake is greater than consumption, increasing fat synthesis [54]. The main external causes are inadequate exercise and excessive food intake. In addition to genetic and neuropsychiatric factors, the internal causes are mainly due to hyperinsulinemia and abnormal brown adipose tissue [55].

The persistent inflammatory state accelerates the deterioration of metabolic disorders [56]. Obesity is essentially a chronic low-level inflammatory state, which releases inflammatory mediators in the form of endocrine or paracrine of visceral adipose cells [57, 58]. These inflammatory mediators act on the post-receptor signaling pathway, blocking the intracellular insulin signal transduction, eventually resulting in IR. Subfatin also has anti-inflammatory effects, which may block the above molecular mechanisms and reverse the occurrence of IR. However, the mechanism underlying its beneficial effects is poorly understood. In addition, Sobieh *et al.* [59] showed that higher serum subfatin levels might reduce the prevalence of osteoarthritis in obese patients, which supports the anti-inflammatory effect of subfatin.

As a novel secretory protein, subfatin increases upon exercise or cold stimulation and plays a key role in white fat browning, indicating that it may mediate between exercise and thermogenesis. In addition, the decrease of subfatin in obese individuals promotes fat proliferation and inhibits fat differentiation, resulting in adipocyte hypertrophy, which further reveals its function in the process of energy consumption. Du *et al.* [60] proposed that there was a negative correlation between serum subfatin level and visceral fat obesity.

As we all know, diet therapy and exercise are the optimal treatments for obesity [3, 61, 62]. Exercise training benefits various body systems and promotes lipid metabolism and energy homeostasis by regulating bio-activity [63]. It has been found that exercise increased the level of subfatin in circulation and adipose tissue, promoted energy consumption, improved glucose and lipid metabolism, increased the thermogenesis of brown fat, and strengthened the anti-inflammatory mechanism.

4.2 Subfatin and T2DM

Subfatin may improve glucose tolerance and ameliorate IR. Serum subfatin level was associated with IR, but not with ß-cell function in T2DM patients [64, 65]. Studies have shown that the serum level of substatin in patients with T2DM is decreased, which is related to vascular adhesion molecules, suggesting that substatin may play a role in T2DM and endothelial dysfunction [66], and may participate in the occurrence of chronic vascular complications in type 2 diabetes.

Bariatric surgery is currently one of the effective treatments for T2DM. It increases the concentration of serum subfatin, in correlation with improvements in glucose and lipid homeostasis [67]. Given this, can we achieve the hypoglycemic effect by intravenous injection of exogenous subfatin? The answer is possibly negative. Acute intravenous injection of recombinant subfatin has no hypoglycemic effect, and 1-week intravenous administration of subfatin is unable

to retrieve IR exacerbated by adipocyte subfatin deficiency. Lee *et al.* [68] proposed that intraperitoneal injection of recombinant subfatin could improve glucose tolerance in obese or T2DM mice induced by a high-fat diet. Adipocyte subfatin is an innate insulin sensitizer and may become a therapeutic target for IR. However, the particular mechanism and the interaction between cellular pathways need to be further investigated [26].

Although there have been several reported studies on the association between serum levels of subfatin in T2DM, the findings have been controversial. For example, several studies showed that the level of subfatin increased in patients with T2DM, while others decreased. Increasing the sample size to overcome the bias caused by ethnic differences and other factors may be a solution. Because of contradictory data on serum levels and expression of subfatin in the context of T2DM. Several groups have conducted further studies. Fadaei *et al.* [66] showed that the serum level of subfatin in the T2DM group and prediabetes group was lower and negatively correlated with vascular adhesion molecules. In addition, the level of subfatin in obese T2DM patients was lower than that in emaciated T2DM patients. Onalan *et al.* [69] suggested that a low level of subfatin in diabetic patients may participate in the pathogenesis of T2DM by increasing IR.

4.3 Subfatin and CAD

Adipose tissue secretes adipokines which play pivotal roles in metabolic and cardio-cerebrovascular homeostasis [16]. It was reported that significant associations between serum subfatin and the presence and severity of CAD, suggesting subfatin might be a promising therapeutic target for CAD. Subfatin may also serve as a surrogate marker for endothelial dysfunction and atherosclerosis [70]. Liu *et al.* [71] showed that the level of serum subfatin in patients with coronary heart disease was significantly lower, and the degree of reduction was related to the number of stenotic vessels. Further data statistics showed that subfatin was negatively correlated with body mass index, total cholesterol, low-density lipoprotein, cholesterol and other metabolic parameters, as well as high-sensitivity C-reactive protein, IL-1β, IL-11 and other inflammatory indicators. In a study to explore the changes and significance of subfatin in patients with the acute coronary syndrome (ACS), the serum levels of subfatin in ACS patients were significantly increased, and was positively correlated with N-terminal pro b-type Natriuretic Peptide (NT-proBNP), high-sensitivity C-reaction protein (CRP), cardiac troponin I (cTnI), and negatively correlated with left ventricular ejection fraction [72]. Among them, the most significant correlation was between serum subfatin and NT-proBNP in ST-segment elevation myocardial infarction (STEMI) patients. It is reasonable to infer that subfatin might be a predictor of cardiac systolic dysfunction in STEMI patients. Rupérez *et al.* [73] proposed that the specific overexpression of subfatin in the heart prevents the development of cardiac remodeling. In addition, subfatin was a novel biomarker of heart failure and had an independent prognostic value.

MS was found to worsen blood pressure control probably through the mechanism of accelerating arterial stenosis, and it was also a significant determinant of common carotid artery intima-media thickness (IMT) but not of carotid-femoral pulse wave velocity(PWV), although IMT and PWV were closely related in hypertensive patients [74–76]. It is suggested that subfatin could also be related to this subclinical target organ damage, which entails further studies on correlations between them.

4.4 Subfatin and excersice

Exercise promotes numerous phenotypic adaptations in skeletal muscle that contribute to improved function and metabolic capacity [77, 78]. Emerging evidence suggests that skeletal muscle also releases a myriad of factors during exercise, termed "myokines" [79–81]. As a kind of fibronectin of actin, substatin can be induced by exercise to activate muscle energy sensing network. Its mRNA expression is responsive to both acute high-intensity interval exercise and short-term high-intensity interval training [82, 83]. Exercise-induced myostatin upregulated the protein of myostatin in the surrounding tissues, effectively reduced fat accumulation and improved the systemic metabolism by increasing the content of myostatin in adipose tissue, which might be a target for the treatment of chronic obesity [28].

Additionally, studies have shown that exercise in warm water appeared to increase the level of subfatin, and to stimulate and accumulate immune cells compared to temperate and cold water. This feature can be used to stimulate the production of hormones such as subfatin and IL-4 to enhance brown fat, although more studies are needed in this regard [84]. This information may shed light on the novel mechanisms of the positive effects of physical training and suggest an effective therapeutic tip for treating MS.

5. Conclusions

In conclusion, subfatin is a novel secretory protein identified by emerging bioinformatic techniques, which is induced by exercise and cold stimulation in skeletal muscle and adipocytes, respectively. It promoted white adipose tissue browning, increased thermogenesis of adipose tissue, accelerated decomposition of adipose tissue and improved IR. It may play a pivotal role in the occurrence of MS. Based on this, it is considered that it has the potential to become a therapeutic target for MS. However, the current studies barely reveal the mechanism of its interaction with various signaling pathways. Therefore, it is still far from clinical application. Moreover, the relationship between subfatin and fatty liver has never been studied. This suggests that there is another angle to further expand the influence of subfatin in MS from the correlation between subfatin and fatty liver.

Abbreviations

MS, metabolic syndrome; BWT, browning of white adipose tissue; IR, insulin resistance; AMPK, AMP-activated

protein kinase; PPAR-δ, peroxisome proliferator-activated receptor δ; T2DM, type 2 diabetes mellitus; CAD, coronary artery diseases; ACS, acute coronary syndrome; CRP, C-reaction protein; STEMI, ST-segment elevation myocardial infarction; Metrn, meteorin; IL, interleukin.

Author contributions

SH and LC conducted the literature manufacture and drafted the manuscript. DL and YL provided technological support and contributed to the project discussion. HC and ZW had contributions to the conceptualization of this study and authentication of the validity of the reported results.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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