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The Impact of IGFBP-3/IGFBP-3R System on Obesity-associated Insulin Resistance

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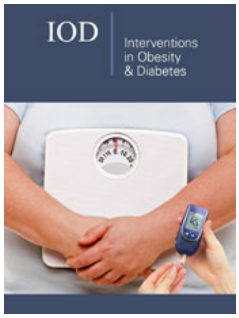

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Abstract

Obesity is a major risk factor associated with insulin resistance [1-4]. The Visceral fat in obesity secretes various pro-inflammatory and pro-atherogenic adipokines resulting in chronic systemic inflammation and insulin resistance [5,6]. Insulin-like growth factor binding protein-3 (IGFBP-3) inhibits production of proinflammatory adipokines, cytokines as well as inflammatory NF-κB activity through the receptor (IGFBP-3R), which may improve many metabolic disorders including insulin resistance in obesity [7,8]. However, the IGFBP-3/IGFBP-3R system appears to be dysregulated in obesity due to neutrophil serine protease (NSP)-induced IGFBP-3 proteolysis in circulation, thereby resulting in loss of its anti-inflammatory function [8]. The complete characterization of the underlying mechanism of the NSP/IGFBP-3/IGFBP-3R cascade in obesity will be benefit for identifying diagnostic and prognostic value of the IGFBP-3/IGFBP-3R axis and therapeutic potential of IGFBP-3R agonists and NSP inhibitors for insulin resistance.

Keywords: IGFBP-3; IGFBP-3R; Insulin resistance; Neutrophil serine proteases inhibitors

Abbreviations: T2DM: Diabetes Mellitus; CVD: Cardiovascular Disease; IR: Insulin Resistance; IGF: Insulin-like Growth Factor; IGFBPs: IGF-Binding Proteins; NSP: Neutrophil Serine Proteases; IGFBP-3R: IGFBP-3 Receptor

Obesity-Associated Insulin Resistance

Nearly two thirds of the adults are overweight or obesity in the United States [9,10]. Overweight and obesity is the significant cause of premature death [11-13]. Obesity is a major risk factor for serious comorbidities including hypertension, type 2 diabetes mellitus (T2DM), and other metabolic disorders [14-18]. Most of obesity related comorbidities are associated with insulin resistance (IR) [19-22]. Low grade adipose tissue inflammation contributes to the burden of IR [23,24]. However, the pathophysiology of IR is complex and multifactorial [25]. Thus, elucidation of the mechanisms leading to obesity associated IR is necessary to identify novel targets for the prevention and treatment of many IR driven conditions [1,26].

IGF System

The insulin-like growth factor (IGF) system is complex, consisting of IGF ligands (IGF-I and IGF-II), the IGF receptors (IGF-IR and IGF-IIR), and six high affinity IGF-binding proteins (IGFBPs) [7,27] Ample evidence indicates that the IGF system plays an important role in cell growth and proliferation [7,27,28] In addition to alteration in other metabolic pathways, perturbations in the IGF-I axis have been implicated in the pathogenesis of IR [28-31]. IGF-I has structural homology with insulin, and also promotes the peripheral uptake of glucose and fatty acids [32]. IGFBP-3, the major binding protein for IGF-I in circulation, forms the 150kDa ternary complex consisting of IGFBP-3, acid labile subunit (ALS) and IGF-I [33-35]. This ternary complex reduces the passage of IGF-I to the extravascular compartment to extend its half-life [36,37]. In addition to its role as a carrier protein, ample studies point to an IGF-IGF receptor independent action of IGFBP-3 in a variety of human diseases including asthma, other inflammatory diseases and cancer [7,27,32,37-42]. Moreover, a novel IGFBP-3 specific receptor (IGFBP-3R) has been identified, and it is expressed in a variety of human tissue and mediates IGFBP-3's intrinsic biological functions including anti-inflammatory functions [7,39,42].

IGFBP-3/IGFBP-3R Axis and Insulin Resistance

Current dogma of adipocyte biology indicates that visceral adipocytes not only function as a fuel tank for the storage of lipids and triglycerides but also play more active endocrine role through production of a variety of adipokines and cytokines including leptin, adiponectin, interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α) [43-49]. In obesity, visceral adipocytes enhance the inflammatory milieu by directly secreting pro-inflammatory cytokines and recruiting in situ inflammatory cells including macrophages and lymphocytes [50-53]. IGFBP-3 has been implicated in the pathogenesis of IR [8,54]. Interestingly, recent studies demonstrated that IGFBP-3, via activation of IGFBP-3R, inhibits cytokine-induced NF-κB activity, restore insulin signaling, and negates the TNF-α-induced inhibition of glucose uptake in human primary adipocytes [8]. However, these anti-inflammatory actions of IGFBP-3 appear to be dysregulated in obesity due to degradation of serum-circulating IGFBP-3 in obesity. Recent study has shown that individuals with obesity demonstrate increases in proteolytic IGFBP-3 fragments and IGFBP-3 protease activity, and corresponding decreases in functional intact IGFBP-3 levels when compared with their normal weight counterparts [8]. Furthermore, IGFBP-3 proteolysis positively correlates with adiposity parameters such as waist circumference, body mass index (BMI), fasting insulin, and insulin resistance index (HOMA-IR) in overweight and obese individual [8].

Obesity is associated with activation of neutrophils and the innate immune system [55,56]. Activated neutrophils secret proteinase 3 (PR3) involving in bacterial defense and regulating non-infectious inflammatory processes by modulating the activities of cytokines such as TNF-α, IL-1β, IL-8, IL-18 and IL-32 [57-61]. Recent studies suggest that neutrophil serine proteases (NSPs) such as PR3, neutrophil elastase (NE) and cathepsin G (CG), contribute to neutrophil-dependent inflammation and progression of chronic inflammatory disease including diabetes, cystic fibrosis and glomerulonephritis [62-66]. Conversely, NSP inhibitors such as α-1-antitrypsin (AAT) have been proposed as treatments in patients with chronic inflammatory diseases including diabetes, cystic fibrosis and ischemic heart disease [67-74]. Interestingly, recent studies reported that increased PR3 and IGFBP-3 fragments in the urine of diabetic patients and in the serum of obese individuals [75-77]. In addition, it has shown that PR3 represents an IGFBP-3 specific protease in the serum of obese individuals, whereas AAT completely inhibits PR3-induced IGFBP-3 proteolysis *in vitro* [75-77]. These findings strongly suggest that IGFBP-3 proteolysis induced by NSPs such as PR3 may result in loss of IGFBP-3R binding ability and subsequent its anti-inflammatory function, and further linking the NSP/IGFBP-3/IGFBP-3R axis in IR and T2DM.

Conclusion

The rapidly increasing prevalence of obesity, IR and T2DM continues to be a great health problem so that more effective preventive and therapeutic strategies are needed. Thus, a clearer understanding of pathophysiology and the mechanisms involved in obesity-associated IR is necessary to identify novel targets for the prevention and treatment of many IR-driven conditions. The chronic low-grade adipose tissue inflammation contributes substantially to the burden of IR. Recent findings on existence of functional IGFBP-3/IGFBP-3R system in insulin target cells and obesity-induced proteolysis of IGFBP-3 strongly suggest that this anti-inflammatory IGFBP-3/IGFBP-3R signaling plays a critical role during the processes of obesity-associated IR. In this respect, further investigation of the NSP/IGFBP-3/IGFBP-3R axis in obesity will warrant identification of diagnostic or prognostic value of IGFBP-3, IGFBP-3 proteolysis and NSPs, and therapeutic potential of IGFBP-3R agonists (IGFBP-3 and IGFBP-3 mimetics) and NSP inhibitors (AAT and novel small peptide inhibitors) in obesity-associated IR, T2DM and diabetes complications.

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