Beneficial metabolic activities of inflammatory cytokine interleukin 15 in obesity and type 2 diabetes

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Abstract In obesity, chronic inflammation is believed to induce insulin resistance and impairs adipose tissue function. Although this view is supported by a large body of literature, it has been challenged by growing evidence that pro-inflammatory cytokines may favor insulin sensitivity through induction of energy expenditure. In this review article, interleukin 15 (IL-15) is used as a new example to explain the beneficial effects of the pro-inflammatory cytokines. IL-15 is secreted by multiple types of cells including macrophages, neutrophils and skeletal muscle cells. IL-15 expression is induced in immune cells by endotoxin and in muscle cells by physical exercise. Its transcription is induced by transcription factor NF-κB. IL-15 binds to its receptor that contains three different subunits (α, β and γ) to activate JAK/STAT, PI3K/Akt, IKK/NF-κB and JNK/AP1 pathways in cells. In the regulation of metabolism, IL-15 reduces weight gain without inhibiting food intake in rodents. IL-15 suppresses lipogenesis, stimulates brown fat function, improves insulin sensitivity through weight loss and energy expenditure. In human, circulating IL-15 is negatively associated with body weight. In the immune system, IL-15 stimulates proliferation and differentiation of T cells, NK cells, monocytes and neutrophils. In the anti-obesity effects of IL-15, T cells and NK cells are not required, but leptin receptor is required. In summary, evidence from human and rodents supports that the pro-inflammatory cytokine IL-15 may enhance energy expenditure to protect the body from obesity and type 2 diabetes. The mechanism of IL-15 action remains to be fully uncovered in the regulation of energy expenditure.

Keywords inflammation; obesity; cytokine; energy expenditure; insulin resistance

Introduction

In obesity, white adipose tissue together with other tissue (liver and brain hypothalamus) has a low-grade chronic inflammation [1–9]. It is generally believed that the chronic inflammation contributes to systemic insulin resistance in the pathogenesis of type 2 diabetes. The concept was originally developed from mouse models and has been tested in patients in many clinical trials. However, most (70%) clinical studies failed to prove this concept in humans although the concept continues to receive support from rodent studies [10–13]. This status has been discussed in a couple of recent review articles including ours [14–16]. Although there is no consensus yet about the cause of discrepancy, emerging evidence suggests that some inflammatory molecules are required for the maintenance of energy expenditure (EE), which is called “beneficial activity” of inflammation by us [14]. We suggest that the controversy is likely a result of poor understanding of the beneficial effects of inflammation. We would like to address the controversy in this review article using the pro-inflammatory cytokine IL-15 as a new example. Pro-inflammatory cytokine IL-6 has been known for its activity in the induction of energy expenditure and protection of insulin sensitivity [17–19]. IL-6 will not be discussed here.

IL-15

IL-15 belongs to the 4-helix bundle cytokine family and uses β- and γ-chains of the IL-2 receptor (IL-2R) in the
signal transduction [20]. As a result, IL-15 shares many biological activities with IL-2, even though it has no sequence homology with IL-2. IL-15 is produced by multiple types of cells including macrophages, muscle cells, fibroblasts, epithelial cells, keratinocytes, astrocytes, and bone marrow stromal cells [20] (Fig. 1). In macrophages, IL-15 expression is induced by NF-κB activators such as LPS [21,22]. IL-15 gene promoter contains a NF-κB response element that induces IL-15 transcription upon NF-κB activation [21,22]. IL-15 expression in muscle myotubes is induced by treadmill running in healthy individuals [23], in which IL-15 may promote endurance and fuel supply as suggested by a study of muscle in mice [24]. IL-15 expression in muscle is likely regulated by growth hormone. It was reported in 2012 that IL-15 mRNA expression was enhanced in skeletal muscle after inactivation of growth hormone receptor (mGHRKO) by gene knockout in mice [25]. In the immune system, IL-15 induces differentiation of NK cells and various T cell subsets, including NK T cells and memory CD8 T cells. IL-15 is a potent inhibitor of several pathways of apoptosis in lymphocytes via induction of anti-apoptotic molecules. IL-15 blocks TNF-mediated cell death in fibroblasts by inhibition of the apoptotic cascade of TNF-receptor. IL-15 may be useful in the control of cell apoptosis and septic shock, in which TNF-α and IL-1 induce multiple organ dysfunction through cell apoptosis. IL-15 transgenic (Tg) mice are more tolerant to LPS and bacterial infection [26]. However, this activity is under debate as IL-15 deficient mice are also protected from septic shock [27]. IL-15 enhances septic shock in the presence of IL-12 [20].

**IL-15 receptor**

IL-15 receptor is formed by 3 subunits, α, β and γ [28] (Fig. 1). IL-5 binds to the α subunit and then activates the other two subunits (β and γ) [29]. The molecular cloning of murine IL-15R α chain was reported in 1995 [29]. The α subunit displays a high binding affinity to IL-15. The gene of α subunit has a complex biochemistry, encoding both membrane-bound and soluble forms which can modulate IL-15 secretion and bioactivity. The gene resides on human chromosome 10p, a location linked to obesity and type-2 diabetes [30]. The distribution of IL-15 and IL-15R α mRNA suggests that IL-15 may have biological activities distinct from IL-2.

IL-15 receptor may activate multiple signaling pathways in IL-15 target cells [20]. Those include JAK1/STAT3, JAK3/STAT5, Tyk/STAT6, PI3K/Akt, IKK/NF-κB, Ras/Raf/ERK and JNK/AP1 pathways (Fig. 1). In the IKK/NF-κB pathway, IL-15 induces the transcriptional activity of NF-κB to enhance gene expression in NK cells [31], myeloid cells [32,33], and endothelial cells [34]. The signal from IL-15 and α subunit interaction is mediated by the β and γ subunits into cells. IL-15 also activates the JAK/STAT signaling pathways in NK cells and CD8+ T cells, in which JAK1 and JAK3 mediate the phosphorylation of STAT3 and STAT5, respectively [28]. Activation of

![Cellular sources and signaling pathways of IL-15.](image.png)