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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- κ B. IL-15 binds to its receptor that contains three different subunits (α , β and γ) to activate JAK/STAT, PI3K/Akt, IKK/NF- κ B 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

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Compliance with ethics guidelines

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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- κ B activators such as LPS [21,22]. IL-15 gene promoter contains a NF- κ B response element that induces IL-15 transcription upon NF- κ B 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-15 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- κ B, Ras/Raf/ERK and JNK/AP1 pathways (Fig. 1). In the IKK/NF- κ B pathway, IL-15 induces the transcriptional activity of NF- κ B 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 PI3K/Akt, Ras/Raf and JNK/AP1 pathways may contribute to cell differentiation and proliferation in response to IL-15 [33,35]. PI3K/Akt pathway promotes glucose uptake and lipids synthesis in muscle cells.

Through the signaling pathways, IL-15 receptor induces production of a number of pro-inflammatory cytokines and chemokines, including MCP-1, IL-12, and TNF- α in myeloid cells [28]. IL-15 signaling *in vivo* has been shown to be critical for chemokine CCL5 (RANTES) production [33]. In a mouse model of contact hypersensitivity, 2,4-dinitro-1-fluorobenzene (DNFB) induced a significant reduction in inflammation and local production of CCL5 in IL-15R $\alpha^{-/-}$ mice compared with wild-type mice. IL-15 stimulation of T cells also has been shown to induce CCL5 production in a dose-dependent fashion *in vitro*, and the inhibition of IL-15 signaling in human dendritic cells leads to a significant decrease in the production of CCL5 by these cells [28].

IL-15 inhibits obesity

Plasma IL-15 level is negatively associated with visceral fat in human obesity [36]. IL-15 is expressed in human skeletal muscle, which may be a major source of plasma IL-15 [30]. IL-15 decreases lipid synthesis in preadipocytes *in vitro* and reduces white fat mass in rats, indicating that IL-15 may regulate adiposity (Fig. 2). The relation between skeletal muscle IL-15 mRNA expression, plasma IL-15, and adipose tissue mass was studied in 199 humans divided into four groups on the basis of obesity and type 2 diabetes [36]. In humans, the result of multiple regression analysis suggests a negative association between plasma IL-15 and total fat mass ($P < 0.05$), trunk fat mass ($P < 0.01$), and percent fat mass ($P < 0.05$), which is independent of type 2 diabetes. A negative association is also found between muscle IL-15 mRNA and obesity parameters. IL-15 reduces visceral fat mass, but not subcutaneous fat mass in mice [37]. The results indicate that IL-15 may regulate visceral fat mass in the muscle-fat cross talk.

IL-15 administration was reported to induce fat tissue shrinking without reducing muscle mass in obese mice in 2001 [37]. To test IL-15 effect in muscle, IL-15 was administered to adult rats for 7 days. While IL-15 did not change muscle mass or muscle protein content, IL-15 induced significant changes in the fractional rates of both muscle protein synthesis and degradation, with no a net change in protein accumulation. IL-15 administration resulted in a 33% decrease in white fat and a 20% decrease in circulating triacylglycerols, which was associated with a 47% lower hepatic lipogenic rate and a 36% lower plasma VLDL triacylglycerol content. No changes were observed in the rate of lipolysis after cytokine

administration. These findings indicate that IL-15 may inhibit lipogenesis in hepatocytes and adipocytes.

In 2009, it was reported that elevation of plasma IL-15 by overexpression of IL-15 in muscle led to a lean phenotype in transgenic mice [38]. To test IL-15 in the cross talk of muscle and fat tissue, two lines of transgenic mice were made to overexpress IL-15 mRNA in skeletal muscle. One of the transgenic lines exhibited an elevation of IL-15 in the circulation, which was associated with a significant reduction in body fat and an increase in bone mineral content. There was no alteration in lean body mass or other cytokines. The phenotype was observed in the male mice on chow diet or HFD (high fat diet), but not in female mice. Female mice with elevated serum IL-15 exhibited increased deposition of lean body mass on chow or HFD. The other line of Tg mice that did not have IL-15 elevation in serum did not exhibit such a lean phenotype. These findings indicate that muscle-derived circulating IL-15 can modulate adipose tissue in the control of metabolism.

IL-15 gene inactivation increases risk of obesity

To study IL-15 in obesity, mice with IL-15 overexpression and knockout were tested [39]. Overexpression of IL-15 (IL-15tg) was associated with lean phenotype whereas lack of IL-15 (IL-15^{-/-}) results in significant increase in adiposity without alteration in food intake. Interestingly, there were no differences in proinflammatory cytokines such as IL-6 and tumor necrosis factor- α (TNF- α) in serum between the overexpression and KO mice. However, the number of natural killer (NK) cells was increased in fat tissue of IL-15 overexpression mice compared to IL-15 KO mice. IL-15 treatment results in significant weight loss in the KO mice and diet-induced obese mice without a reduction in food intake. Fat pads are decreased in the overexpression mice and adipocyte shrinkage is observed. IL-15 treatment induces a reduction in lipid content in adipocytes. Treatment of differentiated human adipocytes with recombinant human IL-15 protein decreases lipid deposition. In the study, obese patients exhibit a lower serum IL-15 compared to lean individuals. These results clearly suggest that IL-15 may be involved in adipose tissue regulation.

IL-15 does not inhibit food intake

Food intake determines energy balance in the body. A reduction in food intake is often used in the control of obesity in calorie restriction and bariatric bypass surgery. An impact of IL-15 in food intake was investigated in mice. It was reported that IL-15 treatment did not reduce food intake in diet-induced obese mice where the antiobesity activity was observed for IL-15 [39]. In a different study, IL-15 was shown to reduce obesity through a leptin receptor-dependent mechanism [40]. IL-15 was studied in two genetic models of obesity: the leptin receptor-negative *fa/fa* Zucker rats and the leptin-deficient *ob/ob* mice. Infusion of IL-15 reduced adiposity in leptin-deficient *ob/ob* mice (that have leptin receptor) without a decrease in food intake. In contrast, the IL-15 activity was not observed in *fa/fa* Zucker obese rats, which lack leptin receptor. The author concluded that IL-15 reduces adiposity by direct interaction with IL-15 receptor in adipose tissue. All three subunits (α , β and γ) of the IL-15 receptor complex were found in white adipose tissue of rats or mice. The study

suggests that the IL-15 activity is dependent on leptin receptor as leptin receptor deficient rats did not respond to IL-15. Leptin reduces food intake by interaction with the leptin receptor in neuronal cells. Since IL-15 does not change food intake, the leptin receptor in neuronal cells may not involve in the IL-15 activity. The leptin receptor in peripheral tissue (fat, liver or muscle) may play a role in IL-15 activity. It remains unknown how the leptin receptor mediates the IL-15 activity.

IL-15 may enhance energy expenditure through brown fat

IL-15 administration was found to enhance UCP-1 and UCP-3 expression in brown fat in rats [41]. In the study, IL-15 treatment in rats led to a decrease in both white and brown fat (35% and 24%, respectively). In brown fat, mRNA content of thermogenic proteins (UCP1 and UCP3), lipid-related transcription factors (PPAR δ and PPAR α), fatty acid transport protein (FATP), mitochondrial transport [carnitine palmitoyl transferase-I (CPT-I and CPT-II)] and consumption of fatty acids were all increased as a consequence of the IL-15 treatment. The authors concluded that IL-15 may induce brown fat function to stimulate energy expenditure, which provides a mechanism for IL-15 activity in the control of obesity.

IL-15 induces fat oxidation and inhibits lipogenesis

IL-15 directly induces fatty acid oxidation in muscle [42] (Fig. 2). Chronic administration of IL-15 (100 μ g/kg body weight) to rats decreased the incorporation of lipid into adipose tissue and significantly increased the total (14 C) labeled CO₂ formation from 14 C-triolein. In incubated EDL muscle, IL-15 increased CO₂ formation from fatty acids by 39%. IL-15 treatment resulted in a significant increment in the gene expression of PPAR δ , a transcription factor with strong activity in the induction of lipid catabolism in skeletal muscle. IL-15 inhibits lipid synthesis (lipogenesis) in fat tissue and liver [43] (Fig. 2). IL-15 decreased lipogenic rate (per g of tissue) in both adipose tissue (53%) and liver (36%). The decrease in hepatic lipogenesis was associated with lower hepatic citrate levels (49%) and a reduced activity of lipogenic enzymes.

Glucose metabolism

IL-15 was reported to improve glucose metabolism and insulin sensitivity in DIO mice [44]. Administration of IL-15 significantly improves insulin sensitivity and oral glucose tolerance in DIO mice. The study suggests that IL-15 may be a novel therapeutic target for the treatment of obesity and its associated abnormal glucose regulation.

IL-15 in immune system

IL-15 in the regulation of immune cells is well documented in an early review article [20]. In a recent study [33], IL-15 exerts a variety of effects on the innate and adaptive immune systems. IL-15 is crucial for the survival, maintenance, and functions of NK cells, CD8⁺ memory T cells, and CD8 α ⁺ and TCR $\gamma\delta$ ⁺ intestinal intraepithelial lymphocytes. IL-15 promotes functional maturation of macrophages and dendritic cells (DCs) upon microbial infection. IL-15 is also important for promoting DC survival, delaying apoptosis in bone

marrow cells of lymphoid origin, and stimulating the proliferation of follicular DCs, myeloid (CD11b⁺) and lymphoid (CD11b⁻) bone marrow cells.

Anti-obesity effect of IL-15 is independent of NK or lymphocytes

In the immune system, a major activity of IL-15 is to induce NK cells and lymphocytes. These cells were tested in the anti-obesity effect of IL-15 [45]. NK cell accumulation was increased in adipose tissue of IL-15 overexpressing mice in the lean condition. The accumulation was reduced in obese IL-15^{-/-} mice. Acute IL-15 treatment resulted in fat loss in wild type mice, in which accumulation of NK, NKT, and CD3⁺ Tcells was observed in adipose tissue. A similar magnitude of fat loss was observed in mice with depletion of NK and NKTcells. The same result was observed in mice with lymphocyte deficiency (RAG2^{-/-}, γ c^{-/-}). Tissue slide analysis suggests that IL-15 induces adipocyte shrinkage. In the study, the fat loss was not associated with a reduction in food intake. These results suggest that NK cells or lymphocytes are not required for IL-15 inhibition of obesity (Fig. 2).

Summary

IL-15 is a proinflammatory cytokine with activities in the inhibition of obesity and in the improvement of glucose metabolism (Figs. 1 and 2). The mechanism is likely induction of energy expenditure by activating brown fat. IL-15 joins other pro-inflammatory cytokines including IL-1, IL-6 and IL-18 in the promotion of energy metabolism [14]. This activity of pro-inflammatory cytokines suggests that inflammation is a part of the control system of energy homeostasis. In terms of biological significance, the inflammatory cytokines coordinate energy supply and demand in inflammatory response, which is an energy consumption process to take care of stresses from tissue damage or infection. Inhibition of the cytokine activities may lead to a decrease in energy expenditure for weight gain. The metabolic activity of IL-15 further supports our hypothesis that chronic inflammation in obesity is a protective response to reduce energy surplus by promoting energy expenditure [14].

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Fig. 1.
Cellular sources and signaling pathways of IL-15.

Fig. 2.
Regulation of fat and glucose metabolism by IL-15.