Role of spleen-derived IL-10 in prevention of systemic low-grade inflammation by obesity

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Abstract. Obesity can be associated with systemic low-grade inflammation that leads to obesity-related metabolic disorders. Recent studies raise the possibility that the inflammation in hypothalamus, liver and white adipose tissue (WAT) contributes to the pathogenesis of diet-induced obesity. We focus on the role of interleukin (IL)-10, an anti-inflammatory cytokine produced from spleen in obesity because it is indicated that obesity decreases the expression of pro-inflammatory cytokines in spleen. Obesity results in decrease of IL-10 synthesis from spleen, probably due to reduction of B-cells expression by promoting oxidative stress and apoptosis in spleen. Splenectomy (SPX) aggravates the inflammatory response in hypothalamus, liver and WAT. These SPX-induced alterations are inhibited by systemic administration of IL-10. Moreover, in IL-10 deficiency, SPX had little effect on the inflammatory responses in these multiple organs. We show the role of spleen-derived IL-10 on inflammatory responses in obesity.

Key words: Obesity, Spleen, IL-10, Inflammation

1. Introduction

Obesity is associated with insulin resistance, diabetes, dyslipidemia, and hypertension. Collectively, these conditions comprise metabolic syndrome, which is believed to involve a low-grade chronic inflammation [1, 2]. Indeed, feeding of a high-fat diet (HF) results in tissue inflammation caused by recruitment and activation of macrophages, and subsequent local or systemic release of pro-inflammatory cytokines can induce insulin resistance [3, 4]. For example, HF feeding increases the expression of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-1β, and IL-6, in hypothalamus of the brain, which suggests that hypothalamic inflammation contributes to several effects in HF-induced obesity [5]. This low-grade chronic inflammation promotes “the irreversible remodeling in the organization” by the adaptive failure of the cell during a long-term stress reply and develops in the functional disorder of multiple organs, and finally causes the lifestyle-related disease such as metabolic syndrome. Although the mechanisms underlying obesity-associated inflammation in peripheral tissues, such as liver and WAT as well as brain, are well characterized, the primary cause of obesity-induced inflammation is not well understood. In this review, we focus on spleen-derived IL-10 synthesis, based mainly on recent publications, including our own.

2. Relation between Obesity and Spleen

The spleen is the largest lymphoid organ in the body and plays an important role in host immune function and blood filtration via removal and destruction of damaged erythrocytes [6]. Splenic gene expression of pro-inflammatory cytokines, such as TNF-α and IL-6, is decreased in the setting of obesity [7]. In contrast, IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of pro-inflammatory cytokines. IL-10 is synthesized within multiple organs, including spleen. Large amounts of IL-10 are produced from activated B-cells that mature in the marginal zone of spleen. Recent studies suggest that IL-10-producing B-cells play a regulatory role in suppressing harmful immune responses [8]. In fact, obesity is associated with low IL-10 production capacity [9, 10].
3. Effects of HF Feeding on the Spleen

We demonstrate that HF feeding down-regulates the expression of CD20, a surface molecule present on B-cells in spleen, indicating that HF feeding reduces the expression of B-cells that play a large role in the immune response including IL-10 synthesis. Moreover, levels of 4-HNE, a marker of oxidative stress, and apoptosis percentage are elevated in the marginal zone of spleen by HF feeding, implying that HF-induced obesity leads to reduction of B-cells expression by promoting oxidative stress and apoptosis of B-cells in spleen [11]. Interestingly, HF feeding attenuates the expression of pro-inflammatory cytokines (TNF-α, IL-1β) as well as IL-10 in the spleen whereas decreases serum levels of IL-10, but not pro-inflammatory cytokines. It is indicated that serum levels of pro-inflammatory cytokines are probably maintained by induction from other organs, such as liver and WAT when the expression of these pro-inflammatory cytokines from spleen is downregulated by HF feeding. On the other hand, serum IL-10 levels remained low even during HF feeding, suggesting that large amounts of serum IL-10 might be derived from spleen [11].

4. Effects of Splenectomy

4.1 Energy regulation

It is well known that hypothalamic inflammation may exert a paradoxical effect on energy metabolism [12]. For example, hypothalamic inflammation by obesity promotes hyperphagia and body weight gain, while hypothalamic inflammation induced in response to a systemic inflammatory process (e.g. bacterial sepsis) results in anorexia and weight loss. Prior study has demonstrated that, in the context of sepsis, IL-10 is synthesized mainly by peritoneal neutrophils, while splenic leukocytes produce comparatively little IL-10 [13]. We confirm that the reduction of spleen-derived IL-10 by SPX gives rise to activation of microglia and induction of hypothalamic inflammation, which may explain why anorexia and weight loss occur in the setting of sepsis-induced hypothalamic inflammation [11]. Furthermore, we suggest that mild reduction of spleen-derived IL-10 by HF feeding leads to hyperphagia, whereas severe reduction of splenic IL-10 by SPX causes hypophagia [11]. It is also observed that TNF-α can exert a dual effect in hypothalamus, depending on the dose employed; central injection of high dose TNF-α had an anorexigenic effect, while central injection of low dose TNF-α had an orexigenic effect [14]. Moreover, other study presents that intrahypothalamic infusion of recombinant IL-10 blocks IKK/NF-κB signaling and endoplasmic reticulum stress and restores Akt and STAT3 phosphorylation promoting anti-obesity, indicating that modulation of hypothalamic IL-10 expression could constitute to inhibition of hypothalamic inflammation and endoplasmic reticulum stress related to obesity [15]. Thus, we presume that this paradox between hypothalamic inflammation and energy metabolism might be due to the difference in the magnitude of IL-10 induction from spleen (Fig. 1).

4.2 Liver and WAT

Inflammation is generally accepted as being closely related to fat accumulation in liver and WAT [16]. SPX facilitates both inflammatory responses and fat accumulation in liver, and systemic IL-10 treatment inhibits these SPX-induced responses, supporting that TNF-α expression in the liver is related to hepatic inflammation and fattiness [17, 18]. Meanwhile, SPX reduces fat accumulation but promotes inflammatory responses in WAT. Furthermore, IL-10 treatment restores the SPX-induced reduction of fat accumulation whereas suppressed SPX-induced inflammation in WAT [17]. These findings suggest that SPX-induced inflammation may be independent of fat accumulation in WAT, which is very interesting. One possible explanation is that the reduction of spleen-derived IL-10 could shift

![Fig. 1 Hypothalamic inflammation exerts a dual effect in energy regulation, depending on the magnitude of IL-10 induction from spleen.](image-url)
HF-feeding induced fat accumulation from WAT to liver although the detailed mechanism is uncertain. In any case, spleen-derived IL-10 has a protective effect against pathological inflammation in liver and WAT, supporting previous reports that treatment with the anti-TNF-α antibody infliximab significantly reduces fat accumulation in liver of obese rats and that exogenous IL-10 improves liver fibrosis caused by carbon tetrachloride [19, 20]. Taken together, IL-10 originating in the spleen may prevent the low-level chronic inflammation induced by obesity in liver and WAT.

4.3 Glucose metabolism

We observe that SPX induces impaired glucose tolerance as well as reduction of serum adiponectin levels, and systemic IL-10 treatment suppresses these SPX-induced alterations, compatible with other findings that TNF-α represses the synthesis of adiponectin in adipocytes [21, 22]. It is indicated that spleen-derived IL-10 might improve glucose metabolism by inhibiting the production of pro-inflammatory cytokines, including TNF-α. In fact, the inhibition of TNF-α activity by infliximab improves insulin signaling in the liver of HF-fed rats [19]. Moreover, depleting Kupffer cell (KC) in liver prevents the development of insulin resistance, and KC-derived TNF-α plays a role in mediating the detrimental effects of KCs on insulin action [23].

5. SPX-induced Inflammatory Response in IL-10 Deficiency

Although the spleen is the largest lymphoid organ, it is possible that IL-10 derived from other lymphoid organs, such as mesenteric lymph nodes (MLN), might also be decreased during HF feeding. A previous study reported that obese rats induced higher concentrations of IL-10 in MLN compared to lean rats, but produced approximately 25% lower concentrations of IL-10 in the spleen [24]. For this reason, we focused on spleen-derived IL-10 in the present study.

We examine whether IL-10 deficiency would affect SPX-induced inflammation in hypothalamus, liver and WAT using IL-10 deficient (IL-10KO) mice. It is observed that food intake and body weight decrease in IL-10KO mice compared with wild-type mice, in agreement with previous findings that spontaneous weight loss occurs in IL-10KO mice [25]. However, SPX-induced hypophagia and body weight loss observed in wild-type mice are not seen in IL-10KO mice, although IL-10 treatment restores these alterations in both SPX-treated mice [11]. These results indicate that spleen-derived IL-10 affects the regulation of energy metabolism. Furthermore, we identify that SPX-induced inflammation in liver and WAT observed in wild-type mice are not seen in IL-10KO mice and IL-10 treatment also inhibits SPX-induced inflammatory responses in both organs [26]. Therefore, spleen-derived IL-10 may be closely related to inflammatory responses in multiple organs (Fig. 2). In addition, the SPX-induced abnormalities in glucose metabolism observed in wild-type mice are not seen in IL-10KO mice, and the administration of IL-10 to both SPX-treated mice improves glucose tolerance, indicating that spleen-derived IL-10 is be also involved in glucose metabolism [26].

6. Summary

In conclusion, we propose that obesity reduces IL-10 synthesis from spleen and spleen-derived IL-10 plays a critical role in the inflammation of multiple organs and insulin resistance in the obese state. Interestingly, mild reduction of spleen-derived IL-10 by obesity causes hyperphagia, while severe reduction of splenic IL-10 by SPX induces hypophagia. Although additional studies are required to determine why obesity elicits an inflammatory response, we note that targeting the spleen may be a potential therapeutic strategy for treating metabolic syndrome.
References


