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LIGHT/TNFSF14 enhances adipose tissue inflammatory responses through its interaction with HVEM

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ABSTRACT

Obesity-induced adipose tissue inflammation is characterized by increased macrophage infiltration and cytokine production, and is associated with metabolic disorders. LIGHT/TNFSF14, a member of the TNF superfamily, plays a role in the development of various inflammatory diseases. The purpose of this study was to examine the involvement of soluble LIGHT (sLIGHT) in obesity-induced adipose tissue inflammatory responses. LIGHT gene expression on macrophages/adipocytes was upregulated by treatment with obesity-related factors. sLIGHT displayed chemotactic activity for macrophages and T cells, and enhanced inflammatory cytokine release from macrophages, adipocytes, and adipose tissue-derived SVF cells. The sLIGHT-induced inflammatory responses were blunted by neutralizing anti-HVEM antibody or knockout of HVEM, a receptor for sLIGHT. These findings indicate that sLIGHT enhances adipose tissue inflammatory responses through its interaction with HVEM.

1. Introduction

Obesity-induced inflammation is closely associated with the development of metabolic complications such as type II diabetes and atherosclerosis. Recent progress has led to the identification of several adipose tissue inflammatory components such as immune cells (e.g. macrophages/T cells) and cytokines/chemokines that account for obesity-induced inflammatory responses and insulin resistance [1–3]. However, the intrinsic factors that trigger adipose tissue inflammation are not yet completely understood.

LIGHT/TNFSF14 (lymphotoxin-related inducible ligand that competes for glycoprotein D binding to herpes virus entry mediator on T cells) is a member of the TNF superfamily (TNFSF) that binds to the membrane receptor HVEM/TNFRSF14 (herpes simplex virus glycoprotein D for herpes virus entry mediator). It is widely and constitutively expressed in various human and rodent tissues, and strongly expressed on resting and activated T cells, B cells, and monocytes [4]. The interaction between LIGHT and its receptor is involved in various inflammatory processes such as inflammatory bowel disease, rheumatoid arthritis and nephritis [5–8]. Recent studies have shown that soluble LIGHT (sLIGHT) promotes atherogenesis by inducing pro-inflammatory cytokines and matrix metalloproteinases in macrophage/foam cells and endothelial cells [9]. More recently, involvement of LIGHT (sLIGHT) and HVEM has been suggested in human obesity and metabolic disorders [10,11], but the mechanism by which sLIGHT mediates adipose tissue inflammatory responses remains elusive.

In this study, we demonstrate that sLIGHT plays a crucial role in adipose tissue inflammatory responses by enhancing macrophages/T-cell infiltration and activating the cells to release inflammatory cytokines. The inflammatory action of sLIGHT is mediated by interaction with its receptor HVEM. LIGHT and HVEM are potential targets for modulating obesity-induced adipose tissue inflammatory responses.

2. Materials and methods

See Supplementary material [19,20].

2.1. Statistical analyses

Data are presented as means ± S.E.M. Statistical analysis was performed using ANOVA and Duncan's multiple-range test. Differences were considered to be significant at $P < 0.05$.

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3. Results

3.1. LIGHT/HVEM gene expression in macrophages, adipocytes, and adipose tissue

To test whether LIGHT expression is associated with adipose tissue inflammatory responses in obesity, we treated macrophages and adipocytes with obesity-related factors such as free fatty acid (palmitate), oxidative stress (hydrogen peroxide), and adipose tissue-conditioned medium. Free fatty acid and oxidative stress enhanced LIGHT gene expression in 3T3-L1 adipocytes as well as Raw264.7 macrophages (Fig. 1A and B). Adipose tissue-conditioned medium prepared from obese mice also upregulated LIGHT gene expression in the macrophages (Fig. 1B). Expressions of HVEM gene were also stimulated by free fatty acid and/or adipose tissue-conditioned medium in adipocytes, macrophages, and adipose tissue-derived SVF cells (Fig. 1A–C).

We further examined whether the expression of HVEM or its ligand LIGHT in adipose tissue is altered in obese condition. C57BL/6 mice were fed a high-fat diet (obese mice) or a regular diet (lean mice) for 10 weeks, and using RT-PCR analysis the expression levels of HVEM and LIGHT in the adipose tissue of the obese and lean mice were measured. LIGHT mRNA level in adipose tissue was significantly higher in the obese mice than the lean control mice (Fig. 1D), and HVEM mRNA level was also upregulated in the obese mice (Fig. 1D). Additionally, we also examined coinhibitory receptors such as B and T lymphocyte attenuator (BTLA) and CD160 that bind to HVEM. Interestingly, BTLA mRNA level was significantly downregulated in the obese adipose tissue, but CD160 was not (Fig. 1E).

3.2. Chemotactic activities of sLIGHT for T cells and macrophages

Since the accumulation of T cells and macrophages in adipose tissue is crucial for adipose tissue inflammatory responses, we examined whether sLIGHT can induce macrophage/T cell infiltration. sLIGHT promoted the infiltration of Raw 264.7 macrophages (Fig. 2A) and peritoneal macrophages (Fig. 2B) as well as T cells (CD4+ and CD8+) (Fig. 2C) in a dose dependent manner. Adipose tissue-conditioned medium, which induced macrophage and T cell migration, was significantly more effective in inducing cell migration when sLIGHT was added (Fig. 2D). These findings suggest that adipose-derived sLIGHT may play a role in enhancing macrophage/T cell infiltration, and thus participate in adipose tissue inflammatory responses.

3.3. Effect of sLIGHT on cytokine/chemokine production by macrophages and adipocytes

To examine the effect of sLIGHT on inflammatory cytokine release from adipose cells, macrophages (Raw 264.7) and adipocytes (3T3-L1) were treated with sLIGHT and cytokine release was measured. sLIGHT treatment increased TNFα and IL-6 release from macrophages (Fig. 2E), MCP-1 and IL-6 from adipocytes (Fig. 2F), and MCP-1 and IL-6 from adipose tissue-derived SVF cells (Fig. 2G). This indicates that adipose tissue-derived sLIGHT may enhance inflammatory responses in obesity in an autocrine and/or paracrine manner.

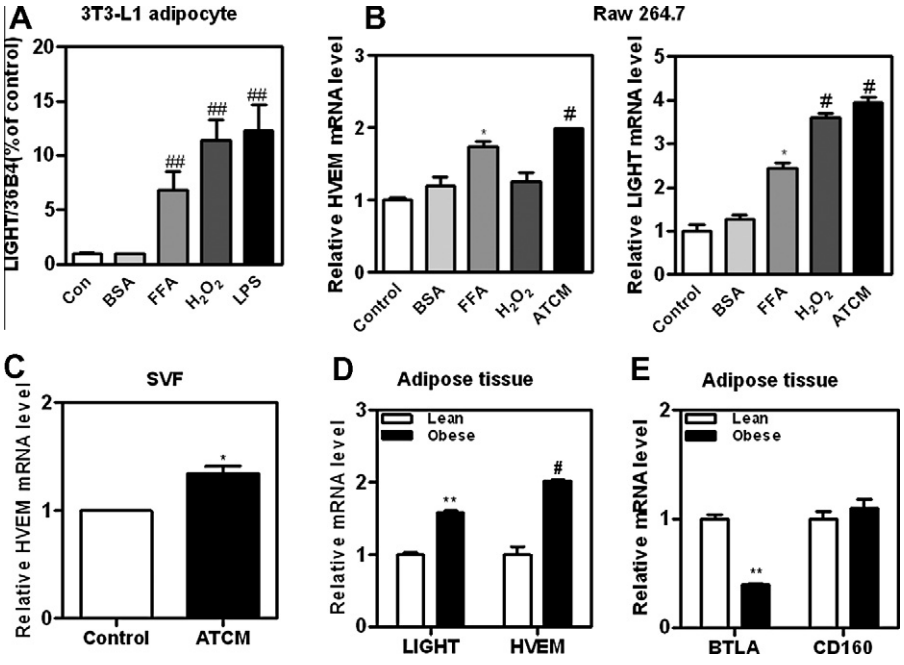

Fig. 1. Upregulation of LIGHT and/HVEM on macrophages and adipocytes by obesity-related factors and adipose tissue-conditioned medium. Macrophages (Raw 264.7), adipocytes (3T3-L1), and adipose tissue-derived SVF cells were treated with obesity-related factors (H_2O_2 50 μM, free fatty acid 500 μM) and/or adipose tissue-conditioned medium. Free fatty acid (palmitate) was prepared in ethanol containing bovine serum albumin (BSA, 50 μM). (A) LIGHT mRNA expression levels in adipocytes (3T3-L1) determined by semiquantitative reverse transcriptase-PCR analysis. 3T3-L1 adipocytes were treated with obesity-related factors for 24 h. Levels of mRNA were normalized to levels of 36B4 mRNA. Levels of HVEM or LIGHT mRNA in (B) macrophages or (C) adipose tissue-derived SVF cells were measured by a real-time reverse transcriptase-PCR analysis. Raw 264.7 macrophages were treated with obesity-related factors for 3 h. Levels of mRNA were normalized to levels of β-actin mRNA. Data represent results of three independent experiments. Values are means ± S.E.M. $^{*}P < 0.05$, $^{\#}P < 0.005$, $^{\#\#}P < 0.001$ compared to untreated control. Levels of (D) LIGHT, HVEM, (E) BTLA, and CD160 mRNAs in the epididymal adipose tissue of obese and lean mice. Levels of mRNA were estimated by real-time reverse transcriptase-PCR. Data are means ± S.E.M. of four animals for each group. $^{**}P < 0.01$, $^{\#}P < 0.005$ compared to the lean control.