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IL-17 IN OBESITY AND ADIPOGENESIS

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Abstract

The pro-inflammatory cytokine interleukin (IL)-17 (also known as IL-17A) has been associated with induction of tissue inflammation. Obese individuals exhibit many symptoms of chronic low-grade inflammation, suggesting that IL-17A may impact adipose tissue. However, the role of IL-17A in obesity is largely unexplored. Emerging studies indicate that obesity selectively promotes expansion of the Th17 T-cell lineage, exacerbating disease in murine models of autoimmunity such as EAE and colitis. Human studies support this concept, as new clinical studies suggest that IL-17A is expressed at elevated levels in obese individuals. Conversely, however, an anti-adipogenic role for IL-17A is becoming evident, and therefore the interconnections between IL-17A and fat metabolism may be quite complex. Here, we consolidate the potential implications of IL-17 in relation to obesity and describe the emerging data regarding the role of IL-17A in adipose tissue.

Introduction

The recently discovered T helper 17 (Th17) cells represent a novel subset of CD4 effector T cells. The hallmark cytokine of Th17 cells, Interleukin (IL)-17A, is the first member of a family of six pro-inflammatory cytokines: IL-17A through IL-17F (1). IL-17A signals through a receptor composed of IL-17RA and IL-17RC. Since receptors for IL-17A are distributed ubiquitously, Th17 cells (and other IL-17A-producing cells (2) have been implicated in interactions between the immune system and somatic tissues (3, 4). IL-17A is involved in tissue inflammation by release of other pro-inflammatory cytokines and inducing neutrophil chemotaxis (5). New evidence indicates that the biological roles of IL-17A include several non-immune functions, which have yet to be thoroughly explored. Hence, we review the effects of IL-17A on adipose tissue and the implications for obesity and inflammation.

Connections between obesity and inflammation

Adipose tissue, apart from being a storage depot for lipids, plays a significant role in the integration of endocrine, metabolic, and inflammatory signals (6, 7). Adipocytes form the functional units of adipose tissue and produce various pro-inflammatory cytokines including IL-6, IL-8, TNF- α , IL-10 and IL-18 (6, 8, 9), potentially linking fat and inflammation. Adipocytes and their precursors interact with the immune system, as revealed from numerous studies on inflammation in obesity and other metabolic diseases (10, 11). By virtue of its production by adaptive and innate cells and its actions on somatic tissues, IL-17A may serve as a significant link between adipose tissue and inflammatory immune responses.

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Obesity in many senses is considered to be an inflammatory predisposition. For example, low levels of chronic inflammation and macrophage infiltration into adipose tissue are associated with obese conditions (12). Obesity is also noted to predispose to autoimmune disorders, including inflammatory bowel disease (IBD) and psoriasis (13, 14). The Th17 lineage and IL-17A are now recognized to play detrimental roles in a wide variety of autoimmune and inflammatory conditions, such as IBD, psoriasis, systemic lupus erythematosus (SLE) and rheumatoid arthritis (15-18). Therefore it is compelling to identify and understand the interface between the pro-inflammatory cytokine such as IL-17A and obesity.

Thus far only a few reports explore the role of IL-17A in conjunction with adipogenesis or obesity, but the ubiquitous nature of IL-17A in inflammation suggests this is only the tip of the iceberg. This review discusses current findings in relation to the potential association between obesity and Th17 expansion and the effects stimulated by IL-17A on adipogenesis in various model systems (Table 1).

Obesity promotes expansion of Th17 cells and subsequent IL-17 production

Obesity is associated with a state of chronic low-grade inflammation, as illustrated by increased levels of acute-phase proteins and pro-inflammatory mediators in serum of obese individuals compared with lean subjects (6). Under obese conditions, adipose tissue contributes a significant proportion of circulating serum IL-6 (19). IL-6 expression is associated with diet-induced obese mice (DIO) as well as in obese humans (20, 21). Furthermore, IL-6 is required for the differentiation of naïve CD4 T cells into the Th17 lineage (22, 23), and is a major downstream gene target of IL-17A (24, 25).

Accordingly, the association of IL-6 with obesity has prompted recent studies to evaluate a connection between obesity and IL-17A-mediated autoimmunity, in particular trinitrobenzene sulfonic acid (TNBS)-induced colitis (a model of IBD) and experimental autoimmune encephalomyelitis (EAE, a model of multiple sclerosis) (Fig. 1) (26). In DIO, mice express higher numbers of Th17 cells, while the sizes of CD4⁺, IFN γ ⁺ (Th1), Foxp3⁺ regulatory T cells (Tregs) and GATA⁺ Th2 cell pools were unaffected, indicating that obesity specifically predisposes to induction of Th17 cells. Following immunization with myelin oligodendrocyte glycoprotein 35-55 (MOG₃₅₋₅₅), a well-characterized target antigen used in EAE, DIO also increased Th17 numbers dramatically. However, IL-6-deficient DIO mice did not have enhanced Th17 responses, indicating that IL-6 is crucial for polarizing Th17 responses in this model. Similarly, in TNBS colitis (27), enhanced Th17 responses that were associated with more severe disease outcomes (Table 1, Fig. 1) (26). These intriguing data suggest that obesity predisposes to the generation of Th17 responses at least in part via IL-6, which may in turn exacerbate autoinflammatory diseases such as MS and colitis.

Leptin is an IL-6-family cytokine secreted by adipocytes. Leptin plays a key role in fat turnover, weight control and satiety and also acts as an immunostimulatory molecule with both pro- and anti-inflammatory properties (28, 29). In Th17-mediated inflammation models such as EAE, collagen induced arthritis (CIA), and autoimmune hepatitis, leptin is pro-inflammatory (30, 31). However in inflammatory models that are independent of adaptive immune responses, leptin shows anti-inflammatory properties (32). Murine zymosan-induced (ZY) peritonitis is a well studied model of acute inflammation (33). Leptin-deficient mice (*ob/ob*) have an exacerbated and prolonged inflammatory response to ZY-induced peritoneal inflammation, associated with high levels of IL-6 (29). Hence, leptin appears to play a protective role exhibiting anti-inflammatory properties during ZY-induced peritonitis in mice. Using the ZY-induced peritoneal inflammation model of acute inflammation, a

recent study further probed whether the increase in IL-6 levels in leptin-deficient *ob/ob* and DIO mice was Th17-dependent (Table 1). Pini and Fantuzzi (34) found that IL-17A levels were increased in obese mice in response to ZY, which coincided with increased IL-6 levels. Neutralization of IL-17A in ZY-treated obese mice also resulted in decreased IL-6. However, neutralization of IL-6 surprisingly did not reduce the levels of IL-17 in the *ob/ob* mice, thus de-linking IL-6 in this setting.

Although IL-17 is traditionally thought to be expressed by CD4⁺ Th17 lymphocytes, the cellular source of IL-17A in this acute inflammatory model was reported to be neutrophils, based on intracellular flow cytometry. This issue remains controversial, as most other groups fail to find that neutrophils are a bona fide source of IL-17A. Indeed, this observation contrasts with other studies where IL-17A production is enhanced in CD4⁺ T cells during DIO (26). Regardless of its source, neutralization of IL-17A in ZY-treated obese mice resulted in decreased neutrophilic recruitment, correlating to decreased levels of neutrophil-recruiting chemokines such as CXCL1 and CXCL2. IL-17A is a strong inducer of CXC chemokines and subsequent neutrophil infiltration, and IL-17-deficiency is associated with marked neutrophil defects *in vivo* (35). New clinical studies also suggest a potential role for IL-17A in obesity (36). Data in this report show that obese women exhibit increased levels of circulating IL-23 and IL-17, which is statistically independent of leptin or other inflammatory factors such as macrophage migration inhibitory factor (MIF) (36). Interestingly, under inflammatory conditions polarized human Th17 cells have been shown to adhere to mesenchymal stem cells, which leads to their conversion to a Treg-like phenotype (37). Thus in the context of an inflammatory environment, differentiated Th17 cells may exhibit plasticity. However, this is at odds with the idea that obesity induces a pro-inflammatory state, and therefore there seems to be a more complex relationship that warrants much more investigation.

IL-17A inhibits adipogenesis

Unlike classic proinflammatory mediators such as TNF- α and IL-6, T-cell-derived cytokines such as IL-17A and interferon- γ (IFN- γ) have not been investigated extensively in the context of obesity (10, 38). Data from two recent studies indicate that IL-17A inhibits adipogenesis, suggesting an unexpected suppressive role for this cytokine in fat development (Table 1, Fig. 2). IL-17RA^{-/-} mice are known anecdotally to be overweight. While investigating the role of IL-17RA in osteoporosis, our group discovered a surprising anti-adipogenic effect of IL-17A (39). Specifically, a mouse model of osteoporosis was employed to evaluate the role of IL-17A signaling in bone loss caused by estrogen deficiency (induced by ovariectomy, OVX). Since IL-17A drives bone loss in CIA and also induces expression of cytokines known to promote bone loss in osteoporosis models, it has long been presumed in the field that IL-17A would likely promote systemic bone loss following OVX. However, unexpectedly IL-17RA^{-/-} mice showed accelerated systemic and spinal bone loss, which was concomitant with significant weight gain. Phenotyping analysis of serum revealed elevated leptin levels in IL-17RA^{-/-} mice subjected to OVX (39). Thus, the role of IL-17A in regulating bone is more complex than might be inferred from its activities in RA models, and these results hinted at a connection to fat metabolism.

Although leptin promotes satiety, obesity is often associated with leptin resistance and elevated leptin levels (40). Hence the high basal levels of leptin in IL-17RA^{-/-} mice may reflect an altered metabolism that predisposes to obesity. Leptin has been shown to cause bone loss through a central pathway in the hypothalamus (40). Conversely, leptin can be bone-protective through a peripheral pathway (40, 41). Since the accentuated bone loss in the IL-17RA^{-/-} mice correlated with elevated leptin, one possible mechanism is that leptin acts via the central pathway to trigger increased bone loss. According to this model, IL-17A

would be expected to inhibit leptin expression. Indeed, IL-17A (and the closely related cytokine IL-17F) both downregulated adipogenesis and subsequent leptin production in the 3T3-L1 adipocyte-differentiation system (39). Consistently, IL-17A impaired adipocyte differentiation in human mesenchymal stem cells (MSC) (42). Intriguingly, IL-17A was found to accelerate differentiation of human MSC into mature osteoblasts (43). Together, these observations suggest that IL-17A can skew MSC development. Hence, the balance of MSC differentiation in IL-17RA^{-/-} mice appears to be tipped in favor of adipogenesis rather than osteoblastogenesis during bone remodeling, ultimately favoring accelerated bone destruction in the context of OVX (Fig 2).

Mechanisms for inhibition of adipocyte differentiation by IL-17A

a. C/EBP β

IL-17A has been implicated as a possible player in the crosstalk between adipose tissue and Th17 associated immune responses, but the detailed mechanisms remains poorly defined. Crucial transcription factors that promote adipocyte differentiation include CCAAT/Enhancer Binding Protein (C/EBP) β , C/EBP δ and peroxisome proliferator-activated receptor γ (PPAR γ), among others (44, 45). During adipogenesis, C/EBP β undergoes sequential phosphorylation at three sites in its internal regulatory domain (Thr¹⁸⁸, Ser¹⁸⁴ and Thr¹⁷⁹) (46). Despite its inhibitory role in adipogenesis, IL-17A causes increased abundance of both C/EBP β and C/EBP δ in osteogenic and adipogenic cell lines (24, 25, 47). Moreover, IL-17A induces phosphorylation of C/EBP β on Thr¹⁸⁸ and Thr¹⁷⁹ in the adipogenic ST-2 cell line (48). Thus, it is unclear how IL-17A acts to inhibit adipogenesis while paradoxically activating the adipogenic potential of C/EBP β . Alternate transcription factors may be implicated downstream of IL-17A signaling leading to the inhibition of differentiating adipocytes, but this has not yet been explored in any detail.

b. COX-2

In studies of adipogenic differentiation of human MSCs, induction of cyclooxygenase 2 (COX-2) was proposed to be at least partially responsible for the inhibitory effect of IL-17A on differentiation. In this study, IL-17A treatment of differentiated adipocytes led to increased COX-2 mRNA levels and subsequently elevated prostaglandin E2 (PGE₂). Moreover, COX-2 inhibition reduced the inhibitory effects of IL-17A in this setting (42). PGE₂ has been shown to inhibit adipocyte differentiation in mammalian adipocytes (49). Since human adipocytes express PGE₂ receptors (50), PGE₂ could potentially regulate adipocyte differentiation in either an autocrine or paracrine manner.

IL-17A promotes IL-6 production in differentiated adipocytes

IL-17A influences production of pro-inflammatory cytokines from adipose tissue as well as other mesenchymal cell types (5, 51). Despite the fact that IL-17A stimulation of IL-6 is a prominent response in most somatic cells, the role of IL-17A on regulation of IL-6, if any, during adipogenesis inhibition remains unclear (19). Results from Shin et al, (42) showed significantly lower levels of IL-6 in differentiated adipocytes compared to undifferentiated MSCs (Table 1, Fig 2). This dampening of IL-6 expression could be due to phosphorylation of C/EBP β during differentiation. Phosphorylation of C/EBP β is required for adipocyte differentiation, but the modification also downregulates C/EBP β -responsive genes such as *il6* (46, 48). However, in human MSC cultures, IL-17A triggers a significant rise in the levels of IL-6 in differentiated adipocytes (42). This increased IL-6 may favor Th17 cell differentiation, which may in turn lead to IL-17A-induced IL-6 upregulation. Although IL-17A induces IL-6 expression in many somatic tissue cells, it remains unclear whether IL-17A can modulate obesity and metabolic status, or whether the increase in IL-6 levels in the adipose tissue under conditions of obesity affects differentiation of naïve T lymphocytes.

Summary and Future Perspectives

Given the close proximity of the adipose tissue and lymphatic tissue, adipocytes as well as their precursors interact intimately with the immune system. Adipocytes not only produce adipogenic cytokines, but can participate in the regulation of the immune system via secretion of cytokines such as IL-6. In turn, inflammatory cytokines such as IL-6 and IL-17A regulate the differentiation of adipocytes and their capacity to secrete adipokines and chemokines. Emerging studies reveal a role for IL-17A in obesity, and the observations made in rodents are probably relevant models of human disease. Furthermore, IL-17A inhibits adipocyte development in both murine and human systems. These findings in concert indicate that IL-17A mediates many important interactions between adipose tissue and the immune system.

Understanding the role of IL-17A in metabolic processes has direct clinical implications. In particular, clinical trials using anti-IL-17 therapies are underway for treating rheumatoid arthritis, psoriasis and other autoimmune conditions (52). Although this strategy shows promise for alleviating disease, reducing IL-17A may also cause complications with respect not only to opportunistic infections but also obesity.

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Abbreviations

C/EBP	CCAAT/Enhancer Binding Protein
CIA	collagen-induced arthritis
DIO	diet-induced obesity
EAE	experimental autoimmune encephalomyelitis
IBD	inflammatory bowel disease
MSC	mesenchymal stem cell
OVX	ovariectomy
PPARγ	peroxisome proliferators-activated receptor γ

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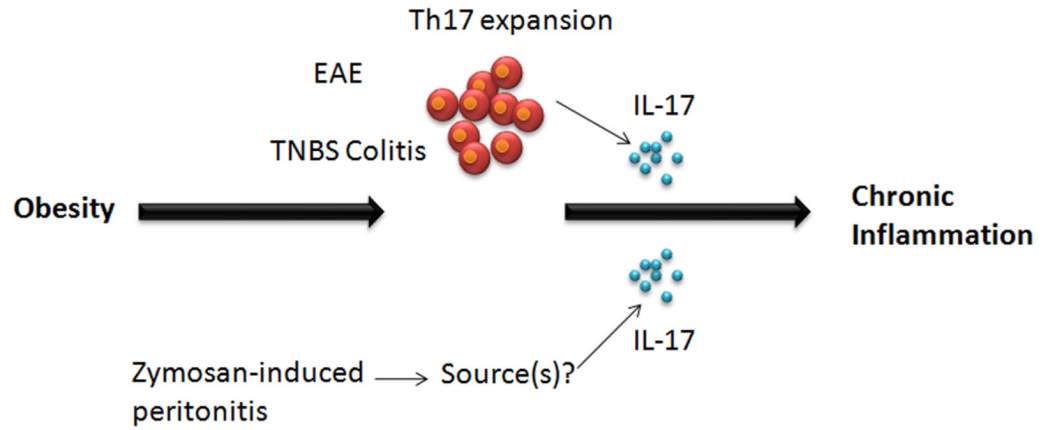


Figure 1. Effects of IL-17A during acute inflammation associated with obesity

(A) T-cells from diet-induced obese (DIO) mice expand Th17 cell pools and produce progressively more IL-17 than lean littermates, in what has been shown to be an IL-6-dependent process. The increased Th17 bias is associated with more pronounced autoimmune disease during EAE and trinitrobenzene sulfonic acid colitis. In both models DIO mice developed more severe early autoimmune disease, with increased pools of IL-17⁺ T-cells (26). (B) Levels of IL-17A in peritoneal fluid in response to ZY are elevated in obese leptin-deficient *ob/ob* mice compared with lean animals. IL-17A is increased in obese mice during acute inflammation and contributes to exacerbation of inflammatory responses, but the cellular sources of IL-17A remain controversial (34).

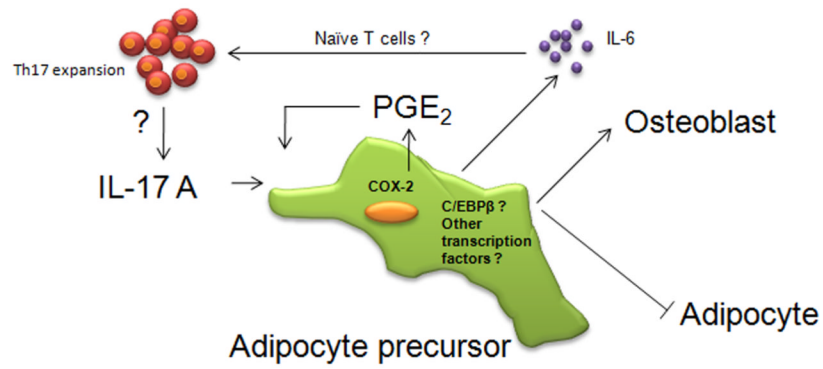


Figure 2. Model for inhibition differentiation of adipocytes by IL-17A

IL-17A promotes mesenchymal stem cells to undergo osteoblastogenesis and inhibit adipogenesis (39, 43). IL-17A exhibits the inhibitory effect on adipogenesis in part by the secretion of PGE₂ via COX-2 induction in differentiated adipocytes (42). During the inhibition of adipogenesis it is not clear whether IL-17RA signaling involves C/EBPβ or other transcription factors. It is also unclear whether the IL-17A-induced expression of IL-6 from adipose tissue under conditions of obesity affects differentiation of naïve T lymphocytes into Th17 cells.

Table.1

Roles of Th17 cells and IL-17 in relation to obesity

System	Model	Finding	Reference
Obesit			
Diet Induced Obese Mice DIO	TNBS colitis and EAE	DIO predisposes to IL-6-dependent Th17 expansion associated with more severe disease conditions	Winer et al, 2009
DIO and leptin- deficient <i>Ob/Ob</i> Mice	Zymosan- induced peritonitis	IL-17A derived from neutrophils increased in obese mice in response to ZY, and coincided with increased IL-6 levels	Fantuzzi & Pini, 2010
Obese and lean women	-	Increased levels of IL-17 in addition to IL-23 in blood were detected in obese women than in lean subjects.	Sumarac-Dumanovic et al 2009
IL-17 mediated inhibition of adipogenesis			
IL-17RA ^{-/-} (KO) mice, 3T3-L1 cells	Ovariectomy- induced - osteoporosis (OVX)	IL-17RA ^{-/-} mice showed elevated levels of leptin after OVX than controls, leading to increased bone loss. IL-17A and IL-17F treatments of 3T3- L1 preadipocytes cells inhibited adipogenesis.	Goswami et al, 2009
Human bone marrow- derived mesenchymal stem cells	-	IL-17A inhibited adipocyte differentiation of hBM-MSCs via COX-2 induction.	Shin et al, 2009