



The Role of Leptin in the Association between Obesity and Psoriasis

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Abstract

Adipose tissue secretes many adipokines which contribute to various metabolic processes, such as blood pressure, glucose homeostasis, inflammation and angiogenesis. The biology of adipose tissue in an obese individual is abnormally altered in a manner that increases the body's vulnerability to immune diseases, such as psoriasis. Psoriasis is considered a chronic inflammatory skin disease which is closely associated with being overweight and obese. Additionally, secretion of leptin, a type of adipokine, increases dependently on adipose cell size and adipose accumulation. Likewise, high leptin levels also aggravate obesity via development of leptin resistance, suggesting that leptin and obesity are closely related. Leptin induction in psoriatic patients is mainly driven by the interleukin (IL)-23/helper T (Th) 17 axis pathway. Furthermore, leptin can have an effect on various types of immune cells such as T cells and dendritic cells. Here, we discuss the relationship between obesity and leptin expression as well as the linkage between effect of leptin on immune cells and psoriasis progression.

Key Words: Obesity, Psoriasis, Leptin, Adipose tissue, Pro-inflammatory cytokines

INTRODUCTION

The worldwide obesity rate has tripled since 1975, and is now reported to be one of the major causes of several immune and metabolic diseases. Consequently, obesity has become a national concern. According to WHO statistics in 2016, about 2 billion adults, globally, were overweight and over 650 million of those overweight adults were obese.

Adipose tissue is a type of energy-storage tissue that is closely associated with obesity, this association has led to it being considered to be, not only an endocrine gland, but also an immune organ that produces several kinds of immune cells, including macrophages, neutrophils, mast cells, eosinophils, and T and B cells (Huh *et al.*, 2014; Vieira-Potter, 2014). In adipose tissue, adipocytes secrete various types of cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin (IL)-1, leptin, IL-6, and IL-17 (Mohamed-Ali *et al.*, 1998;

Ahima and Flier, 2000). Importantly, several studies have argued that adipose tissue is an immune organ because it produces various inflammatory-related cytokines (Table 1) (Guzik *et al.*, 2006; Poeggeler *et al.*, 2010). When people or animals become obese, macrophages accumulate in adipose tissue and cytokine secretion significantly increases (Schenk *et al.*, 2008; Kosteli *et al.*, 2010). Thus, obesity enhances levels of various pro-inflammatory cytokines, which cause obesity-related metabolic diseases or inflammatory diseases by activating various pathways (Weisberg *et al.*, 2003; Xu *et al.*, 2003; Fain, 2010; Ouchi *et al.*, 2011).

Adipocytes produce one of the main adipokines, Leptin which is encoded by the LEP gene (Scotece *et al.*, 2014). Leptin is activated by the class I cytokine receptor, "leptin receptor" (LEPR or Ob-R). LEPR has at least six forms of cytoplasmic domain (Münzberg and Morrison, 2015). Several forms of LEPR activate various signaling pathways, such

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Table 1. Inflammation-related adipokines and their effect on obesity

Adipokine	Functions	Changes in obesity compared with normal condition	References
Leptin	Controls appetite Promotes energy consumption Pro-inflammatory	Increases	de Heredia <i>et al.</i> , 2012; Jung and Kim, 2013; Pujanek <i>et al.</i> , 2013
TNF- α	Promotes insulin signaling Pro-inflammatory	Increases	Balistreri <i>et al.</i> , 2010; Ouchi <i>et al.</i> , 2012
Resistin	Promotes insulin resistance Promotes inflammatory cytokines	Increases (Not certain in human)	Benomar <i>et al.</i> , 2013; Onuma <i>et al.</i> , 2013
MCP-1	Pro-inflammatory	Increases	Kanda <i>et al.</i> , 2006
CCL2	Promotes macrophage infiltration Pro-inflammatory	Increases	Ouchi <i>et al.</i> , 2011
TGF- β	Reduces immune cell activation Pro-inflammatory	Increases	Cristancho and Lazar, 2011
IL-1	Pro-inflammatory	Increases	Juge-Aubry <i>et al.</i> , 2003
IL-6	Promotes insulin signaling Pro-inflammatory	Increases	Maury and Brichard, 2010
IL-10	Reduces macrophage activity Reduces Inflammatory cytokines	Decreases	Esposito <i>et al.</i> , 2003; Chang <i>et al.</i> , 2013
IL-18	Pro-inflammatory	Increases	Ahmad <i>et al.</i> , 2017
Adiponectin	Promotes insulin sensitivity Promotes glucose metabolism Anti-inflammatory	Decreases	Leal and Mafra, 2013; Ye and McGuinness, 2013
SFRP5	Anti-inflammatory	Decreases	Ouchi <i>et al.</i> , 2010

Adipose tissue produces various adipokines. Molecules in this table are those adipokines and are related to inflammation. According to the data, pro-inflammatory cytokines increase and anti-inflammatory cytokines decrease with obesity.

as p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), Janus kinase (JAK), extracellular signal-regulated kinase (ERK) 1/2, protein kinase C (PKC), signal transducer and activator of transcription (STAT), and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (PKB). These activated signaling pathways can regulate appetite by inhibiting orexigenic neuropeptides and inducing anorexigenic factors (Al-Suhaimi and Shehzad, 2013; Rosenbaum and Leibel, 2014). Thus, leptin is an important metabolic factor. Interestingly, because leptin secretion increases dependently on adipose cell size and adipose accumulation, obesity leads to high leptin levels (Poeggeler *et al.*, 2010). In fact, high leptin levels can develop leptin resistance, which aggravates obesity (Enriori *et al.*, 2006), demonstrating the close relationship between leptin and obesity.

OBESITY AND LEPTIN

In an endogenous hyperleptinemia state, leptin does not function properly, leading to increased food intake, impaired nutrient absorption, and inhibition of peripheral functions such as lipid and glucose metabolism (Sáinz *et al.*, 2015). This is called leptin resistance, and its mechanism can be broadly divided into three categories: gene mutation, blood-brain barrier (BBB) permeability, and impairment of leptin receptor signaling (Gruzdeva *et al.*, 2019). First, there have been cases where structural changes in the leptin molecule occur due to a single-gene mutation in an OB gene encoding leptin. This

can cause overeating or congenital obesity, but is observed very rarely and is not considered a major cause of leptin resistance (Gruzdeva *et al.*, 2019). Next, leptin resistance can develop when transport of leptin through the BBB is decreased, which makes it difficult to recognize leptin circulating in the hypothalamus (Yang and Barouch, 2007). Circulating leptin is bound by leptin receptors expressed in brain blood vessels and transferred from the blood to the brain and cerebrospinal fluid. It maintains energy balance through a network formed between the inner and outer neurons of the hypothalamus (Zhou and Rui, 2013). With high levels of leptin in the blood, leptin concentration is low in brain tissue, cerebrospinal fluid, and even spinal fluid. This implies that a high circulating leptin concentration accelerates leptin resistance and obesity by reducing BBB permeability (Gruzdeva *et al.*, 2019). Finally, impairment of the intracellular signaling cascade of the leptin receptor can cause leptin resistance. Hypothalamic inflammation and endoplasmic reticulum stress caused by obesity also mediate leptin receptor signaling. For example, reducing endoplasmic reticulum stress or blocking inflammatory signals can enhance leptin signaling in obesity (Myers *et al.*, 2010).

PSORIASIS

Psoriasis is a chronic autoimmune skin disease characterized by abnormal skin patches that appear red, dry, itchy, and scaly (Menter *et al.*, 2008a). Psoriasis is estimated to affect approximately 125 million people around the world and oc-

curs in any age group (Parisi *et al.*, 2013). Its symptoms vary by age, region and race, and are thought to be triggered by a combination of environmental and genetic factors. Psoriasis is associated with being overweight or obese, and obesity is more prevalent among psoriatic people than non-psoriatic people. Being overweight is a contributing risk factor for psoriasis development, and obesity significantly enhances this risk (Naldi *et al.*, 2008). Body mass index (BMI) ≥ 25 kg/m² was considered a long-term predicted clinical risk factor for psoriasis (Sakai *et al.*, 2005).

Current pathogenic psoriasis models start with an environmental trigger and/or loss of tolerance, which activates the following pathway: plasmacytoid dendritic cells (pDCs) and IL23-producing dendritic cells (DCs) produce pro-inflammatory cytokines, like IL-23, which causes polarization and expansion of T17 cells. Activated T17 cells express main cytokines such as TNF- α , IL-17, IL-26, IL-29, which act on epidermal keratinocytes to facilitate skin inflammatory reactions; in this process, IL-17 works alone or synergistically with TNF- α . From keratinocytes, chemokine receptor (CCR) 20 promotes TIP-DC and IL-17 generation by recruiting CCR6+ DC to further promote inflammation. IL-23 works with IL-19/IL-36 γ to promote aortic expansion and differentiation of Th22 cells that produce IL-22 cells that change terminal differentiation and keratinocyte proliferation. IL-12, which is produced

by activated keratinocyte-derived CXCL9/10/11 and DCs, facilitates Th1 cell introduction into lesional psoriatic skin. In the skin, ILC3 also produces IL-17 and IL-22 which contribute to skin inflammation.

TREATMENTS OF PSORIASIS

Before the late 1990s, common psoriasis treatment included topical drugs, like methotrexate or cyclosporine, which have significant toxicities when administered chronically, and narrowband ultraviolet B/psoralen ultraviolet A (NB-UVB/PUVA) light therapy. These drugs were available as psoriasis treatments, but they were toxic when used repeatedly over many years (Stern, 2001). By the late 1990s, studies began to argue that consistent infiltration by T lymphocytes caused psoriasis (Lowe *et al.*, 2014). In 2003, the first “broad” immune-targeting agents, alefacept and efalizumab, were approved by the US Food and Drug Administration. Because there are many types of cytokines and immune cells involved in psoriasis development, many therapeutics are useless. Consequently, narrow immune-targeting drugs that suppress specific subsets of T cells, and which are more effective and safer for repeated treatments, are commonly used (Kim and Krueger, 2017). Treatments that targeted monoclonal antibodies, such

Table 2. Current therapeutics for psoriasis treatment.

Target	Name/Company	Route	Efficacy		References
			Week	PASI75 PASI90	
TNF	Adalimumab (Humira [®])/AbbVie (IL, USA)	SC	16	71.0 45.0	Menter <i>et al.</i> , 2008b;
				79.6 51.9	Saurat <i>et al.</i> , 2008
	Etanercept (Enbrel [®])/Amgen (CA, USA)	SC	12	47.3 20.9	Leonardi <i>et al.</i> , 2003;
				49.4 22.0	Papp <i>et al.</i> , 2005; Tying
Infliximab (dyyb/abda) (Remicade [®])/Janssen (Beerse, Belgium) (Inflectra [®])/Pfizer (NY, USA) (Renflexis [®])/Merck (Darmstadt, Germany)		IV	10	49.5 20.6	<i>et al.</i> , 2006
				75.5 45.2	Reich <i>et al.</i> , 2005; Menter
				80.4 57.1	<i>et al.</i> , 2007
Certolizumab pegol (Cimzia [®])/UCB (Brussels, Belgium)		SC	12	46.7 22.2	Mease <i>et al.</i> , 2014
				47.4 19.7	
IL-12/IL-23 p40	Ustekinumab (Stelara [®])/Janssen	SC	12	66.4 36.7	Leonardi <i>et al.</i> , 2008;
				73.8 44.7	Papp <i>et al.</i> , 2008;
				75.7 50.9	Griffiths <i>et al.</i> , 2010
IL-23 p19	Guselkumab (Tremfya [®])/Janssen	SC	16	81.0 57.1	Gordon <i>et al.</i> , 2015
	Tildrakizumab-asmn (Ilumya [®])/SUN (Mumbai, India)/Merck	SC	16	74.4 52.4	Papp <i>et al.</i> , 2015
	Risankizumab/AbbVie	SC	12	92.3 53.8	Krueger <i>et al.</i> , 2015
IL-17	Secukinumab (Cosentyx [®])/Novartis (Basel, Switzerland)	SC	12	77.1 54.2	Leonardi <i>et al.</i> , 2008
				81.6 59.2	
	Ixekizumab (Taltz [®])/Eli Lilly (IN, USA)	SC	12	87.3 68.1	Griffiths <i>et al.</i> , 2015
				89.7 70.7	
Brodalumab (Siliq [®])/Valeant (Laval, Canada)		SC	12	85.1 N/A	Lebwohl <i>et al.</i> , 2015
				86.3	

FDA, US Food and Drug Administration; IL, interleukin; IV, intravenous; PASI75, reduction of 75–89% in Psoriasis Area and Severity Index; PASI90, reduction of at least 90% on Psoriasis Area and Severity Index; SC, subcutaneous; TNF, tumor necrosis factor.

as TNF- α antagonists, failed to elicit a primary response or maintain gradual efficacy (Hawkes *et al.*, 2018). Current therapeutics for psoriasis show that the IL23/helper T (Th)17 axis pathway is very important in psoriasis. In fact, TNF-targeting drugs are less effective than IL23- or IL17-targeting drugs (Table 2). The Psoriasis Area Severity Index (PASI) is the most widely used tool to measure psoriasis. Achieving clear skin in affected areas is the purpose of psoriasis therapy. A PASI score of 75 means that a patient achieved 75% symptom improvement, and a PASI score of 90 indicates a 90% reduction in symptoms (Fredriksson and Pettersson, 1978). We will focus our discussion on pathologies of the IL23/Th17 axis pathway (Fig. 1).

OBSESITY, PSORIASIS, AND LEPTIN

Leptin affects appetite and is one of the major adipokines associated with obesity. Leptin also affects immune cells, including dendritic cells (DC), neutrophils, natural killer (NK) cells, and T and B cells, through leptin receptors located on the surface of immune cells, and regulates the production of various cytokines. These signaling patterns induce a wide range of physiological effects by altering immune and inflammatory responses (Scotece *et al.*, 2014). In particular, leptin-induced changes in various immune cells and the production of various cytokines are considered a main factor in psoriasis development, one of the most common inflammatory immune

diseases. Consequently, in this review, the effects of leptin on the immune cells and cytokines involved in the pathogenesis of psoriasis were discussed and summarized (Table 3). We also consider that leptin may be an important signaling transducer, linking obesity and psoriasis.

LEPTIN AND CYTOKINES

Leptin affects the immune cells and cytokines involved in the pathogenesis of psoriasis. Granulocytes are affected by leptin, which acts as a survival cytokine. Leptin strongly activates granulocytes by stimulating chemokinesis and delaying apoptosis (Suzukawa *et al.*, 2011; Sun *et al.*, 2013). Monocytes and macrophages are also affected by leptin. Leptin increases the proliferation of monocytes *in vitro* and enhances their activation by inducing the production of TNF- α and IL-6 and stimulation of surface markers (e.g., cluster of differentiation [CD] 25, HLA-DR, CD 38, CD 71) (Santos-Alvarez *et al.*, 1999). Leptin increases M1 phenotype macrophages that can produce pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β . In contrast, leptin decreases apoptosis of dendritic cells and upregulates expression of TNF- α , IL-1 β , IL-6, IL-12, and MIP-1 α ; it also contributes to improvement of immature DC migration and chemotactic responsiveness. In addition, leptin promotes CD4+ T cell polarization, leading to a Th1 response (Fig. 2) (Mattioli *et al.*, 2005). Finally, leptin exerts a negative effect on Treg proliferation as well as increasing pro-inflammatory cytokines (IL-6, IL-1 β , IL-12, TNF- α , and IL-17).

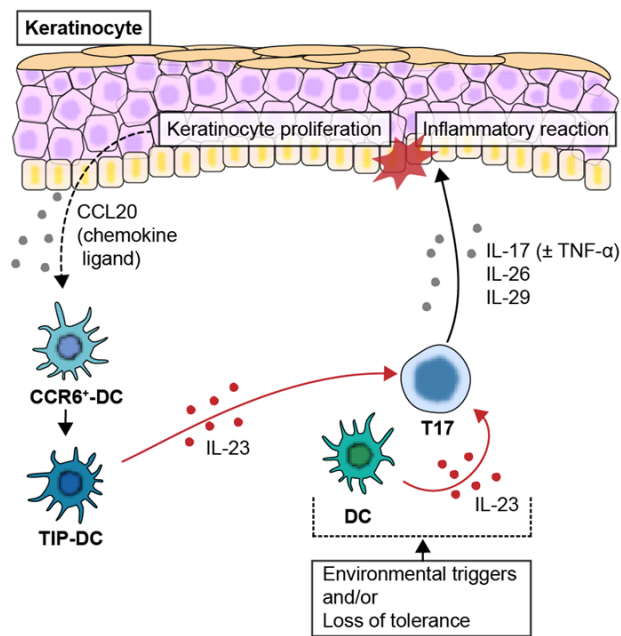


Fig. 1. A schematic diagram of the interleukin (IL)-23/helper T (Th)17 axis pathway. Environmental triggers and loss of tolerance induce initiation of psoriasis, with DCs triggering polarization and clonal expansion of T17 cells. Activated T17 cells secrete key cytokines such as IL-17, which trigger a feed-forward inflammatory response on epidermal keratinocytes in the skin. In turn, keratinocyte-derived CCL20 activates CCR6+ cells that induce IL-23-secreting TIP-DCs, which produces IL-17-secreting T cells that further promote inflammation.

LEPTIN, RESISTIN, AND ADIPONECTIN IN PSORIASIS

In addition to leptin, there are other adipokines such as resistin and adiponectin. These adipokines contribute to immune and inflammatory processes. Leptin and resistin increase the expression of proinflammatory cytokines such as TNF- α and CXCL8, whereas adiponectin is an anti-inflammatory adipokine (Kyriakou *et al.*, 2018). Accordingly, many studies have investigated circulating concentrations of adipokines in patients with psoriasis. Meta-analysis of such studies showed that leptin and resistin levels in patients with psoriasis are higher than they are in the general population, while adiponectin concentrations are lower (Kyriakou *et al.*, 2017). This result suggested a relationship between psoriasis and metabolic syndrome or obesity. In contrast, researchers have also investigated the effects of topical and systemic treatment on circulating adipokine concentrations in patients with psoriasis. After treatment, concentrations of leptin and adiponectin were similar to those before treatment, while resistin was significantly lower (Kyriakou *et al.*, 2018), suggesting that the change in resistin concentration has clinical significance in psoriatic patients. Therefore, these reports indicate that the relationship between adiponectin, resistin, and leptin is involved in the pathophysiology of psoriasis.

OBSESITY, LEPTIN, AND GRANULOCYTES

Leptin acts as a type of survival cytokine in granulocytes. Neutrophils, eosinophils, and basophils have different forms

Table 3. Effects of leptin on immune cells and cytokines involved in the pathogenesis of psoriasis

Types	Changes with increased leptin	References
Granulocytes	Activated to promote pro-inflammatory cytokine secretion	Lin <i>et al.</i> , 2011; Suzukawa <i>et al.</i> , 2011
Monocytes	Increased proliferation	Santos-Alvarez <i>et al.</i> , 1999
Macrophages	Increased number of M1 macrophages	Acedo <i>et al.</i> , 2013
Dendritic cells (DCs)	Decreased apoptosis, which supports DC survival	Lam <i>et al.</i> , 2006; Al-Hassi <i>et al.</i> , 2013
T cells	Promoted CD4+ T cell polarization.	Mattioli <i>et al.</i> , 2005
Th17 cells	Increased number of cells	Orlova and Shirshv, 2014)
T regulatory cells (Treg)	Suppressed proliferation	De Rosa <i>et al.</i> , 2007; Francisco <i>et al.</i> , 2018
TNF- α	Increased expression	Santos-Alvarez <i>et al.</i> , 1999
IL-1 β , IL-6, IL-12, IL-17	Increased expression	Santos-Alvarez <i>et al.</i> , 1999; Mattioli <i>et al.</i> , 2008; Deng <i>et al.</i> , 2012

Leptin affects various immune cells and cytokines involved in the pathogenesis of psoriasis. According to this table, psoriasis-related immune cells (granulocytes, monocytes, macrophages, DCs, and T cells) and pro-inflammatory cytokines (IL-6, IL-1 β , IL-12, TNF- α , and IL-17) changed in response to increased leptin levels in manners favorable to psoriasis induction.

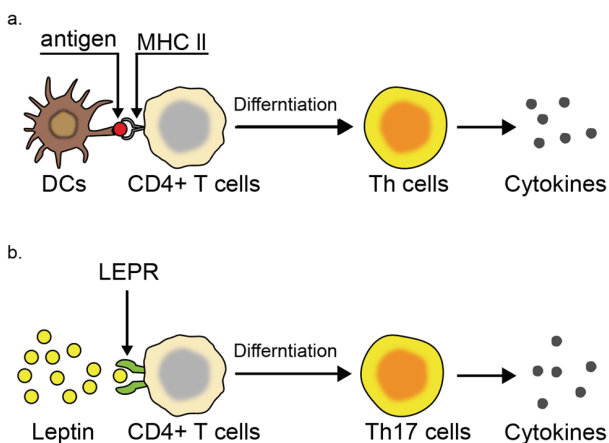


Fig. 2. The secretion mechanism of cytokines. (a) Normal cytokine production. The binding of an antigen-MHC II complex to CD4+ T cells induces differentiation of Th cells that secrete cytokines. (b) The possible secretion of cytokines is induced by leptin through LEPR. The combination of a leptin-LEPR complex and CD4+ T cells produces mature Th cells that produce cytokines.

of LEPR in their membrane; thus, it is possible that all these granulocytes can stimulate chemokinesis and delay cell apoptosis in different signaling pathways, such as JAK (not in neutrophil), PI3K, nuclear factor-kappa B (NF- κ B), and the MAPK pathway. Leptin strongly activates these granulocytes by chemokinesis stimulation and apoptosis delay (Suzukawa *et al.*, 2011; Sun *et al.*, 2013). Although neutrophil gathering has been frequently observed on psoriatic skin, their function has not been elucidated. However, one study showed that neutrophils are connected to pathogenic function of IL-17, which is associated with formation of neutrophil-extracellular traps (Schon *et al.*, 2017). Under psoriatic conditions, IL-17+ mast cells and neutrophils show higher density than IL-17+ T cells, and IL-17 is also secreted during the forming of the special structure called an extracellular trap. Neutrophils can be a major source of IL-17A, and they also produce IL-17F or IL-22 (Lin *et al.*, 2011). IL-17 induces expression of psoriasis-related genes, and IL-22 alters differentiation and growth of cornified

cells (Albanesi *et al.*, 2018). Eosinophils are also much more activated by leptin, which promotes secretion of several cytokines such as TNF- α , IL-1 β , and IL-6. Various group data have shown that eosinophils facilitate psoriasis inflammation by fostering inflammatory conditions and promote activation and erosion of neutrophils (Suzukawa *et al.*, 2011). Moreover, TNF- α produced during this time stimulates BDCA-1+ DC, which affects IL-23, IL-1 β , and IL-6 production to facilitate psoriasis progression (Kunze *et al.*, 2017).

OBESITY, LEPTIN, AND MONOCYTES/MACROPHAGES

Functional LEPR is expressed in macrophages in the same way as other immune cells (O'Rourke *et al.*, 2001). Leptin induces proliferation of human circulating monocytes, *in vitro*, and enhances their activation by inducing TNF- α and IL-6 production and stimulating surface markers (e.g., cluster of differentiation (CD) 25, HLA-DR, CD 38, CD 71) (Santos-Alvarez *et al.*, 1999). Leptin treatment (50 ng/mL) of human macrophages induces "alternatively activated" or M2-phenotype surface markers that secrete M1-phenotype cytokines (monocyte chemoattractant protein-1 (MCP-1), TNF- α , macrophage inflammatory protein 1-alpha (MIP-1 α), IL-6, IL-1 β , IL-1ra, and IL-10). Leptin has been found to affect macrophage phenotypes (Acedo *et al.*, 2013). In particular, leptin-induced cytokine production (e.g., TNF- α , IL-6, IL-1 β) by macrophages is related to psoriasis aggravation. Additionally, leptin induces M2 macrophages to express more LEPR, which stimulates more cytokine production in macrophages (Cao *et al.*, 2016). Mast cells are also involved in leptin-induced macrophage regulation. In particular, both human and mouse mast cells from lean adipose tissue induce lower leptin expression compared with obese individuals. Anti-inflammatory activity of mast cells is promoted by leptin deficiency, which causes a shift in macrophage polarization from M1 to M2 (Zhou *et al.*, 2015). In contrast, obese people with high leptin levels may have many M1 phenotype macrophages that can produce pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , consequently aggravating psoriasis.

OBSESITY, LEPTIN, AND DENDRITIC CELLS (DCS)

Dendritic cells (DCs) are antigen-presenting cells of mammalian immune systems. Their main function is to process antigenic material and present it to T cells in the immune system. They serve as messengers between the innate and adaptive immune systems. Leptin is an activator of human DCs, as demonstrated by up-regulation of TNF- α , IL-1 β , IL-6, IL-12, and MIP-1 α , and by improvement of immature DC migration and chemotactic responsiveness. Leptin activation of human DCs prepares them for Th1 priming (Mattioli *et al.*, 2008). Moreover, leptin treatment supports DC survival through decreased apoptosis via activation of the NF- κ B and PI3K-PKB signalings, together with an increase of bcl-2 and bcl-xL gene expression. LEPR-deficient db/db mouse bone marrow culture yielded a reduced number of DCs, which was attributable to dysregulation of the bcl-2 genes and a consequent increase in apoptosis (Lam *et al.*, 2006; Al-Hassi *et al.*, 2013). Several key studies that aimed to identify the initial psoriasis trigger demonstrated that injured keratinocytes enable concomitant myeloid dendritic cell (mDC)- and plasmacytoid dendritic cell (pDC)-driven immune events through LL37 nucleic acid complexes, which are heavily released in the psoriatic epidermis after skin trauma (Ganguly *et al.*, 2009; Mattioli *et al.*, 2009; Lowes *et al.*, 2013; Harden *et al.*, 2015; Capon, 2017; Girolomoni *et al.*, 2017). These multimeric LL37 nucleic acid complexes induce overproduction of type I IFN by pDC and of TNF- α and IL-6 by mDC (Albanesi *et al.*, 2009). In addition, LL37 induces CXCL1 and CXCL8 chemokines by activating IL-36R signaling in psoriatic keratinocytes, which would, in turn, contribute to the neutrophil recruitment and bursting in lesional skin that is typical of early-phase psoriasis. Importantly, LL37 induces CCL20 and CXCL10 in psoriatic keratinocytes and is most likely responsible for the first flare of the acquired immunity established in later phases of psoriasis by DC and Th17.

OBSESITY, LEPTIN, AND T LYMPHOCYTES

Skin is the organ where T cell-mediated inflammatory diseases such as psoriasis occur most often (Kim and Krueger, 2017). A psoriasis lesion begins after autoantigens, such as LL37/cathelicidin, ADAMTSL5, and PLA2G4D-generated neolipid Ags, are recognized (Cheung *et al.*, 2016). Next, the autoantigens present themselves within the DCs, allowing CD4+ T or CD8+ T cells to recognize the DCs. If an antigen is present within a DC with antigen MHC Type I, CD8+ T cells recognize it as being cytotoxic, which results in the cell being targeted for direct lysis. On the other hand, if an APC displays antigen using MHC Type II, CD4+ cells recognize it and become T helper cells (Th cells) that cause multiple downstream effects, including pro-inflammatory cytokine synthesis, which triggers psoriasis; IL-23, IL-17, IL22 instigate psoriasis in similar manners (Zinkernagel and Doherty, 1974; Katz *et al.*, 1975; Goldrath and Bevan, 1999; Starr *et al.*, 2003; von Boehmer *et al.*, 2003). T cells have a long isoform of LEPR on their surface, which is much higher in peripheral CD4+ T cells than in CD8+ T cells (Sanchez-Margalet *et al.*, 2002). In other words, if leptin is present, CD4+ T cells with many leptin receptors can differentiate into other cell types (Reis *et al.*, 2015). In one example, differentiation of naive CD4+ T cells into Th17 cells

occurs with the help of LEPR *in vitro* and *in vivo*. Similarly, leptin promotes CD4+ T cell polarization, resulting in a Th1 response (Mattioli *et al.*, 2005). The Th cells induced in psoriasis development are Th17, Th1, and Th22 cells, all of which secrete pro-inflammatory cytokines. Th17 cells play an important role in the early innate and acquired immunity (Albanesi *et al.*, 2018). T regulatory cells (Treg) play an important role in the late phases of psoriasis, including amplification and chronicization (Wittamer *et al.*, 2003). How these cell types affect psoriasis, and then how leptin, which is elevated under obesity conditions, can influence cell behavior are described below.

OBSESITY, LEPTIN, AND TH17 CELLS

Th17 cells are derived from various types of DC cell populations. BDCA-1+DC, mature DC, and TIP-DC produce pro-inflammatory cytokines, foster Th17 cell differentiation (Hawkes *et al.*, 2018). Once Th17 cells are activated, they induce expression of various psoriasis-inducing effector cytokines such as IL-26, IL-29, TNF- α , and IL17 (Wang *et al.*, 2013a). Particularly, IL17-A and IL17-F, derived from Th17 cells directly affect the initial psoriasis phase. Various types of proteins (LL37/cathelicidin, LCN2, hBD2, and S100 proteins) that affect psoriasis are expressed from keratinocytes, while crucial cytokines are produced (Lande *et al.*, 2014; Arakawa *et al.*, 2015; Cheung *et al.*, 2016). Additionally, IL-22, IL-19, and IL-36 γ , which are made by inducing IL-17, cause epidermal hyperplasia, which makes the skin thick (Zaba *et al.*, 2007). A feed-forward inflammatory response plays a critical role in psoriasis development, and IL17 is at the center of this. In one example, IL17C, in response to IL-17 A/F, amplifies psoriasis-related genes, one of which induces Th17 cells to produce IL-17 A/F. Another dynamic in the positive feedback loop involves Th17 cell induction of STAT1 through IL-26 and IL-29, which foster psoriasis maintenance (Wolk *et al.*, 2013; Stephen-Victor *et al.*, 2016). Consequently, IL-17-producing Th17 cells play a crucial role in psoriasis promotion and maintenance. Several studies show that leptin is positively correlated with Th17 cells. In the autoimmune disease systemic lupus erythematosus (SLE), leptin promotes increased Th17 levels (Yu *et al.*, 2013; Fujita *et al.*, 2014; Reis *et al.*, 2015). In a collagen-induced arthritis mouse model, the number of Th17 cells in the joint tissue increased after injecting leptin, which also increased disease severity (Deng *et al.*, 2012). Leptin concentration in blood was found to be dramatically high during pregnancy (Henson and Castracane, 2000). Additionally, elevated leptin concentration is similar to concentrations found in pregnancy-promoted peripheral blood CD4C cells that differentiated into Th17 cells (Orlova and Shirshv, 2014). In other words, Th17 cell counts were increased by leptin, which derived from CD4+ T cells, not just plasma leptin (Wang *et al.*, 2013b). Furthermore, CD4+ T cells without LEPR only partially differentiated into Th17 cells (Reis *et al.*, 2015). Leptin presence indicated that it plays a role in the differentiation process. In conclusion, it can be inferred that obesity-driven leptin might enhance Th17, consequently leading to severe psoriasis.

OBESITY, LEPTIN, AND T REGULATORY CELLS (TREG)

Treg cells are lymphocytes that contribute to regulation of excess or autoimmune responses. They are able to directly interact with each other via the immune cell membrane receptor (memory and natural killer (NK) cells, B lymphocytes, effector T-lymphocytes, antigen-presenting cells) by producing suppressed cytokines (galectin-1, IL-10, TGF- β , IL-35,) or by direct cytotoxic action (granzyme B and perforin release) (Birch *et al.*, 2005; Vignali *et al.*, 2008). Obese individuals show a reduction in the number of CD4⁺CD25⁺CD127⁻Foxp3⁺ Treg cells, which correlates with body weight, BMI, and plasma leptin levels (Wagner *et al.*, 2013). In humans, leptin had a negative effect on Foxp3⁺CD4⁺CD25⁺ Treg proliferation; *in vitro* leptin neutralization, during anti-CD3 and anti-CD28 stimulation, resulted in proliferation of isolated human Treg cells (De Rosa *et al.*, 2007). Moreover, leptin-deficient mice have a higher number of peripheral Tregs than wild-type mice, but after inoculation with leptin, the trend reversed (De Rosa *et al.*, 2007). Thus, leptin is found in greater abundance in obese people than in standard-body weight people, and it is considered that leptin has an inverse relationship with the number of Treg cells because the number of Tregs is lower in obese people. Pathogenesis is a chronic inflammatory disease induced by activation of the Th1/Th2 axis and an imbalance in the Th17/Treg axis (Deng *et al.*, 2016). From the point of view of Treg cells and effector T cell number imbalance, T cell functionality and metabolism are closely related (Maclver *et al.*, 2013); effector T cells, including Th1 and Th17, require a high glycolytic metabolism to support proliferation and function, while Treg cells require oxidative metabolism to support suppressive activity. Recently, in a mouse model of experimental autoimmune encephalomyelitis, leptin directly promoted glycolytic metabolism in T cells, which, in turn, induced Th17 cell differentiation, while Treg cells remained unchanged (Gerriets *et al.*, 2016). Leptin upregulated the glucose transporter Glut1, thereby regulating glucose metabolism (Saucillo *et al.*, 2014). Furthermore, the ability of T cells to secrete IL-2 and IFN γ was reduced during fasting, and glucose uptake and glycolytic systems could not be upregulated (Saucillo *et al.*, 2014); meanwhile Treg levels increased (Liu *et al.*, 2012). However, leptin treatment (1 mg/g body weight) recovered peripheral T cell metabolism and function in fasted mice (Saucillo *et al.*, 2014). Synthetically, the above studies show the function of leptin to enhance immune activity by controlling T cell number and function. Leptin can induce proliferation of naive T cells and Th1 and Th17 cells and also increase cytokine production, but leptin suppressed Treg cell proliferation (Francisco *et al.*, 2018). From this point of view, high leptin levels in obese people affect effector T cell and Treg function, which leads to abnormalities in the Th17/Treg balance, which could trigger psoriasis.

CONCLUSIONS

The mechanism by which obesity induces psoriasis is not fully understood. For this reason, many obese people suffer from psoriasis and are looking for effective treatments to improve it. Furthermore, there is no perfect cure for psoriasis. However, several studies have shown that leptin is produced

at higher levels in the adipose tissue of obese people than in lean people. Leptin affects metabolism activation and the immune system, instigating inflammatory diseases like psoriasis. In this review, we suggest that leptin plays a central role in the correlation between obesity and psoriasis. Specifically, obesity-induced leptin secretion may be involved in psoriasis induction in the skin by altering a subpopulation of immune cells, as illustrated in Fig. 3. The role of immune cells in the development of psoriasis can be summarized as follows: in the early stage of psoriasis, innate immune cells secrete key cytokines that activate myeloid dendritic cells. Once dendritic cells are triggered by antigens, they secrete mediators such as IL-23. This induces differentiation of Th17, which produces pro-inflammatory cytokines like IL-17A. An IL-17A-triggered positive-feedback loop leads to the amplification/chronicization phase of psoriasis. During this phase, continuous activation between immune cells and keratinocytes increases in-

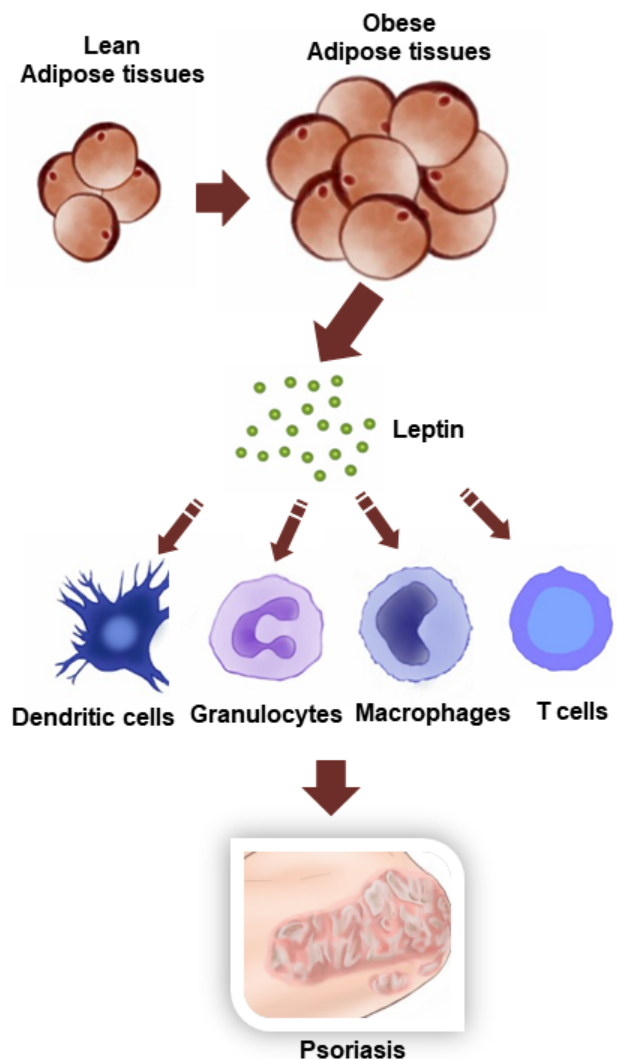


Fig. 3. The role of leptin in the association between obesity and psoriasis. Obese adipose tissue increases the production and secretion of leptin, which activates dendritic cells, granulocytes, macrophages and T cells, consequently inducing psoriatic symptoms in the skin.

flammation severity. Also, this review implies that suppressing leptin production could be a possible approach for psoriasis therapy. However, more research is required to understand the pathophysiological functions of leptin in psoriasis development and the relationship between obesity and psoriasis. In addition, since pro-inflammatory cytokines are involved in the production of leptin molecules, it is important to investigate the possibility that psoriasis promotes adiposity and adipose inflammation.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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