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Opinion

Leptin Regulation of Immune Responses

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Leptin is a regulatory hormone with multiple roles in the immune system. We favor the concept that leptin signaling 'licenses' various immune cells to engage in immune responses and/or to differentiate. Leptin is an inflammatory molecule that is capable of activating both adaptive and innate immunity. It can also 'enhance' immune functions, including inflammatory cytokine production in macrophages, granulocyte chemotaxis, and increased T_h17 proliferation. Leptin can also 'inhibit' cells; $CD4^+$ T cells are inhibited from differentiating into regulatory T cells in the presence of elevated leptin, while NK cells can exhibit impaired cytotoxicity under the same circumstances. Consequently, understanding the effect of leptin signaling is important to appreciate various aspects of immune dysregulation observed in malnutrition, obesity, and autoimmunity.

Trends

Leptin signaling can regulate innate inflammatory responses, such as cytokine production in macrophages and mast cells, as well as leptin-mediated chemotaxis in granulocytes.

Leptin signaling can regulate adaptive immunity. It is required for T_h17 differentiation through upregulation of transcription of RORγt.

Leptin signaling can suppress regulatory T cell (Treg) differentiation.

Inhibition of the leptin receptor blocks macrophage microbicidal and phagocytic functions, as well as the maturation of dendritic cells.

Leptin can inhibit natural killer (NK) cell activation under certain circumstances, a unique effect not observed in other cell types.

The Leptin Hormone: An Indicator of Energy

Leptin is an important signal of energy availability. It has a role in metabolism by signaling satiety, and is often paired with the hormone ghrelin, acting as a counter to the increased hunger effect mediated by ghrelin. However, ghrelin is dynamic, with peaks and dips reflecting an individual's hunger and satiety [1,2]. Leptin levels vary diurnally, but exist at a steadier level overall than those of ghrelin [3]. Furthermore, when exogenous leptin is administered, it does not cause satiety, but reduces eating to normal levels in obese mice [4,5]. Leptin concentrations are dramatically altered with nutritional dysfunction; indeed, high and low concentrations are seen in obesity and malnutrition, respectively [2,6]. Therefore, leptin is considered an energy indicator, signaling when sufficient energy is available for the metabolism of an organism.

Nutritional disruption of leptin signaling is common. Malnutrition results in hypoleptinemia, while obesity results in hyperleptinemia. These outcomes can have opposite effects on immune cells, which can be partially attributed to leptin function. For instance, studies of malnourished children reported qualitative differences in cytokine production, where reduced levels of certain cytokines were observed [7–10]. *In vitro* studies have also shown that human T cell activation and cytokine production can be induced or 'rescued' upon exogenous incubation with leptin following nutritional rehabilitation [7,11]. In contrast to malnutrition, upregulated inflammatory responses have been typically observed with obesity.

Recent discoveries have uncovered greater detail about how leptin regulates the immune system. Research into the effects of elevated leptin in biology has solidified the concept that leptin is a powerful proinflammatory molecule that is responsible not only for the upregulation of cellular functions, but also for the differentiation of immune cell lineages into proinflammatory subsets. Additionally, conditions of hypoleptinemia have shown that normal leptin is required for full functionality. Here, we discuss some of the latest advances in leptin regulation and immunity, at an urgent time when treatments are being sought for various conditions, including obesity and autoimmunity.

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Leptin Receptor Signaling in the Immune System

Leptin Receptor Signaling

The leptin receptor (LepR) is ubiquitously expressed on the surface of immune cells, both peripheral and bone marrow-derived cells [12,13]. There are six isoforms that arise from one coding gene, the three most common being the long, short, and soluble forms. The long and short forms of LepR are most commonly expressed on cell surfaces [14,15]. The long-form LepR contains an extracellular domain and an intracellular domain that bears a JAK2 signaling site, as well as three tyrosines (Tyr) that can be phosphorylated (see Figure I in Box 1). The short-form LepR contains only the JAK2 intracellular signaling site, which suggests that the binding of JAK2 is particularly important downstream of leptin.

The extensive signaling pathways triggered by leptin make it challenging to associate specific signaling molecules to particular leptin-mediated biologic effects. However, the JAK2–PI3K, JAK2-Tyr 985–ERK1/2, and JAK2-Tyr 1138–STAT3 pathways have recently emerged as examples of pathways by which leptin can induce immune cell activation (Box 1). Further understanding of these and other pathways may facilitate our ability to induce or prevent leptin-mediated immune activation in a context- and cell-dependent manner.

Leptin Impacts Adaptive Immunity: T Lymphocyte Function and Differentiation

Leptin Deficiency Impairs T Cell Functions

Although the mechanisms of leptin regulation of T cell function are not fully understood, leptin signaling has considerable effects on T cells, and leptin also functions as an inflammatory cytokine [12,13]. Leptin deficiency in mice and humans leads to a reduction in total $CD4^+$ T cell numbers, and a shift from Type 1 Th_1 (proinflammatory) to Type 2 helper (Th_2) T cell phenotypes [12,13]. Infection has been shown to induce increased leptin levels; the finding that acute infection coincides with increased human serum leptin has been observed particularly with bacterial infections (e.g., *Staphylococcus aureus*) and sepsis in the bloodstream [16,17]. While adipocytes are the primary leptin producers, recent evidence has revealed that leptin is also produced by other cell types (e.g., phagocytes) at sites of bacterial or parasitic infection (Box 2). As such, it is clear that leptin is implicated in the regulation of inflammatory as well as immune responses.

In T cell function, defective T cell activation and metabolism have shown in fasting mice exhibiting reduced leptin levels [18]. In one study, decreased $CD4^+$ T cell proliferation in the periphery correlated with diminished leptin concentrations [18]. Remaining T cells exhibited reduced secretion of proinflammatory cytokines IL-2 and IFN-γ following anti-CD3 and anti-CD28 stimulation *in vitro*. These effects could be rescued following the addition of exogenous leptin to cultures. Moreover, the proliferation of $CD4^+$ T cells from leptin-deficient **db/db** (or $db^{-/-}$ mice, see Glossary) was also reduced relative to wild-type cells, and the T cell defects in mice were abolished *in vivo* upon leptin injection [18]. In addition, leptin deficiency resulted in low glucose uptake in $CD4^+$ T cells, suggesting that leptin directly regulates T cell metabolism, to indicate a potential lack of available energy for activation inside a cell [18]. In murine bone marrow **adoptive transfer** experiments, effects of leptin were shown on activated T cell function and metabolism and were found to be hematopoietic cell-intrinsic. The use of T cell-specific LepR conditional knockout mice also indicated a T cell-specific leptin-signaling requirement for cytokine secretion and glucose uptake regulation [18].

In addition to its impact on T cell function, leptin also has a role in T cell differentiation; in particular, the $CD4^+$ helper T_h17 and regulatory T cell (Treg) lineages appear to be affected antagonistically by leptin signaling.

Glossary

Adoptive transfer: the transfer of a small population of immune cells from a donor into a host, most commonly via the blood stream.
Db/db mice: mice that have a genetic deficiency in the leptin receptor resulting in the absence of expression of the long-form leptin receptor on all cell types. They are obese, diabetic, and infertile.
Diet-induced obesity (DIO): most commonly used to refer to animals fed a high-fat diet to induce weight and adiposity gain.
Ob/ob mice: mice that have a genetic deficiency in leptin expression and no detectable circulating leptin. They are obese, diabetic, and infertile.
***Rag1*$^{-/-}$ mice:** mice that are immunodeficient and produce no mature B or T cells.
Q223R leptin receptor variant: a glutamine to arginine single nucleotide polymorphism in the extracellular domain of the leptin receptor, resulting in reduced leptin receptor signaling