Molecules at the interface between immune and metabolic regulation: a major role for leptin?

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Metabolism controls production, maintenance and destruction of biomolecules and, more importantly, how energy is made available to organisms. Physiological variables that control energy balance are continuously adjusted in response to food intake, leading to weight loss under conditions of food deprivation and rapid recovery of lost weight when food becomes available. A corollary of these phenomena is that changes in food intake and the related energy expenditure tightly regulate body fuel stores. Clearly, the adipose tissue is the most prominent store of body fuels. To explain how adaptive changes in food intake respond to changes in body adiposity, it has been suggested that humoral signals are generated in proportion to fat stores and act on feedback control systems to influence food intake and energy expenditure. Recently, it has become evident that the control of orexigenic and anorexigenic circuits not only affects the regulation of body weight but also dramatically influences other important physiological functions including immune homeostasis. In particular, several cytokines, hormones, neuropeptides and transcription factors play relevant roles in both metabolic processes and immune functions. These findings have opened novel areas of research that lead to unexpected acquisitions on intriguing connections between metabolic and immune regulation. Dissection of such intricate networks could help with the understanding of how the organism balances the energetic costs of immune responsiveness with that of vital needs; in turn, this could lead to the identification of new pharmaceutical targets of intervention in immune-mediated diseases.

Cytokines, hormones and neuropeptides regulate metabolism and immune function: a major role for leptin?

The immune function is influenced by the neuroendocrine system through a series of common mediators such as cytokines, hormones and neurotransmitters. Cytokines mediate inter and intracellular communication and, among other functions, contribute to the regulation of innate and adaptive immunity, inflammation and metabolic function. Most cytokines exert their function in a complex intermingled network where one cytokine can influence production of, and respond to, other cytokines. In recent times, it has become clear that the adipose tissue can produce hormones and cytokines that significantly affect both energy status and immune reactivity of the organism. Consequently, the adipocyte-derived molecules that bridge metabolism and immune homeostasis are called adipokines. The growing family of adipokines includes leptin, interleukin-1 (IL-1), IL-6, IL-8, interferon-γ (IFN- γ), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), leukemia-inhibiting factor (LIF) and chemokines, such as monocyte chemotactic protein-1(MCP-1) and macrophage inflammatory protein-1 (MIP-1).

Leptin is a typical adipokine produced in proportion to the body fat mass. A major role of leptin is to gauge the total amount of body fat, which indirectly reflects food availability, to stop food intake and increase basal metabolism. Under the conditions of food deprivation and the subsequent reduction in the mass of body fat, lowered leptin levels lead to reduced metabolic expenditure to conserve energy required for supporting the functions of vital organs such as heart, kidney and brain. Although leptin effects might favor survival under hostile conditions, starvation concomitantly induces immunosuppression and impaired fertility, because leptin switches off energy-consuming processes. Leptin has an immunomodulatory effect on both innate and adaptive immunity. Together with IL-1, IL-6 and TNF-α, leptin acts as an acute-phase reactant during inflammation. In natural immunity, leptin is required for phagocytosis of bacteria mediated by polymorphonuclear neutrophils (PMN) because leptin-deficient ob/ob mice exhibit impaired phagocytosis of Klebsiella pneumoniae. In PMNs that express the Ob-Rb phenotype, leptin also stimulates chemotaxis and release of oxygen radicals such as superoxide and hydrogen peroxide.

In adaptive immunity, leptin differentially modulates the functions of naïve and memory T cells, stimulating proliferation of naïve T cells, whereas only promoting the secretion of T helper 1 (Th1) cytokines but not the proliferation of memory T cells. Recent evidence also suggests a role for leptin in the pathogenesis of some autoimmune diseases, because leptin-deficient mice are resistant to experimentally induced autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE), autoimmune arthritis, autoimmune colitis and hepatitis; in addition, administration of leptin triggers the onset, and accelerates the progression of autoimmunity.

Taken together these observations suggest that leptin may represent one of the major mediators linking nutritional status, metabolism and adipose tissue to an appropriate immune reactivity.