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Metabolic control of immune tolerance in health and autoimmunity

Fortunata Carbone[a,1], Claudia La Rocca[a,1], Paola De Candia[b], Claudio Procaccini[a], Alessandra Colamatteo[c], Teresa Micillo[c], Veronica De Rosa[a,c], Giuseppe Matarese[a,d,*]

[a] Laboratorio di Immunologia, Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR), Napoli 80131, Italy
[b] IRCCS MultiMedica, Milano 20138, Italy
[c] Unità di NeuroImmunologia, Fondazione Santa Lucia, Roma 00143, Italy
[d] Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli "Federico II", Napoli 80131, Italy

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ABSTRACT

The filed that links immunity and metabolism is rapidly expanding. The adipose tissue, by secreting a series of immune regulators called adipokines, represents the common mediator linking metabolic processes and immune system functions. The dysregulation of adipokine secretion, occurring in obese individuals or in conditions of malnutrition or dietary restriction, affects the activity of immune cells resulting in inflammatory autoimmune responses or increased susceptibility to infectious diseases. Alterations of cell metabolism that characterize several autoimmune diseases strongly support the idea that the immune tolerance is also regulated by metabolic pathways. The comprehension of the molecular mechanisms underlying these alterations may lead to the development of novel therapeutic strategies to control immune cell differentiation and function in conditions of autoimmunity.

Contents

* Corresponding author at: Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli "Federico II", via Pansini 5, 80131 Napoli, Italy.
E-mail address: giuseppe.matarese@unina.it (G. Matarese).
[1] These authors equally contributed to this work.

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1. Introduction

It is well known that the adipose tissue functions as an endocrine organ that acts as a sensor of nutrient availability and represents the primary site for the storage of nutrients [1]. During starvation, the adipose tissue is reduced and adipocytes signal to the body to increase the efficiency of energy usage and to reduce metabolic activity. On the other hand, when nutrients increase as a consequence of food intake, it induces fat accumulation in the adipocytes [2].

By producing specific hormones, adipose tissue is able to communicate with the body, regulating feeding, nutrient uptake and several metabolic pathways such as gluconeogenesis.

While the brown adipose tissue (BAT), is associated with energy expenditure and thermogenesis specifically in infants and hibernating animals [3], the white adipose tissue (WAT) is the energy storage depot for excess nutrients in the form of lipids that serves as a sensor for energy balance of the body. WAT is localized in different sites of the body and can be found under the skin as subcutaneous adipose tissue (SAT) and in abdominal cavity as visceral adipose tissue (VAT) [4].

It is becoming more and more clear that metabolism is able to control immune responses. Specific metabolic pathways affect T cell function and differentiation and, therefore, influence the final outcome of adaptive and innate immune responses. A common mediator linking metabolic processes and immune system functions is actually represented by the adipose tissue itself.

2. Adipose tissue: linking metabolism with immune function

Although the adipose tissue is mainly involved in the energy storage, it is now well described that its endocrine activity comprises the secretion of several bioactive molecules, referred to as adipokines, that regulate metabolic processes and also immune functions. It has been observed that after starvation, when adipose tissue decreases in size, the function and cellularity of immune cells are significantly reduced [5]. In addition, the discovery of leptin in 1994 clarified that adipose tissue is much more than a mere storage of nutrients, since it works as an endocrine organ able to control systemic metabolic processes, as well as immune cell function. After the discovery of leptin, many other adipokines secreted by adipose tissue and involved in the control of immunological functions have been identified [6]. Depending on the effect that these adipokines play on the immune system, they are divided into two groups based on their pro- or anti-inflammatory role.

3. Pro-inflammatory adipokines

3.1. Leptin

Leptin, product of the obese (*ob*) gene, is mainly generated by the adipose tissue in proportion to the body fat mass and, at lower levels, by skeletal muscle, stomach and placenta [7]. Although leptin was originally described as an important factor for the regulation of body weight through the inhibition of food intake and stimulation of energy expenditure, recent evidence has shown that leptin is much more than a 'satiety sensor' since it affects both innate and adaptive immunity [8].

In innate immunity, leptin up-regulates phagocytic function [9] and secretion of proinflammatory cytokines by macrophages and monocytes [10,11] and, in obese mice, both the number and function of dendritic cells (DCs), the major antigen presenting cells (APCs) involved in T lymphocyte activation, are found altered [12]. Leptin is also involved in NK cell development, differentiation, proliferation, activation, and cytotoxicity [13] and, in addition, it stimulates chemotaxis of neutrophils and the release of oxygen radicals (such as superoxide anion and hydrogen peroxide) [14,15]. Regarding the role of this hormone in adaptive immunity, leptin has been shown to generally increase the proliferation of $CD4^+$ T cell in a mixed lymphocyte reaction (MLR) in a dose-dependent manner [16]. The effects of leptin on human naive (CD45RA) and memory (CD45RO) $CD4^+$ T are very different: while it stimulates proliferation and interleukin (IL)-2 secretion of naïve T cells, it promotes the switch towards T helper (Th)1-cell immune responses by increasing interferon (IFN)-γ and tumor necrosis factor (TNF)-α secretion on memory T cells [16]. Leptin also induces activation and migration of immune cells toward the sites of inflammation by increasing the expression of adhesion molecules [17]. Leptin decreases thymic T cell apoptotic rate thus influencing their generation, maturation and survival [18].

Leptin-deficient (*ob/ob*) and leptin-receptor-deficient (*db/db*) mice are characterized by not only severe obesity, but also alterations in cell-mediated and humoral immunity [16,19,20]. In agreement with these data, patients with congenital leptin deficiency display a higher incidence of death as a result of recurrent infections during childhood [21] and recombinant human leptin administration is able to restore the absolute number of naive $CD4^+CD45RA^+$ T cells and the lymphocytes proliferative response [22]. Leptin can also impact the generation and proliferation of $CD4^+CD25^{high}Foxp3^+$ regulatory T (Treg) cells, a T cell subset involved in the suppression of auto-reactive responses and in prevention of immune diseases. Obese subjects are characterized by a lower frequency of Treg cells and their number inversely correlates with leptin levels and body mass index (BMI) suggesting that increased leptin concentration could have an inhibitory effect on Treg production [23]. Fasting-induced hypoleptinemia in lupus-prone mice is followed by an expansion of functional regulatory T cells that can be reversed by leptin replacement [24]. Interestingly, freshly isolated Treg cells produce leptin and express high levels of leptin receptor (ObR) and, *in vitro*, leptin is shown to act as a negative signal for Treg cell proliferation since leptin *in vitro* neutralization with anti-leptin monoclonal antibody (mAb) following anti-CD3/CD28 stimulation is able to induce Treg cell proliferation [25], and this induction is dependent on the modulation of the mammalian target of rapamycin (mTOR) pathway [26].

Leptin may also influence the differentiation of $CD4^+$ T cells into Th17 cells. Leptin receptor deficiency results in a defect of the $CD4^+$ T cell differentiation toward a Th17 phenotype and in a reduction of Th17 response secondary to an inefficient activation of signal transducer and activator of transcription (STAT)3 and its downstream targets [27]. Mice with T cell–specific ablation of leptin receptor, display an impaired RORγt expression and a reduced IL-17/IL-22 secretion *in vitro* and *in vivo* [27]. Th17 cell number is also reduced in *ob/ob* mice, and leptin administration can restore its numbers to values comparable to those found in wild-type animals [28].