

Immunometabolism: Where Immunology and Metabolism Meet

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In the last two decades, “Immunometabolism” has emerged as a continuously increasing area of research with significant impact on biomedicine [1, 2]. The term immunometabolism defines the interface between immunology and metabolism. The crosstalk between these two major research directions has multiple facets. For instance, immune cells present in the adipose tissue or liver regulate tissue homeostasis and metabolic functions, such as lipolysis or the actions of insulin [3–6]. Intake of nutrients, such as sugars, fat, or proteins, and the metabolism thereof may modulate immune responses [4]. Furthermore, the presence of chronic metabolic inflammation, also called “metaflammation” is a central hallmark of metabolic disorders [7]. Metabolic inflammation, orchestrated by cellular and molecular components of the immune response and affecting the adipose tissue, the liver, or the pancreas, contributes to pathogenesis and progression of conditions associated with obesity, such as

type 2 diabetes or non-alcoholic fatty liver disease [1, 3, 5, 7]. For instance, both accumulation and activation of macrophages in the adipose tissue and the liver in obesity are implicated in the progression of metabolic disorders [3, 5]. Interestingly, the function of macrophages in the adipose tissue and liver in obesity is regulated by adaptations of their metabolism, triggered by the lipid-rich tissue environment [3]. Accordingly, the obese adipose tissue and liver are characterized by the enrichment of a macrophage subpopulation with a lipid metabolism-related signature, designated “lipid-associated macrophages,” as recently identified by analysis at the single-cell level [8, 9].

An important additional layer of the crosstalk between immunology and metabolism is illustrated by the fact that cellular metabolism is a central regulator of the function and activation of immune cells [3, 10]. Distinct activation states of innate immune cells, especially macrophages, are associated with different cellular metabolic states; hence, cell metabolic adaptations facilitate macrophage phenotype and plasticity [3, 10]. Metabolic reprogramming of innate immune cells is also an essential component of innate immune memory, also designated trained immunity, which defines that certain stimuli may promote unспе-

cific memory in innate immune cells, exemplified by their increased inflammatory preparedness; trained innate immune cells exert higher inflammatory responses upon secondary challenges [11, 12]. Cellular metabolism not only regulates the functions of mature myeloid cells, but also their generation in the bone marrow, a process termed myelopoiesis [13]. Adaptations in the metabolism of innate immune cell precursors, the hematopoietic stem and progenitor cells, in the bone marrow are integral to differentiation and lineage decisions in the context of myelopoiesis at steady-state and under conditions of stress [13].

The aforementioned examples of the multifaceted and continuously increasing field of immunometabolism illustrate the wide importance of the immunometabolic crosstalk in several pathologies. For instance, immunometabolic processes, including alterations in the metabolism of different immune cell populations, are integral constituents of the tumor microenvironment and hence influence tumor growth [14]. Additionally, immunometabolism has been implicated in autoimmune disorders, including type 1 diabetes and multiple sclerosis, as the loss of immunological tolerance and the accompanying emergence of autoreactive immune cells may be facilitated by specific alterations in the metabolism of immune cells [15]. Consistently, targeting the dysfunctional immunometabolic crosstalk represents a relevant approach for developing novel therapies not only for metabolic diseases but also for inflammatory disorders [2]. Along the same line, given the substantial contribution of innate immune cells, such as macrophages, to the hyperinflammatory response associated with severe COVID-19 disease, immunometabolic modulators could be potentially leveraged therapeutically for COVID-19 as well [16].

Due to the extraordinary relevance of the immunometabolism field and its major implications for health and disease, the current issue of the *Journal of Innate Immunity* includes a series of four review articles on this special topic. Two of the articles, written by Michailidou et al. and by Nati et al., review recent advances on the role of innate immune cells in the adipose tissue and liver, respectively [17, 18]. Michailidou et al. review the role of macrophages, neutrophils, innate lymphoid cells, natural killer cells, and other innate immune cells in the adipose tissue in the lean state and in obesity and discuss the role of adipose tissue inflammation as well as its regulation by hypoxia in the context of obesity-associated metabolic disease [17]. Nati et al. discuss the role of neutrophils and macrophages in the liver in the context of non-alcoholic fatty liver disease [18]. The other two review articles by

Kolliniati et al. and Ferreira et al. focus, respectively, on the regulation of macrophage biology and the process of innate immune memory, by metabolic processes, such as glycolysis, the tricarboxylic acid cycle, lipid metabolism, or oxidative phosphorylation [19, 20]. Kolliniati et al. review the impact of metabolic adaptations on macrophage plasticity and function in the context of different diseases, including cancer [20]. The article by Ferreira et al. provides insights on the important contribution of metabolic and epigenetic rewiring of innate immune cells in the context of trained immunity [19]. Importantly, all four review articles dedicated to the topic of immunometabolism provide relevant translational implications of how targeting immunometabolic processes may be leveraged in different pathologies and raise important open questions that should be addressed in future studies aiming at a better understanding of the intimate crosstalk between immunological and metabolic processes.

Conflict of Interest Statement

The author has no conflicts of interest to declare in relation to this work.

Author Contributions

T.C. wrote the manuscript.

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