Immunity
Review

The Cellular and Molecular Basis of Translational Immunometabolism

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The immune response requires major changes to metabolic processes, and indeed, energy metabolism and functional activation are fully integrated in immune cells to determine their ability to divide, differentiate, and carry out effector functions. Immune cell metabolism has therefore become an attractive target area for therapeutic purposes. A neglected aspect in the translation of immunometabolism is the critical connection between systemic and cellular metabolism. Here, we discuss the importance of understanding and manipulating the integration of systemic and immune cell metabolism through in-depth analysis of immune cell phenotype and function in human metabolic diseases and, in parallel, of the effects of conventional metabolic drugs on immune cell differentiation and function. We examine how the recent identification of selective metabolic programs operating in distinct immune cell subsets and functions has the potential to deliver tools for cell- and function-specific immunometabolic targeting.

Introduction

The metabolic state of immune cells and its dynamic changes during homeostasis and inflammation have become the focus of intense investigation, as was highlighted in excellent reviews elsewhere (MacIver et al., 2013; O'Neill and Hardie, 2013; Pearce and Pearce, 2013; Pollizzi and Powell, 2014; Wang and Green, 2012). Two critical aspects that are key to the potential therapeutic manipulation of immunometabolism have emerged from these studies. First, different immune cell functions are associated with distinct metabolic configurations: resting immune cells utilize energetically efficient processes such as the tricarboxylic acid (TCA) cycle, linked to the generation of ATP via oxidative phosphorylation (OXPHOS) (Pearce and Pearce, 2013). Upon activation, interferon-γ (IFN-γ)-stimulated macrophages (M1 spectrum) and antigen-activated T cells rapidly shift to aerobic glycolysis (MacIver et al., 2013), whereas both interleukin-4 (IL-4)-stimulated macrophages (M2 spectrum) and induced regulatory T (iTreg) cells rely on oxidative phosphorylation (MacIver et al., 2013).

Second, the metabolic status of immune cells can undergo reprogramming, which in turn can lead to changes in their functional properties. When glycolysis is inhibited by modulation of key enzymes such as pyruvate kinase M2 (PKM2) (Palsson-McDermott et al., 2015), macrophages undergo a shift toward a more M2-like state in terms of gene expression and boost, for example, IL-10 production. A similar effect is observed in T helper 17 (Th17) cells, which become more like Treg cells if glycolysis is inhibited with 2-deoxyglucose or if hypoxia-inducible factor-1α (HIF-1α) is ablated (Shi et al., 2011). This plasticity is of particular interest because it paves the way toward the metabolic reprogramming of immune cells from an inflammatory phenotype to an anti-inflammatory or immunomodulatory one or vice versa (as a strategy to boost antitumor immunity, for instance).

Although much is known about the metabolic configuration of immune cells, the effect of systemic metabolism on immune cell function and metabolic status has not been systematically explored. On the basis of nutrient supply and under the influence of the gut microbiota, metabolic organs (liver, pancreas, kidney, gut, and adipose tissue [AT]) can divert metabolites to alternative routes, thus defining systemic metabolic responses. These in turn can profoundly affect immune cell function both indirectly by regulating nutrient availability and directly by delivering signaling metabolites. Studying immune function in genetic disorders associated with insulin resistance, dyslipidemia, and obesity can provide a tool for understanding the connection between immunity and metabolism. Similarly, "in-depth" analysis of the effect of extrinsic modulators of systemic metabolism—such as conventional metabolic drugs or products of the gut microbiota—on immune parameters can offer further important

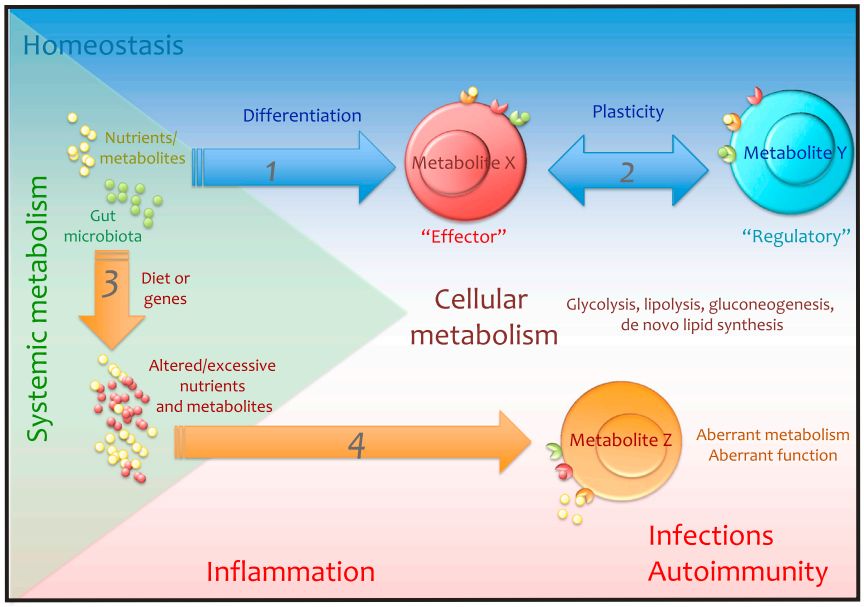

Figure 1. Systemic to Cellular Immunometabolic Crosstalk

Systemic metabolism, which is affected by the diet and gut microbiota, can contribute to immune system homeostasis by affecting the immune cell metabolic setup via nutrient availability and active metabolite-induced signaling, thus regulating their differentiation (1). Reprogramming of the metabolic configuration of immune cells can occur via epigenetic events also influenced by the metabolic microenvironment (2), thus opening a window of opportunity for therapeutic manipulation. Alteration of systemic metabolism due to dietetic overload or genetic defects (3) is associated with altered immune cell metabolism and the development of chronic inflammation and ineffective immunity (4).

clues on how immune functions adapt to systemic metabolic changes. In addition, novel metabolic features and metabolism-regulated functions in immune cells have recently been identified and could be targeted therapeutically by modification of systemic metabolism.

The Crosstalk between Systemic Metabolism and Immune Cells: Lessons from Human Metabolic Diseases

In humans, hyperlipidemia (both hypercholesterolemia and hypertriglyceridemia), diabetes, obesity, and non-alcoholic fatty-liver disease (NAFLD), as well as alterations in the gut microbiota, are often associated with metabolism-related impaired immune functions. Therefore, they provide a powerful "in vivo" working model for investigating the interplay between systemic and immune cell metabolism (Figure 1).

Hyperlipidemia

Primary (genetic) or acquired hyperlipidemias are characterized by increased plasma levels of cholesterol and/or triglycerides (TGs) and of the lipoproteins carrying these lipids. Classically, hypercholesterolaemia has been associated with cholesterol accumulation in macrophages and other immune cells and results in atheroma formation and the development of atherosclerosis. More recently, this event has been associated with direct activation of pro-inflammatory cascades, including Toll-like receptor (TLR) (Erridge, 2010) and inflammasome activation (Sheedy et al., 2013). However, the net effect of this process is debated, given that binding of TLRs by modified lipoproteins has been shown to suppress the downstream pro-inflammatory cytokine response (Kannan et al., 2012).

Do the effects of hyperlipidemia extend beyond the relatively well-defined immune events in atherogenesis? During infection, significant changes in lipid and lipoprotein metabolism are observed: lipopolysaccharides (LPSs) and pro-inflammatory cytokines induce de novo production of free fatty acids, thus favoring a combination of TG synthesis in the liver and a reduction of TG hydrolysis. This then results in reduced clearance of very-low-density lipoproteins (VLDLs) and increased TG levels (Wendel et al., 2007). In addition, the increase in free fatty acids induces insulin resistance, thus contributing to increased glucose levels during systemic inflammation. In contrast, levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) decrease during sepsis mainly as a consequence of lipoprotein removal from the liver, which is implicated in the clearance of lipids from pathogens (Pirillo et al., 2015). Studies in animal models and in humans have shown that conditions leading to reduced lipoprotein removal and hypercholesterolaemia are associated with deteriorated septic shock outcome (Walley et al., 2014). Similarly, a low plasma HDL-C level (associated with a low plasma apoA-I level) is a poor prognostic factor for severe sepsis, given that it is associated with increased mortality and adverse clinical outcomes (Chien et al., 2005).

In turn, bacterial infections affect lipid and lipoprotein metabolism as a result of reduced reverse cholesterol transport and excretion (Castrillo et al., 2003; Gillespie et al., 2015). Under these conditions, the balance between systemic and cellular lipid homeostasis is tightly controlled at the cellular level by different key transcription factors, such as sterol regulatory element binding protein (SREBP), liver X receptor (LXR), and peroxisome proliferator-activated receptors (PPARs), which modulate genes that affect lipid biosynthesis or intake, cellular lipid excretion, and lipoprotein synthesis and catabolism and thus represent important targets for immunometabolic regulation (see below).

In humans, although hyperlipidemia has no effect on Treg cells (Ammirati et al., 2010), it is associated with increased T effector cell memory polarization (Ammirati et al., 2012). Genetically determined conditions with low HDL-C levels and impaired cholesterol efflux in humans are associated with increased classical $CD14^{+}CD16^{-}$ monocytes (Sala et al., 2013). In addition, hyperlipidemia can affect the immune system through an enhanced bone marrow and extramedullary myelopoiesis. For instance, the increased cholesterol content in the plasma membrane upholds the expression and function of the receptors to IL-3, IL-5, and GM-CSF, thus favoring the proliferative response of hematopoietic stem cells (Yvan-Charvet et al., 2010).