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

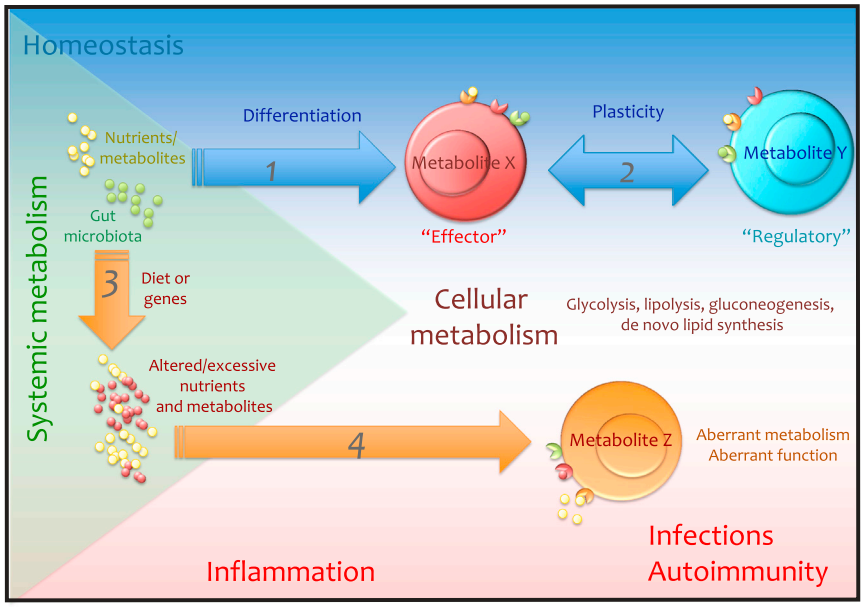

Figure 1. Systemic to Cellular Immunometabolic Crosstalk

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).

Can we learn more from human genetic conditions predisposing to dyslipidemia? To date, genetic conditions associated with extreme hyperlipidemic phenotypes include familial hypercholesterolaemia (FH), which, because of the defective liver catabolism, results in extremely elevated plasma levels of LDL-C and favors atherosclerotic processes (Sniderman et al., 2014); and familial chylomicronemia syndrome (FCS), which is the consequence of a delay in the catabolism of TG-rich lipoproteins and results in extremely elevated plasma TG levels (Tremblay et al., 2011). Homozygous and heterozygous FH patients are at a very elevated risk of premature death due to myocardial infarction within the first two decades of life (Sniderman et al., 2014), whereas FCS results in recurrent acute pancreatitis (Tremblay et al., 2011).

These extreme metabolic disorders lead to a flux of lipid nutrients in the circulation and might therefore be conditions where the interplay between systemic and cellular metabolism on immune cells can be addressed. Despite the fact that changes in immune cell subsets have been described in relation to plasma lipids and lipoproteins levels (Ammirati et al., 2010, 2012), there are no data available on the metabolic immune cell setting in these patients. However, it has to be borne in mind that lifelong metabolic impairment in these patients could trigger adaptation mechanisms; in other words, the potential effect of drugs modulating metabolic responses on immune cells in these patients might be different from that observed in patients with immune diseases.

Obesity, Diabetes, and NAFLD

Obesity predisposes to insulin resistance, diabetes, NAFLD, and atherosclerosis (Kahn et al., 2006). The transition of obese subjects from metabolic health to metabolic dysregulation is thought to be catalyzed by chronic low-grade inflammation in metabolic organs, to which a multitude of immune cells contribute (Chatzigeorgiou and Chavakis, 2015; Chatzigeorgiou et al., 2012; Ip et al., 2015; Osborn and Olefsky, 2012). In the AT and liver, multiple close interactions between immune cells and parenchymal cells (adipocytes and hepatocytes) might contribute to metabolic homeostasis and metabolic dysfunction in the lean and obese state, respectively (Chatzigeorgiou and Chavakis, 2015).

Type 2 immunity predominates in the lean AT, whereby eosinophils, M2-like macrophages, or type 2 innate lymphoid cells (and the cytokines they produce, such as IL-4) promote not only an anti-inflammatory environment but also homeostatic functions of the AT, such as thermogenesis and energy dissipation via a process termed "beige" adipogenesis (white adipocytes with "brown-like" properties) (Brestoff et al., 2015; Chatzigeorgiou and Chavakis, 2015; Harms and Seale, 2013; Osborn and Olefsky, 2012; Qiu et al., 2014; Wu et al., 2011). In contrast, increased energy storage in the expanding AT in obesity might promote adipocyte dysfunction and a pro-inflammatory milieu with enhanced abundance of $CD8^+$ T cells and M1-polarized pro-inflammatory macrophages, which are thought to trigger insulin resistance (Chatzigeorgiou and Chavakis, 2015; Chatzigeorgiou et al., 2014b; Ip et al., 2015; Lumeng et al., 2007; Mathis, 2013; Nishimura et al., 2009; Osborn and Olefsky, 2012). Several overlapping and interdependent mechanisms, including relative hypoxia of the expanding AT and activation of the endoplasmic reticulum (ER) stress response, have been proposed to contribute to obese AT dysfunction and thereby inflammation (Chmelar et al., 2013; Hotamisligil, 2010; Ichiki and Sunagawa, 2014). Furthermore, the enhanced abundance of fatty acids in obesity might directly promote AT inflammation in a TLR4-dependent manner (Shi et al., 2006).

Interestingly, obesity might trigger not only recruitment but also local proliferation of AT macrophages in a manner dependent on the chemokine MCP-1 (Amano et al., 2014). At the same time, the percentage of AT Treg cells shrinks with increasing obesity (Cipolletta et al., 2012; Feuerer et al., 2009; Mathis, 2013). The number of AT Treg cells might be regulated by invariant natural killer T cells, which also promote an anti-inflammatory switch in AT macrophages (Lynch et al., 2015). Moreover, AT Treg cell development and maintenance require IL-33 signaling and the transcriptional regulators BATF and IRF4 (Vasanthakumar et al., 2015), whereas IL-21 negatively regulates IRF4 and AT Treg cells (Fabrizi et al., 2014).

The inflammatory environment of the obese AT directly contributes to insulin resistance. In particular, activation of immune receptors, such as TLRs, IL-1 receptor type I (IL-1RI), and/or tumor necrosis factor receptor (TNFR), results in the activation of NF-κB and JNK signaling, which can induce serine phosphorylation of IRS-1 and IRS-2 and thereby inhibition of downstream insulin signaling. It can also propagate inflammatory gene expression and lead to a positive paracrine loop, contributing further to obesity and insulin resistance (McNelis and Olefsky, 2014).

Besides causing inflammation of the AT, obesity promotes liver inflammation, leading to NAFLD and non-alcoholic steatohepatitis (NASH) (Wree et al., 2013). Obesity-related liver inflammation is mediated by inflammatory activation of Kupffer cells and infiltrated monocytes and/or macrophages (Huang et al., 2010; Miura et al., 2012; Stienstra et al., 2010; Tosello-Trampont et al., 2012). Additionally, cells of the adaptive immunity and NKT cells might promote not only NASH and fibrosis (Sutti et al., 2014; Syn et al., 2010) but also the progression to hepatic carcinogenesis (Wolf et al., 2014). Treg cells might counteract inflammation and NASH development (Ma et al., 2007). For instance, reduction of Treg cells in mice double deficient in the co-stimulatory molecules B7.1 and B7.2 resulted in enhanced obesity-related inflammation in the AT and liver and development of insulin resistance and NASH (Chatzigeorgiou et al., 2014a). Thus, the role of different immune cell subpopulations as modulators of metabolic inflammation and insulin resistance in the AT and liver in obesity is unequivocal.

Several studies have addressed the question of how the cellular metabolism of immune cells and their function is shaped by the alterations of obese metabolic organs. For instance, lipid accumulation in AT macrophages or oxidized LDL accumulation in Kupffer cells promotes the M1 pro-inflammatory state in both cell types, further exacerbating obesity-related AT or liver inflammation, respectively (Bieghs et al., 2013; Prieur et al., 2011). AT macrophages contribute substantially to lipid trafficking. Obesity-related lipid accumulation induces lysosome biogenesis, resulting in lipid catabolism in AT macrophages (Xu et al., 2013). In this context, lipoprotein lipase in AT macrophages enhances their ability to sequester excess lipids in obesity and supports glucose tolerance (Aouadi et al., 2014). On the other hand, macrophage-specific expression of the cholesteryl ester hydrolase promotes the M2 state in Kupffer cells, thereby decreasing NAFLD (Bie et al., 2012).

Insulin itself might promote T cell activation and responsiveness through its ability to enhance glucose uptake, amino acid transport, lipid metabolism, and protein synthesis (Helderman, 1981; Stentz and Kitabchi, 2003). Given that insulin enhances energy and protein-synthesis requirements for appropriate T cell functions, defects in insulin receptor signaling might lead to inappropriate immune responses and chronic inflammation in metabolic states such as obesity and diabetes. Insulin might support Th2 T cell differentiation (Viardot et al., 2007), which can modulate inflammation. In addition, Treg cells express the insulin receptor, and high levels of insulin via activation of the AKT-mTOR pathway can impair the ability of Treg cells to produce IL-10. IL-10 in turn inhibits the production of TNF by macrophages (Han et al., 2014).

The AT-derived hormone leptin represents one of the molecular links connecting nutritional status, AT, and T-cell-mediated immune responses, as extensively reviewed in La Cava and Matarese (2004). Since its discovery in 1994, compelling experimental evidence has shown that both leptin and leptin receptor (LepR) deficiency are associated with increased susceptibility to infections but also resistance to autoimmune diseases, such as type 1 diabetes, multiple sclerosis (MS), and experimental colitis in mice (La Cava and Matarese, 2004). These effects were linked to its capacity to boost both Th1 and Th17 cell immune responses on the one side and to restrain proliferation of Treg cells on the other (La Cava and Matarese, 2004). Because AT Treg cells support AT homeostasis and prevent obesity-related insulin resistance (Cipolletta et al., 2012), the possibility that in overweight subjects the depletion of AT-resident Treg cells might be linked to the capacity of leptin to constrain Treg cell proliferation should be considered (De Rosa et al., 2007).

Another major interaction between metabolism and immunity in diabetes is the impairment of host defense mechanisms in diabetic patients. Epidemiological studies have shown that patients with diabetes have a higher susceptibility to infections than do healthy individuals (Joshi et al., 1999). Several explanations have been proposed for this increased susceptibility to infections in diabetes patients: (1) a microbiological effect inducing bacterial growth by hyperglycemia, (2) inhibitory effects of ketoacidosis on leukocyte phagocytosis and killing of pathogens, and (3) defective activation of cellular and/or humoral immunity due to impaired production of proinflammatory cytokines (Delamaire et al., 1997; Gallacher et al., 1995). This latter effect has been supported by a study reporting a defective production of proinflammatory Th1 cell cytokines, such as IFN-γ, in patients with diabetes. The mechanism leading to this defect has been reported to relate to defective expression of IL-18 receptors on the lymphocyte membrane from diabetes patients and thus a "de facto IL-18 resistance" and decreased capacity to induce IFN-γ production (Zilverschoon et al., 2008). Because IFN-γ has long been known to be crucial for the activation of phagocytosis, the release of oxygen and nitrogen radicals by neutrophils, and increased intracellular bacterial killing (Murray, 1994), this represents an important immune defect in patients with diabetes. A recent study has reported that neutrophils from diabetic patients are more susceptible to forming extracellular traps (NETs) as a result of increased expression of peptidylarginine deiminase 4, a key enzyme of chromatin decondensation (Wong et al., 2015). Although this mechanism could be aimed at improving microbial defense, it might also help in explaining the poor wound-healing capacity of diabetic individuals.

Interestingly, in addition to a generalized immune inflammatory response, activation of adaptive immunity and autoimmune responses against pancreatic beta cells are often detected in obese and type 2 diabetes (T2D) patients, further suggesting the activation of aberrant immune circuits as a consequence of metabolic overload and—possibly—increased insulin secretion (Brooks-Worrell et al., 2013; Sarikonda et al., 2014; Winer et al., 2011). Abnormalities of mucosal-associated invariant T (MAIT) cells, a novel subset of innate-like T cells that recognize bacterial ligands (Dusseaux et al., 2011; Le Bourhis et al., 2011), have recently been described in T2D and obese patients (Magalhaes et al., 2015). In these patients, these cells are dramatically decreased in the circulation and accumulate in the AT, where they display an activated, Th17-cell-like phenotype. The alteration of this T cell subset further emphasizes the link between metabolic stress and the gut microbiota, because vitamin B2 metabolites produced by bacteria are required for generating MAIT-cell-activating ligands (Kjer-Nielsen et al., 2012; Patel et al., 2013).

The Gut Microbiota and Systemic Metabolism

Rising evidence suggests that variation in the gut microbiome at the gene and species levels predisposes individuals to increased risk of obesity-related metabolic disorders, including insulin resistance and T2D (Delzenne et al., 2011). The composition of the gut microbiota differs between obese and lean individuals, between diabetic and non-diabetic patients, and between patients with and without hepatic diseases. The qualitative and quantitative changes in the intake of specific nutrients not only affect the composition of the gut microbiota but also can modulate the expression of genes in host tissues, such as the liver and AT (Delzenne et al., 2011). This in turn might affect the fat mass and lead to metabolic alterations associated with the gut barrier and/or liver function and immunity. The composition of the gut microbiota also defines the differential production of metabolites, which have long been implicated in homeostatic and metabolic events, including inflammatory activation, both inside and outside the gut. The impact of these metabolites on immune cell differentiation and function has only recently begun to be appreciated (Dorrestein et al., 2014; Sharon et al., 2014; Thorburn et al., 2014).

For example, complex carbohydrates, such as dietary fibers, are metabolized by the colonic microbiota to oligosaccharides and monosaccharides and then fermented to short-chain fatty acid (SCFA) end products, mainly acetate, propionate, and butyrate. SCFAs are absorbed in the colon, where butyrate provides energy for colonic epithelial cells, and acetate and propionate reach the liver and peripheral organs, where they are substrates for gluconeogenesis and lipogenesis (Dorrestein et al., 2014; Sharon et al., 2014; Thorburn et al., 2014).

In addition to being energy sources, SCFAs control colonic gene expression by inhibiting the enzyme histone deacetylase (HDAC) (Davie, 2003) and exert metabolic regulation by signaling through G-protein-coupled receptors (GPCRs) (Tan et al., 2014). Probably the best-characterized metabolite-sensing GPCRs are GPR43 and GPR109A, which bind SCFAs. GPR43 and GPR109A appear to be important for gut homeostasis, and both are expressed by the colonic epithelium, by inflammatory

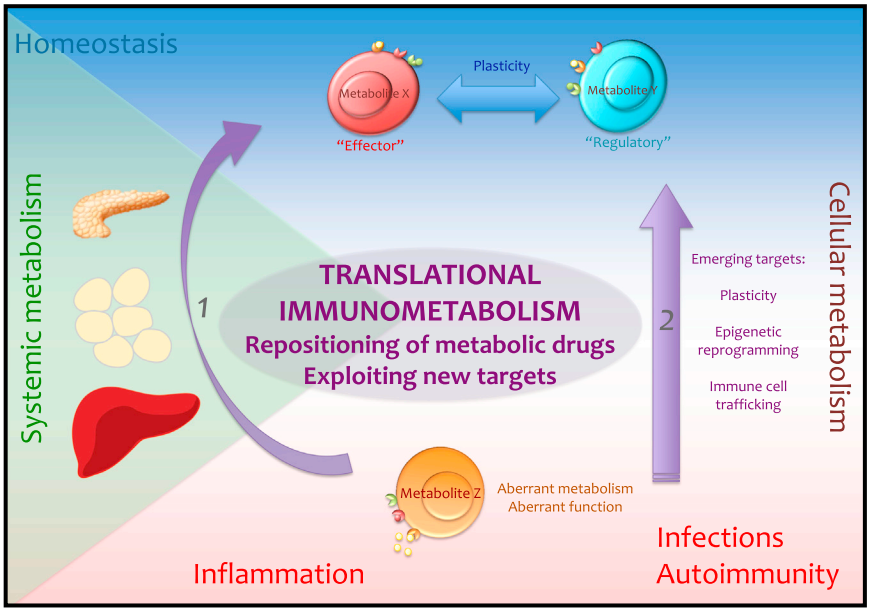

Figure 2. The Molecular and Translational Basis of Immunometabolism

The profound integration of systemic and cellular metabolism suggests that therapeutic manipulation of systemic metabolism could re-establish immune homeostasis. The main challenge in translational immunometabolism is the identification of selective metabolic alterations in pathogenic immune cells and the definition of the molecular pathways selectively engaged by homeostatic metabolic immune cell phenotypes (effector versus regulatory) as an end point of immunometabolic therapies. Effective strategies might involve the following: (1) repositioning of existing ("old") metabolic drugs, which, by improving homeostasis of metabolic organs (liver, adipose tissue, and pancreas), can divert metabolites to alternative routes and thus define systemic and cellular metabolic responses; and (2) reprogramming immune cells via epigenetic events and/or via the control of the metabolite milieu, as well as via modulating metabolic-dependent immune cell trafficking.

leukocytes (such as neutrophils and macrophages), and by Treg cells. Regulation of colonic and peripheral Treg cell numbers relies upon the expression of these metabolite-sensing receptors by colonic macrophages and DCs, which promote Treg cell differentiation (Furusawa et al., 2013; Singh et al., 2014; Smith et al., 2013). Further, butyrate has been shown to promote the extrathymic induction of Treg cells via the intronic enhancer CNS1 (conserved non-coding sequence 1) (Arpaia et al., 2013). This effect was potentiated by propionate capable of HDAC inhibition. Signaling through these receptors also affects other immune functions depending on the cellular type. For example, SCFAs suppress inflammation through GPR43 signaling in immune cells, such as neutrophils (Maslowski et al., 2009; Sina et al., 2009). GPR109A binds the SCFA butyrate but also the tryptophan metabolite nicotinic acid. Nicotinic acid is currently used in metabolic diseases to decrease plasma TG and increase HDL-C levels (Remaley et al., 2014). All of the metabolite-sensing GPCRs are expressed by immune cells, particularly by innate-type cells (Thorburn et al., 2014). They are also expressed on the intestinal epithelium, which probably relates to roles in maintenance of epithelial integrity, and by metabolism-related tissues or cells, for instance, pancreatic islets or white AT (Thorburn et al., 2014). The role of many of these receptors is poorly defined. Given that many specialized metabolites isolated from other microbes, such as rapamycin, are now in clinical use to control immune-mediated diseases and that changes in the gut microbiota can be reversed by dieting and related weight loss, metagenomic and integrative metabolomic approaches could help elucidate which bacteria in the human gut, or more specifically which active metabolites or gene activities, contribute to the control of host energy metabolism and pave the way to a myriad of novel and targeted approaches for immunomodulation.

Metabolism-Targeting Drugs and Immune Function

Several drugs that are currently used in clinic for patients with diabetes, dyslipidemia, and metabolic dysfunctions have been shown to affect immune cell function. By providing information on the overall effect of systemically targeting a given metabolic pathway, a "retrospective" analysis can provide a human experimental model of how systemic and cellular metabolism integrate to have an impact on immune cells, as well as a molecular basis for the repositioning of "old" drugs as immunomodulators (Figure 2).

Targeting AMPK

Metformin (dimethylbiguanide) is a metabolic drug that is widely prescribed for T2D because of its ability to improve insulin sensitivity. Metformin activates AMP-activated protein kinase (AMPK) (Shaw et al., 2005) and reduces redox shuttle enzyme mitochondrial glycerophosphate dehydrogenase (Madiraju et al., 2014). Metformin has effects beyond those on glucose metabolism and decreases plasma inflammatory markers, including soluble intercellular adhesion molecule, vascular cell adhesion molecule 1, macrophage migration inhibitory factor, and C-reactive protein (Caballero et al., 2004; Dandona et al., 2004). As underlined above, an upregulated glycolysis, even in the absence of hypoxia (aerobic glycolysis, or the so-called "Warburg effect"), has been shown to be a feature of activated immune cells (O'Neill and Hardie, 2013). Activation of glycolysis is under the control of mTOR (Yang and Chi, 2012), and metformin inhibits mTOR through activation of AMPK (Isoda et al., 2006). Inhibition of the Akt-mTOR pathway by metformin has been also shown to inhibit the induction of trained immunity and the protection against reinfection induced by beta-glucans (Cheng et al., 2014).

A non-canonical AMPK-mediated pathway has recently been implicated in the regulation of T cell senescence. Cellular senescence is defined as the irreversible loss of proliferative capacity despite continued viability and metabolic activity (Campisi and d'Adda di Fagagna, 2007). This phenotype arises as a consequence of either telomere erosion or DNA damage by reactive oxygen species (ROS) or the activation of cellular-stress pathways (Campisi and d'Adda di Fagagna, 2007; Passos and Von Zglinicki, 2006). T cell senescence is thought to contribute to

the decline of immune function in old age, and a larger proportion of senescent T cells are commonly observed in the elderly and in patients with chronic viral infections and those with autoimmune disorders (Henson and Akbar, 2010). Senescent T cells in humans are characterized by the re-expression of the naive T cell marker CD45RA, loss of CD28 and CD27 expression, poor proliferative responses, and the shortest telomeres (Coppé et al., 2008; Henson and Akbar, 2010). Far from being inert, senescent T cells exhibit potent effector functions, secrete high levels of both TNF-α and IFN-γ, and display potent cytotoxic activity (Coppé et al., 2008; Henson and Akbar, 2010; Henson et al., 2014), for which they require active metabolism. $CD8^+$ effector memory T cells that re-express the naive T cell marker CD45RA have many characteristics of cellular senescence, including decreased proliferation, defective mitochondrial function, and elevated levels of both ROS and p38 MAPK (Coppé et al., 2008; Henson and Akbar, 2010; Henson et al., 2014). Inhibition of p38 MAPK signaling in senescent $CD8^+$ T cells increased their proliferation, telomerase activity, mitochondrial biogenesis, and fitness (Henson et al., 2014); this effect was the consequence of increased autophagy independent of mTOR activation and was the result of enhanced interaction between p38 interacting protein (p38IP) and autophagy protein 9 (ATG9) (Henson et al., 2014).

Further, in senescent T cells, p38 is not activated by canonical MAPK signaling or by T cell antigen receptor (TCR) signals (alternative pathway) (Chang and Karin, 2001), which are defective in these cells. Instead, senescent human T cells engage a distinct mechanism whereby the intracellular metabolic sensor AMPK triggers autophosphorylation of p38 via the scaffold protein TAB1 (Lanna et al., 2014). Activation of p38 through AMPK-TAB1 was induced by endogenous DNA damage and by a decrease in intracellular concentrations of glucose (defined as the ''intrasensory'' pathway) (Lanna et al., 2014). Once triggered, this pathway inhibits T cell proliferation and telomerase activation via p38 signaling, and this can be reversed by inhibition of AMPK, TAB1, or p38 itself (Lanna et al., 2014).

The effect of metformin on immune function opens the possibility of novel therapeutic applications for this drug. Recent epidemiological studies have suggested that metformin has an unexpected anticancer effect, and metformin is currently in clinical trials for several major cancer types (Viollet et al., 2012). Moreover, the anti-inflammatory effects of metformin open the possibility of its therapeutic use in chronic inflammatory and autoimmune diseases, as one recent study has suggested for systemic lupus erythematosus (SLE) (Yin et al., 2015). Even more exciting, the combination of potentiating effects on antimycobacterial capacity of leukocytes and the dampening of inflammation has recently implicated metformin as a novel adjuvant therapy in tuberculosis (Singhal et al., 2014).

Targeting Cholesterol and Fatty-Acid Metabolism

Lipid content and metabolism in immune cells have to be critically balanced; although the pro-inflammatory effect of cholesterol intake by immune cells contributes to diseases associated with chronic metabolic inflammation, including atherosclerosis and obesity, the promotion of inflammatory responses probably has beneficial effects in the response to infections. Activated T cells take advantage of the Warburg effect to funnel acetyl-CoA into mevalonate and fatty-acid-synthesis pathways. The first is involved not only in steroid synthesis but also in isoprenylation, a key process for the plasma membrane attachment of small GTPases, such as Ras, that are critically involved in T cell function (Thurnher and Gruenbacher, 2015). Cell-intrinsic lysosomal lipolysis is critical in macrophage M2 activation (Huang et al., 2014) and contributes to enhance $CD8^+$ T cell memory (O'Sullivan et al., 2014).

All these observations point to a critical role for the transcription factors modulating the availability of intracellular cholesterol and fatty acids: SREBP controls genes that regulate cholesterol biosynthesis and uptake, and it is activated by low cholesterol levels, whereas LXR is activated by oxysterols (oxidative metabolites of cholesterol), which signal excess intracellular cholesterol content and prompt the elimination (Spann and Glass, 2013). This is achieved mainly through the induction of the expression of the ATP-binding cassette (ABC) transporters, which mediate the reverse cholesterol transport to the liver (Tall and Yvan-Charvet, 2015). Importantly, cholesterol serves as an essential component of the membranes and is critical for the formation of lipid rafts, membrane microdomains that promote the assembly of signaling receptors (Catapano et al., 2014). Thus, cholesterol removal from cells might alter the formation of lipid rafts and the organization or signaling of TLRs and other immune receptors (Koseki et al., 2007). Direct functional studies have substantiated the cross-interference between cholesterol transport and TLR signaling by showing that the absence of ABC transporters favors the bactericidal functions of macrophages (Zhu et al., 2012), possibly through both enhanced function of TLR2, TLR3, and TLR4 and inflammasome activation by cholesterol crystals (Yvan-Charvet et al., 2008). However, this hypothesis has recently been challenged by a report showing that cholesterol depletion of human and mouse macrophages does not influence TLR signaling but instead exerts broad anti-inflammatory effects by upregulating the transcriptional repressor ATF3 and modulation of gene transcription (De Nardo et al., 2014).

Activation of LXR also drives the incorporation of polyunsaturated fatty acids into phospholipids through the induction of the remodeling enzyme Lpcat3. In turn, Lpcat3 activity ameliorates ER stress induced by saturated free fatty acids in vitro or by hepatic lipid accumulation in vivo, thus providing an endogenous mechanism for the preservation of membrane homeostasis during lipid stress and inflammation (Rong et al., 2013). This finding reinforces the concept that modulation of cellular lipid composition critically affects inflammatory responses.

Indeed, extracellular acceptors of cholesterol, such as high-density lipoproteins, contribute to the modulation of immune cell function (Norata et al., 2012) and connect cellular and systemic lipid metabolism by depleting cells of cholesterol and phospholipids (Tall and Yvan-Charvet, 2015; Zhao et al., 2012). This tight equilibrium has to be taken into account when pharmacological targeting of lipid metabolism in immune cells is considered.

Besides this caveat, pharmacological inhibition of cholesterol synthesis is to date the most successful example of how targeting systemic metabolism can reprogram immune cell function toward homeostasis. Statins, inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (which catalyzes the formation of mevalonate, the rate-limiting step for cholesterol synthesis), are the most efficient and widely

used agents in treating cardiovascular diseases. Some of these compounds are endowed with dual functions. Originally designed to target elevated plasma lipid levels, the "traditional" cause of atherosclerosis, statins might also confer cardiovascular benefit by modulating the inflammatory component of this disease. Indeed, beyond lowering plasma lipids, some statins provide a cardiovascular benefit that most likely relies on their capacity to diminish levels of many inflammatory markers (Tousoulis et al., 2014). In the presence of statins, cells that participate in atherosclerosis (endothelial cells, smooth-muscle cells, monocytes or macrophages, and T lymphocytes) display diminished pro-inflammatory functions in in vitro assays (Schönbeck and Libby, 2004). For instance, monocytes express fewer integrins and adhesion receptors, and endothelial cells decrease their synthesis of cell-adhesion molecules, and in both cell types, statins can inhibit the IFN-γ-induced MHCII expression (Kwak et al., 2000).

Some of these effects have been clearly shown to be independent of the HMG-CoA reductase functions of statins (Aktas et al., 2003; Weitz-Schmidt et al., 2001). On the other side, the reported effect of statins on the production of chemokines (Diomede et al., 2001), as well as many of their non-lipid-lowering effects, seems to depend, at least in part, on the biosynthesis of isoprenoids (and downstream prenylated proteins) arising from mevalonate; these isoprenoids critically determine Th1 from Th2 cell fate in pathogenic T cells (Dunn et al., 2006). Indeed, statins simultaneously alter several signaling pathways of immune cells because (1) isoprenoid intermediates serve as important lipid attachments for a variety of proteins (including the small guanosine triphosphate binding proteins) and (2) protein isoprenylation is implicated in intracellular signaling events. As an illustration of their potential impact through these pathways, it has been shown that statins can deviate T cell differentiation toward the generation of Treg cells instead of pro-inflammatory Th17 cells via a mechanism dependent on protein geranylation (Kagami et al., 2009; Kim et al., 2010).

Not only isoprenoids but also sterols were shown to critically affect T cell differentiation. Initially, it was reported that Treg cells require lipid and cholesterol metabolism and that the mevalonate pathway is particularly important for coordinating Treg cell proliferation and for upregulating the suppressive molecules CTLA-4 and ICOS to establish Treg cell functional competency (Zeng et al., 2013). Upregulated lipid biosynthesis via the mevalonate pathway and mTOR was shown to promote the expression of effector molecules and the immunosuppressive activity of Treg cells. However, two recent works seem to contradict this finding (Hu et al., 2015; Santori et al., 2015); indeed, programs for cholesterol biosynthesis and uptake are induced during Th17 cell differentiation along with a concomitant suppression of cholesterol metabolism and efflux. More importantly, a precursor of cholesterol, namely desmosterol, functions as a potent endogenous RORγ agonist, thus orchestrating Th17 cell differentiation. Finally, inhibition of cholesterol synthesis prevents Th17 cell differentiation (Hu et al., 2015; Santori et al., 2015).

How does one explain these contrasting findings? First, it is possible that a number of cholesterol precursors and metabolites might possess dual activities—promoting both LXR and SREBP activation—in order to balance cholesterol homeostasis. Alternatively, they might be rapidly metabolized to compounds with activity opposing that of their precursor (Spann and Glass, 2013). It is tempting to speculate that, under physiological conditions, a similar mechanism might occur in immune cells to prevent excessive polarization toward a specific phenotype (yin-yang response); whether an impairment of this intracellular balance occurs under pathological conditions remains to be explored. Second, statin effects in vitro are largely dependent on the dose used (in many cases supraphysiological) and the type of statin. Indeed, not all compounds share the anti-inflammatory properties, and some, such as simvastatin or lovastatin, are prodrugs, which need to be converted to active metabolites (Mauro, 1993). This process occurs in vivo, but not in vitro, and questions the relevance of data obtained from incubating cells with simvastatin and not with the active hydroxy acid metabolite. Finally, whereas statins effectively control cholesterol and isoprenoid biosynthesis in vitro, in vivo they are prevalently distributed in the liver (Reinoso et al., 2002), and it is less likely that they could inhibit HMGCoA reductase in immune cells to a large extent. All these aspects suggest that the effect of statins on immune cells observed in vitro might not fully translate in physiological settings. Thus, although statins improve disease activity and the inflammation factor in patients with rheumatoid arthritis (Lv et al., 2015), MS (Chataway et al., 2014), and SLE (Ulivieri and Baldari, 2014), it remains to be addressed whether the immunomodulatory effects of statins in vivo are the consequence of a systemic reduction of cholesterol levels or arise from a direct metabolic effect in immune cells, or both.

The activation of PPARs also plays a key role in immunometabolic regulation. PPARs are nuclear receptors that regulate gene transcription. PPAR-α is highly expressed in liver and skeletal muscle, controls genes involved in fatty-acid oxidation (FAO), and plays a pivotal role in energy homeostasis and lipoprotein metabolism by inducing lipoprotein lipase and apoA-I expression (Duval et al., 2007). PPAR-γ is highly expressed in adipocytes, in addition to skeletal muscle, liver, and kidney, and has been shown to regulate the expression of genes that mediate adipocyte differentiation, energy metabolism, and insulin action (Lefterova et al., 2014). PPAR agonists were originally designed to normalize metabolic disturbances; later, targeting these nuclear receptors revealed unexpected effects on the inflammatory response during metabolic diseases. PPAR-α mostly displays anti-inflammatory properties in the context of liver inflammation by directly targeting hepatocytes and Kupffer cells (Stienstra et al., 2007), although important effects were also reported in endothelial cells (Mandard and Patsouris, 2013). Furthermore, PPAR-α activators display significant trans-repressional activities on inflammatory genes by interfering with STAT, AP-1, NF-κB, and NFAT and directly induce the expression of IL-1 receptor antagonist (Mandard and Patsouris, 2013). Finally, PPAR-α activators such as fibrates were shown to shift the cytokine secretion of human T cell lines by inhibiting IFN-γ and promoting IL-4 secretion (Lovett-Racke et al., 2004; Marx et al., 2004).

PPAR-γ plays a pivotal role in AT biology by favoring the alternative activation of macrophages (Odegaard et al., 2007) and also facilitating lipid metabolism in metabolically activated macrophages (Kratz et al., 2014). PPAR-γ expression by visceral AT-resident Treg cells is instrumental for their ability to control the inflammatory state of AT and thereby insulin sensitivity (Cipolletta et al., 2012). Thiazolidinedione and other PPAR-γ agonists

have been shown to restore visceral AT Treg cell function in obese mice (Cipolletta et al., 2012). Interestingly, PPAR-γ and its Ser273 phosphorylation play a crucial role in AT Treg cell numbers and function (Cipolletta et al., 2012; Cipolletta et al., 2015). Beneficial effects of PPARs' activation were reported in other conditions, including inflammatory bowel disease, CNS inflammation, and LPS-induced cardiac and pulmonary inflammation (Mandard and Patsouris, 2013).

In summary, PPAR agonists could become an attractive drug candidate for anti-inflammatory therapies. Although only a small number of anti-inflammatory genes have been identified as direct and classical PPAR targets with a functional PPAR response element in genomic DNA, mechanisms involved in the anti-inflammatory properties of PPARs are broader than what might have been thought originally. Furthermore, given that several genes involved in TG metabolism are targeted by PPARs and these appear to be critical for alterative activation of macrophages (Huang et al., 2014), data from clinical trials addressing the impact of PPAR-α and PPAR-γ agonists on immunometabolic disorders will be pivotal for translating the beneficial effects of these drugs in the clinical immunological setting.

Targeting the mTOR Pathway

It has become clear that in vivo, the modulation of T cell function reflects a dynamic metabolic status. mTOR, a key regulator of T cell metabolism, is induced by TCR and co-stimulatory signals downstream of the PI3K-Akt axis and serves to dynamically integrate nutrient-sensing pathways with signaling pathways involved in differentiation, growth, survival, and proliferation (Pollizzi and Powell, 2014). Upon stimulation, conventional $CD4^+$ and $CD8^+$ T cells utilize the mTOR pathway to meet the increased metabolic demands of T cell activation by switching from primarily oxidative phosphorylation, seen in resting T cells, toward a state of enhanced aerobic glycolysis (Pollizzi and Powell, 2014). Of note, mTOR signaling also influences sterol metabolism in T cells (Zeng et al., 2013). The importance of these phenomena in determining T cell fate was first noticed with the selective inhibitor of mTOR, rapamycin, which prevented the generation of effector T cell responses and promoted the generation of Treg cells (Zheng et al., 2007). This is well illustrated by studies of Treg cells, whose generation and homeostasis is a complex and dynamic phenomenon tightly linked to both immune signals and metabolic cues. The current dogma arising from the literature is that specific T cell lineages have unique metabolic profiles essential for their development and function. Regarding Treg cells, it has been shown that lipid oxidation is the key metabolic program sustaining their in vitro proliferation and function (Michalek et al., 2011). However, in vivo data have established that Treg cells exhibit higher glycolytic and proliferative rates than do their effector counterparts (Procaccini et al., 2010). One could speculate that in vivo, immune cell differentiation is a dynamic process regulated by several interrelated factors. In this sense, proper T cell activation, relying on several oscillatory cues (such as TCR-signal strength, cytokine milieu, and nutrient availability), specifically engages the opportune metabolic programs required to ensure T cell activation on one side and to drive Treg cell commitment to constrain the immune responses on the other. In this context, dynamic and oscillatory changes in mTOR activity seem to be crucial in Treg cell homeostasis in vivo and in vitro, particularly in the context of their metabolic regulation. mTOR activity in freshly isolated human Treg cells, and the phosphorylation of mTOR, is significantly higher in Treg cells than in $CD4^+CD25^-$ effector T cells. Treg cell activity was also studied with a novel approach whereby the mTOR pathway was transiently inhibited in vitro with rapamycin (without exogenous IL-2) prior to anti-CD3 and anti-CD28 stimulation. Surprisingly, the acute or transient mTOR inhibition resulted in the reversal of Treg cell anergy and robust proliferation. Whereas both acute and chronic treatment with rapamycin reduced the proliferation of effector T cells, the proliferation of Treg cells did not occur with chronic rapamycin treatment in the absence of exogenous recombinant IL-2 (Procaccini et al., 2010). Thus, Treg cells appear more sensitive than effector T cells to short and transient perturbation of the mTOR pathway. Of note, the abrogation of Treg cell anergy with acute pretreatment with rapamycin was associated with increased IL-2 production by Treg cells and was reversed by the addition of an IL-2-neutralizing antibody to the cultures, indicating IL-2 dependency. Taken together, these data suggest that "oscillating" leptin or nutrient-dependent mTOR activity might set the threshold for responsiveness of Treg cells. It is possible that in vivo, a continuous "oscillatory" change in mTOR activity depending on the fluctuations in the composition of the extracellular milieu controls the high proliferative rate of Treg cells in mice and humans. Therefore, these data might have relevance in setting novel protocols to control autoimmunity and in vitro expansion of therapeutic Treg cells.

Emerging Targets for Metabolic Immunomodulation: Toward Cell- and Function-Selective Reprogramming?

Recent discoveries have highlighted how metabolic configuration can affect a number of key events in immune responses other than cell division and differentiation. For example, aberrant metabolism can affect epigenetic reprogramming of immune cells, as well as autoimmunity; furthermore, cell metabolic products could act as immune signaling molecules. A better understanding of these processes might provide further avenues for tissue-specific and/or cell-function-specific immunometabolic targeting.

Epigenetic-Metabolic Reprogramming of Innate Immune Cells

Epigenetic reprogramming of myeloid cells, also known as trained immunity, represents a de facto memory of innate immune responses and confers non-specific protection from secondary infections (Netea et al., 2011). A key mechanism for the induction of trained immunity in mammalian monocytes and macrophages is epigenetic reprogramming accompanied by changes in histone marks, such as H3K4me1, H3K4me3, and H3K27Ac (Quintin et al., 2012; Saeed et al., 2014). This process is responsible for the increased responses of the trained cell for host defense genes upon restimulation with different stimuli. The critical set of genes that are triggered upon induction of trained immunity includes genes encoding glycolytic enzymes, suggesting a shift in cellular metabolism of glucose. Indeed, trained monocytes display high glucose consumption, high lactate production, and a high ratio of nicotinamide adenine dinucleotide (NAD(+)) to its reduced form (NADH), reflecting a shift in metabolism with an increase in glycolysis dependent on the activation of mTOR through a dectin-1-Akt-HIF-1α pathway. Inhibition of Akt, mTOR, or HIF-1α

blocks the induction of trained immunity in monocytes (Cheng et al., 2014), indicating that metabolic reprogramming is a key step for the induction of trained immunity. For the long-term changes in the macrophage phenotype, the effect of Krebs cycle metabolites (such as succinate and alpha-ketoglutarate) for inhibition or induction of histone demethylases (such as JMJD3) or the important role of NAD^+ for the activity of the sirtuin class of deacetylases are examples of close interaction between cellular metabolism and epigenetic reprogramming.

Given that epigenetic reprogramming of monocytes can be initiated by microbial moietis (Quintin et al., 2012; Kleinnijenhuis et al., 2012) and metabolites (Arts et al., 2015; Cheng et al., 2014), it is possible that this event might contribute to (1) the establishment of inflammation in obesity and atherosclerosis and (2) the alteration of the gut microbiota, thus making this aspect an intriguing target for therapeutic intervention. It remains to be addressed whether therapeutic control of metabolic risk factors in humans affect epigenetic reprogramming.

Metabolic Regulation of Immune Cell Trafficking

It is becoming increasingly clear that intermediate or end products of metabolic pathways not only function as feedback regulators and provide substrates used by other pathways but also can bind to cognate receptors to initiate de novo signaling cascades. An obvious example is provided by the ability of products of the gut microbiota to regulate systemic metabolism. A number of additional paradigms have recently emerged. The glycolysis end product lactate, released by tumor cells, induces the conversion of macrophages to tumor-associated macrophages (TAMs), which show characteristics of M2 macrophages, via a HIF-1α-mediated mechanism (Colegio et al., 2014). In T cells, extracellular sodium lactate and lactic acid can selectively regulate multiple functions of $CD4^+$ and $CD8^+$ T cells, including trafficking and retention in inflamed tissue, via subtype-specific transporters Slc5a12 and Slc16a1, which are selectively expressed by $CD4^+$ and $CD8^+$ subsets, respectively, and inhibit the glycolytic pathway (Haas et al., 2015).

Cytoskeletal rearrangements necessary for migration are one of the most energy-consuming cellular processes (Bernstein and Bamburg, 2003; Daniel et al., 1986). Despite the fact that migratory events dominate during the lifespan of most T lymphocytes, very little is known about the metabolic pathways supporting T cell motility. Indirect evidence suggests that the metabolic status can influence T cell homing patterns. Rapamycin-mediated inhibition of mTOR causes effector T cells to re-express CD62L and CCR7 and home to secondary lymphoid organs (SLOs), where they are trapped away from target sites in the periphery (Finlay and Cantrell, 2011; Sinclair et al., 2008). Therefore, rapamycin can promote immunosuppression by redirecting effector T cells from peripheral tissues to SLOs. A direct contribution of the metabolic machinery—and glycolysis in particular—to the modulation of T cell motility and migration has recently become evident. For example, CCL5-induced CCR5 signaling was shown to activate the mTOR-4E-BP1 pathway to directly modulate mRNA translation and initiate the synthesis of chemotaxis-related proteins in human T cells (Murooka et al., 2008), an event that was shown to be dependent on glycolysis, AMPK signaling, and downstream substrates ACC-1, PFKFB-2, and GSK-3β. In addition, the CCL19- and S1P-mediated signals have been shown to inhibit basal FAO, but not basal glycolysis, of human resting $CD4^+$ effector memory T cells (Taub et al., 2013). However, anti-TCR antibody activation of memory T cells increased their chemotaxis to CCL5, which was dependent predominantly on glycolysis rather than FAO, suggesting that distinct metabolic pathways are engaged by migratory signals depending on the T cell activation status. Further, recent evidence has shown that murine $CD4^+$ and $CD8^+$ T cell migration is highly dependent on aerobic glycolysis in vitro and in vivo (Haas et al., 2015). This new evidence opens the way for function-selective (i.e., migration) targeting of immune cells by metabolic manipulation. This approach might provide the advantage of selectively affecting highly migratory T cells, such as effector T cells, while sparing other populations.

Aberrant Metabolism and Autoimmunity

Dysfunctional T cell responses are a typical feature of autoimmunity and associate with altered metabolic profiles in T cells from murine models of autoimmune diseases (Nath et al., 2009). It has been shown that T cell dysregulation associates with metabolic alterations in several human autoimmune conditions, such as MS and SLE. In MS subjects, increased levels of both glutamine and glutamate have been described, and glutamate concentration correlates with disease severity (Sarchielli et al., 2003; Tisell et al., 2013). This is an important cue, given that TCR engagement of naive $CD4^+$ T cells triggers rapid uptake of glutamine, which relies on the amino acid transporters. Glutamine is critically required for naive $CD4^+$ T cell differentiation toward Th1 and Th17 inflammatory T cells; when activated in glutamine-free medium, naive $CD4^+$ T cells display a severe defect in the generation of both Th1 and Th17 cells. These findings are in line with recent data suggesting that proliferation of Treg cells is impaired in subjects with relapsing-remitting MS (RR-MS) as a result of over-activation of the mTOR pathway associated with reduced IL-2-R-STAT5 signaling (Carbone et al., 2014). A recent report showed that glycolysis and mitochondrial oxidative metabolism were elevated in $CD4^+$ T cells from lupus-affected mice, and inhibition of these pathways (with 2DG and metformin, respectively) reduced IFN-γ production (Yin et al., 2015). Metformin also restored defective IL-2 production by $CD4^+$ T cells from lupus-affected mice. In vivo, treatment with a combination of metformin and 2DG normalized T cell metabolism and reversed disease biomarkers. In addition, enhanced glycolysis and mitochondrial metabolism were observed in $CD4^+$ T cells from SLE patients and correlated with T cell activation status; their elevated IFN-γ production was reduced upon in vitro treatment with metformin. Likewise, metformin has been also shown to reduce Th17 cell response and attenuate disease severity in experimental autoimmune encephalomyelitis (Nath et al., 2009). Because proliferating $CD4^+$ T cells and effector $CD8^+$ T cells are highly reliant on glycolysis, this approach might lead to non-specific immunosuppression. A potential alternative for selective targeting of pathogenic T cells has been provided by observations that these chronically activated lymphocytes in lupus and graft-versus-host disease (GVHD) share several metabolic features, including increased OXPHOS and depleted antioxidants, such as glutathione, as a consequence of low glycolytic activity (GSH) (Wahl et al., 2012). Bz-423 is a non-anxiolytic 1,4-benzodiazepine that targets the mitochondrial F_1F_o ATPase (Johnson et al., 2005), blocking respiratory-chain function and generating superoxide. Depletion of antioxidants in pathogenic T cells renders them selectively susceptible to

enhanced ROS production induced by Bz-423, and it has been reported that Bz-423 rescued mice from lethal GVHD while not adversely affecting the repopulation of donor thymocytes, granulocytes, or lymphocytes (Gatza et al., 2011).

Concluding Remarks

Intense ongoing investigation of immune cell metabolism is yielding an exponentially growing amount of information. Although such information provides potential new tools for therapeutic manipulation of the immune response, it also underlines the complex integration of immune networks and systemic metabolism. Although the modulation of immunometabolism represents a new avenue for tackling several diseases, a transversal expertise involving immunology, endocrinology, and lipidology is required for successfully translating preclinical data for the benefit of human health. To date, most investigations have focused on glucose metabolism and less on beta-oxidation of lipids, and more studies are needed to integrate different anabolic and catabolic aspects of glucose, protein, and lipid metabolism in the context of the immune response.

Another major challenge in the field is to resolve the "big picture" of how a broad array of metabolic pathways differentially integrate into the complexity and variety of immunological responses in health and disease. In other words, basic in vitro studies or investigations in experimental models need to move to the next level, i.e., human physiology, by capitalizing on the treasure throve of basic information that can be obtained from human pathology, as we have described here.

As a starting point, we need to develop standardized techniques allowing assessment of the metabolism of patient-derived immune cell populations. Retrospective review of the immune alterations and the impact of traditional metabolic drugs on inflammation in patients might help modeling the physiologic integration of metabolism and immune function. In parallel, increased understanding of the symbiotic regulation of systemic metabolism by physiologic products of the gut microbiota and the identification of differential metabolic programs operating in distinct immune cell subsets and functions will deliver tools for cell- and function-specific targeting—the "holy grail" of therapeutic immunomanipulation.

AUTHOR CONTRIBUTIONS

G.D.N. and F.M.M.-B. wrote the manuscript, finalized the draft, and prepared the figures. G.C., T.C., G.M., M.G.N., A.N., and L.A.J.O. wrote specific parts of the manuscript and revised the entire draft.

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