Immunometabolism governs dendritic cell and macrophage function


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Recent studies on intracellular metabolism in dendritic cells (DCs) and macrophages provide new insights on the functioning of these critical controllers of innate and adaptive immunity. Both cell types undergo profound metabolic reprogramming in response to environmental cues, such as hypoxia or nutrient alterations, but importantly also in response to danger signals and cytokines. Metabolites such as succinate and citrate have a direct impact on the functioning of macrophages. Immunogenicity and tolerogenicity of DCs is also determined by anabolic and catabolic processes, respectively. These findings provide new prospects for therapeutic manipulation in inflammatory diseases and cancer.

The main challenge of metabolic pathways has always been their complexity. This stems from the number of metabolites (which intracellularly can run into the thousands), their chemical complexity, and the sophisticated regulation of the enzymes that control them. Recent discoveries on the role of metabolic pathways in immune cell function have brought the burgeoning area of immunometabolism to the forefront for many immunologists. In this review, we will discuss recent findings in macrophages and DCs, critical cell types for both innate and adaptive immunity. A primary goal for immunologists is to uncover the molecular players in processes that provide a detailed account of how the effector functions of immune cells are controlled. These processes become dysregulated in disease. The analysis of metabolic reprogramming in macrophages and DCs provides new insights into how these cells perform their functions, including cytokine production, phagocytosis, or antigen presentation. The somewhat surprising finding is that metabolic processes such as glycolysis, the Krebs cycle, and fatty acid metabolism have highly specific effects on macrophage and DC function. The manipulation of these pathways can dramatically alter the functioning of these cells in specific ways, rather than simply being involved in energy generation or general biosynthesis. Metabolic reprogramming as a phenomenon is therefore joining other key immunoregulatory events that govern the nature of the immune response, both in health and disease.

What is metabolic reprogramming?

A simple view of metabolic reprogramming is that it reflects the responses of cells to critical changes in the environment. For example, under normoxic conditions, cells can use oxidative phosphorylation (OXPHOS) to generate ATP. Critical components of the electron transport chain (ETC) use NADH and FADH generated as a result of reactions in the Krebs cycle, which in turn is fueled by glucose, fatty acids, and glutamine. In contrast, when O₂ tensions are low, cells can to a greater or lesser degree generate ATP through glycolysis and independently of OXPHOS, but this pathway is highly dependent on glucose as a sole fuel source. The core metabolic pathways are essential for interchanging carbons between sugars, fatty acids, nucleic acids, and proteins, and therefore, metabolic flexibility can play a critical role as prevailing nutrient and oxygen conditions change. This can be of great importance if a cell is faced with differing functional demands. A critical point from the perspective of this review is that recent work has emphasized the fact that changes in key metabolic regulatory events in immune cells can be initiated not only by nutrient and oxygen conditions, but also in reprogramming events downstream of ligation of pattern recognition receptors (PRRs), cytokine receptors, and/or Ag receptors (and likely other receptors). Thus, in immune cells, there is the potential for metabolic changes to occur in response to instructional signals received from other cells or from changes in the environment unrelated to nutrient or oxygen availability, such as the presence of danger signals or antigen (Fig. 1).

We are only beginning to understand why these events are occurring. What is clear is that to an immunologist, metabolism is coming to mean something other than ATP production, anabolism (which is the term for biosynthesis), and catabolism (the term for degradation of metabolites). Rather, “immunometabolism” encompasses the idea that changes in metabolism actually govern the phenotype of immune cells by controlling transcriptional and posttranscriptional events.
that are central to activation. This has become especially clear in macrophages, although it is also a feature of T cell polarization and DC activation (and likely of other immune cells as well). Early work on leukocyte metabolism had found evidence for increased oxygen consumption during phagocytosis, which was identified as the NADPH oxidase system generating oxygen radicals (Rossi and Zatti, 1964). Also, as far back as 1963, it was observed that monocytes switch to glycolysis when they are phagocytosing particles, whereas when alveolar macrophages are phagocytosing, they use oxidative phosphorylation (Oren et al., 1963). Furthermore, enhanced uptake of glucose was a well-known feature of LPS-activated macrophages, which was pinpointed to induction of the glucose transporter GLUT1 (Fukuzumi et al., 1996). More recent work has confirmed that a shift toward glycolysis and fatty acid synthesis, and away from Krebs cycle and fatty acid oxidation (FAO), makes a macrophage proinflammatory (Newsholme et al., 1986; O'Neill and Hardie, 2013; Jha et al., 2015). This can be achieved by adding LPS, and the metabolic shift is critical for enhanced production of proinflammatory cytokines, notably IL-1β (Tannahill et al., 2013). This is similar to the situation in T cells, where glycolysis is needed for Th17 function (the inflammatory lymphocyte), but if this is blocked, then the T cell becomes a regulatory T cell, which is antiinflammatory (Buck et al., 2015).

The change in metabolism toward glycolysis that is apparent in LPS-activated macrophages and in Th17 cells is termed the Warburg effect (or aerobic glycolysis; Oren et al., 1963; Tannahill et al., 2013). This type of metabolism was first recognized by Otto Warburg during his research on tumor cells. In this setting, aerobic glycolysis occurs in part to generate nucleotides from the pentose phosphate pathway (which branches off glycolysis at glucose-6-phosphate), although why this should be important in macrophages is not particularly clear because LPS-activated macrophages do not proliferate. One possible consequence is the production of NADPH for NO and reactive oxygen species (ROS) production, or possibly nucleotides for mRNA, long non-coding RNA, or microRNA synthesis. Warburg was of the view that this altered metabolism was evident only in tumors and in fact discounted the reported aerobic glycolysis in white blood cells as an artifact of the preparation of the white blood cells (Warburg et al., 1958). What Warburg actually missed was that the white blood cells were becoming activated (probably by adherence to glass) during their preparation, and we now know that Warburg metabolism is indeed a feature of activated macrophages and DCs. The key question now is how changes in metabolism and associated changes in metabolite levels are able to facilitate the specialized activities of these cells.

**Figure 1. Immune signals as metabolic re-programmers in macrophages and DCs.** Normoxia or hypoxia will reprogram the metabolism of cells, with normoxia promoting the Krebs cycle and oxidative phosphorylation and hypoxia promoting glycolysis, both for ATP production. In normoxia, glucose, fatty acids, and glutamine can all feed Krebs cycle, whereas for glycolysis glucose is metabolized. Immune signals can have a similar effect, with helminths driving IL-4 production to produce oxidative phosphorylation and danger signals (e.g., LPS acting via TLR4) promoting glycolysis and fatty acid synthesis. Metabolic reprogramming is therefore not only a consequence of the level of oxygen and nutrients, and instead is being driven by immune signals. The metabolism in IL-4-activated macrophages and DCs allows for long-term responses appropriate for handling parasites, whereas glycolysis is more suited to a rapid response to bacterial infection.

**Macrophage differentiation: Different activators, different metabolic pathways**

A key contribution is the finding that macrophages activated with LPS, either with or without interferon-γ (so-called M1 or classically activated macrophages, which are proinflammatory), have a very different metabolic profile compared with macrophages activated with IL-4 (so called M2 or alternatively activated macrophages, which are more involved in the resolution of inflammation and resistance to helminth parasites). The M1 macrophage utilizes Warburg metabolism, whereas M2 macrophages commit to OXPHOS. This area is reviewed extensively elsewhere (Odegaard and Chawla, 2011; Pearce and Pearce, 2013; Galván-Peña and O’Neill, 2014). Processes that drive the glycolytic switch in M1 macrophages are down-regulated in M2 macrophages. One example is that M1 macrophages express PFK2, an isoform of phosphofructokinase-2 that is highly active, promoting glycolysis (Rodríguez-Prados et al., 2010). In contrast, M2 macrophages express a different isoform, PFKFB1, which is much less active (Kelly and O’Neill, 2015). In contrast, in M2 macro-
phages, the Krebs cycle has a primacy over glycolysis (Vats et al., 2006). FAO in particular has been shown to be critical for feeding the Krebs cycle in these cells (Vats et al., 2006). The source of the fatty acids for oxidation was shown to be triglycerides, which are taken up via CD36 by the M2 macrophage and then hydrolyzed by lysosomal acid lipase (Huang et al., 2014). IL-4 induces this enzyme, possibly via STAT6. The oxidation of the fatty acids feeds the Krebs cycle and if lipolysis is inhibited, the M2 macrophage is less able to mediate resistance to parasitic helminth infection (Huang et al., 2014).

Why do M1 and M2 macrophages adopt markedly different types of metabolism upon activation? One possibility is that the shift to glycolysis in M1 macrophages may be optimally suited to the rapid, short-term bursts of activation that are required at sites of infection or inflammation, whereas FAO in M2 macrophages may be better able to energetically support cell survival, as macrophages continue to fight parasites over a comparatively prolonged time period. However, although these explanations may have weight, a recent study has indicated that the reprogramming of metabolic pathways after classical or alternative activation serve additional critical functions (Jha et al., 2015). The work revealed that in M1 macrophages the Krebs cycle is broken in two places: after citrate and after succinate. In 1986, it had been shown that there was a strong induction of citrate synthase in elicited (inflammatory) macrophages, which would lead to citrate accumulation (Newsom et al., 1986). Both of these metabolites accumulate and have specific functions. In contrast, the M2 macrophage has an intact Krebs cycle and is specialized to generate intermediates for protein glycosylation. Interestingly, these metabolic differences can be used as definitively as other markers to distinguish M1 from M2 macrophages. More importantly though, from the perspective of this review, the findings show that metabolic reprogramming downstream of PRRs and/or cytokine receptors allows cells to initiate the synthesis of important and defining molecules that are critical for distinct cellular functions.

### Metabolic reprogramming in LPS-activated macrophages leading to NO, ROS, and prostaglandins

Citrate accumulation in the M1 macrophage is especially relevant for the production of three important mediators, which make a major contribution to the proinflammatory role of these cells (Fig. 2). These are NO, ROS, and prostaglandins. Citrate has been shown to be involved in the production of these three mediators (Infantino et al., 2011). LPS induces the expression of the mitochondrial citrate carrier, and depletion of this protein by gene silencing decreases the production of NO, ROS, and prostaglandins. Citrate is used to synthesize phospholipids, a source of arachidonic acid needed for prostaglandin synthesis. For NO, citrate can generate NADPH via malic enzyme and pyruvate, and this NADPH can then be used by iNOS to generate NO. The NADPH oxidase will also use NADPH to generate ROS. NADPH can also be generated by the pentose phosphate pathway, which is strongly up-regulated in LPS-activated macrophages (Jha et al., 2015). The sedoheptulose kinase CARKL has been shown to limit the pentose phosphate pathway and is up-regulated in M2 macrophages and strongly down-regulated in M1 macrophages (Haschini et al., 2012), further emphasizing the importance of the pentose phosphate pathway for M1 macrophage function. A single Krebs cycle intermediate is therefore involved in the generation of key mediators of inflammation made by M1 macrophages. M2 macrophages do not make NO, and this is caused by an increase in arginase expression, which decreases arginine levels limiting NO production.

### Metabolic reprogramming leading to the antimicrobial metabolite itaconic acid

Another consequence of citrate accumulation in M1 macrophages is the synthesis of itaconic acid (Michelucci et al., 2013). Itaconate is a nonamino organic acid that is the product of an enzyme encoded by immune responsive gene 1 (Irg1), which converts cis-aconitate (derived from citrate) to itaconic acid.
acid. This metabolite has been shown to have antibacterial properties, with a particular effect on the glyoxylate shunt in *Salmonella typhimurium* and *Mycobacterium tuberculosis* (Michelucci et al., 2013), thereby limiting their viability (Fig. 2). This is perhaps one of the best examples of how metabolic reprogramming has a clear role to play in macrophage effector function: accumulation of citrate leading to itaconic acid, which directly limits the viability of the TB pathogen. Recently, itaconate has been postulated to inhibit Complex II, leading to the build-up in succinate, limiting respiration (Németh et al., 2015). Itaconate may therefore be critical for the switch to glycolysis in LPS-activated macrophages.

**Metabolic reprogramming leading to IL-1β production**

A critical consequence of succinate accumulation in LPS-activated macrophages is induction of IL-1β, a central inflammatory mediator (Fig. 2; Tannahill et al., 2013). It requires two signals to be made. Signal 1 (driven by innate immune receptors) induces transcription of pro–IL-1β and also primes the NLRP3/caspase-1 inflammasome (Wen et al., 2012). Signal 2 activates the inflammasome and is driven by multiple stimuli, including ATP and various materials that are phagocytosed (e.g., the amyloid proteins such as β-amyloid and IAPP). Both of these signals have been shown to involve metabolic reprogramming. First for signal 1, the accumulation of succinate (possibly caused by itaconate inhibiting succinate dehydrogenase) has been shown to lead to HIF1α activation (via inhibition of prolyl hydroxylases). HIF1α then induces IL-1β directly because the gene promoter for IL-1β contains a HIF1α-binding site (Tannahill et al., 2013). Blocking glycolysis with 2-deoxyglucose (2-DG) limits this signal by somehow decreasing succinate, possibly via induction of succinate dehydrogenase. Second, the NLRP3 inflammasome itself needs glycolysis to function (Fig. 2; Moon et al., 2015). The mechanism here appears to involve Hexokinase, which regulates NLRP3 activation, possibly via effects on mitochondria, and again this process is inhibited by 2-DG. IL-1β production in M1 macrophages therefore appears to have an exquisite requirement for the Warburg effect.

**Negative control of metabolic reprogramming in M1 macrophages by ERRα and A20**

A recent interesting finding concerns a connection between the orphan nuclear receptor ERRα and a critical negative regulator of inflammation, the deubiquitinating enzyme A20 (Yuk et al., 2015). ERRα is a well-known regulator of energy metabolism and mitochondrial biogenesis (Villena and Kralli, 2008). A20 has been shown to be a key inhibitor of inflammation in multiple human diseases, recent notable examples being to prevent rheumatoid arthritis and also asthma (Vande Walle et al., 2014; Schuijs et al., 2015). Yuk et al. (2015) have shown that ERRα directly binds to the A20 gene promoter and increases its expression. ERRα-deficient mice are highly susceptible to LPS-induced septic shock and also have elevated glycolysis and decreased oxidative phosphorylation. The inhibition of TLR4 signaling is therefore likely to be two-fold: an increase in oxidative phosphorylation, which might increase the flux through glycolysis and Krebs Cycle, thus decreasing steady-state levels of citrate and succinate, and the induction of A20 (Fig. 2), which will deubiquitinate components in the TLR4 signaling pathway.

**DCs: Glycolysis is critical for activation**

Like macrophages, DCs are specialized to express a range of PRRs that allow recognition of danger signals. After ligation of these receptors, DCs are able to undergo large-scale changes in gene expression that allow them to produce mediators such as chemokines and cytokines that affect the biology of other cells in the environment. In a more specialized way, DCs are also strikingly capable of degrading proteins that they have sampled from the environment to present peptide epitopes in the context of MHC I or II to stimulate T cells and thereby initiate adaptive immunity. The change from resting cell to activated cell is marked in DCs and involves a transition in which the cells become more dendritic, and therefore change appearance, more secretory, and more interactive with other cells. It has become apparent in the last 5 yr that these changes in DC biology are accompanied by profound changes in cellular metabolism that are integral and essential to the activation process (Pearce and Everts, 2015).

As in macrophages, DC activation in response to TLR agonists causes a marked increase in glucose consumption and
lactic acid production (Jantsch et al., 2008; Krawczyk et al., 2010). This is the net result of a rapid increase in glycolytic flux that occurs within minutes of stimulation by TLR agonists in all classical DC subsets examined (Everts et al., 2014), followed by a second metabolic change that occurs particularly in DCs that have been grown from bone marrow in GM-CSF (GM-DCs) and in inflammatory monocyte-derived DCs (Everts et al., 2012). These latter cells commit to Warburg metabolism to generate ATP in the face of inhibitory effects on the ETC of autocrine/paracrine NO production (Everts et al., 2012). The importance of glucose for DC activation is illustrated by the finding that the inhibition of hexokinase, the first enzyme in the glycolysis pathway, by 2-DG strongly blocks the entire activation process (Krawczyk et al., 2010; Everts et al., 2014). It should be noted that detailed metabolic analyses of plasmacytoid DCs are yet to be published.

Although increased glucose uptake by DCs during the early stages after activation is accompanied by lactate production, this does not reflect a commitment to Warburg metabolism as a mechanism for ATP production because during this time ATP is provided by OXPHOS (Everts et al., 2014). Rather, glycolysis fulfills a need of activated DCs for citrate (Everts et al., 2014). Citrate is important for the production of various mediators by LPS-activated macrophages, but in DCs, the export of citrate from mitochondria into the cytoplasm through the citrate transporter SLC25A is particularly important for fueling fatty acid synthesis, which is linked to the requirement of activated DCs to increase the size of key organelles involved in protein synthesis and secretion: the ER and Golgi apparatus. Intriguingly, the enlargement of these compartments occurs simultaneously with increased gene expression downstream of TLRs but is regulated posttranscriptionally by increased glycolytic flux. This is controlled by the Akt-dependent phosphorylation and subsequent activation of hexokinase II, the key enzyme that catalyzes the first step in glycolysis (Everts et al., 2014). In this pathway, Akt is itself activated by TBK1/IKKe, which interestingly are also downstream of RIG-I–like receptor (RLR), so it is possible that the rapid induction of glycolysis is a common response to any innate sensing of pathogens by DCs, allowing them to rapidly respond metabolically to these danger signals.

Switching to Warburg metabolism allows cellular activation and survival in the face of high concentrations of the effector gas NO

In GM-DCs, activation leads to the expression of Nos2 and NO production. NO is a potent inhibitor of the ETC, and these cells adapt by committing to Warburg metabolism to generate ATP and become dependent on this pathway for survival (Everts et al., 2012). It is interesting to speculate about the effect of NO on the metabolism of cells in the vicinity of immune cells that are making this effector gas because, in theory, their relative ability to initiate Warburg metabolism will dictate their ability to survive, and moreover, cells that are restricted to Warburg metabolism might be expected to have limited functional potential. Thus, DCs and macrophages that are making NO may exert strong metabolic control over cells with which they are interacting. Despite the fact that mouse classical DCs do not express Nos2, they do exhibit diminished mitochondrial activity and enhanced glycolysis over the long term after activation with TLR agonists in vivo. These changes are reported to be driven by autocrine type I interferon signaling through HIF-1α (Pantel et al., 2014).

Core nutrient/energy-sensing pathways in metabolic reprogramming in DCs

Cells possess central signaling pathways that are able to sense nutrient and/or energy status and adjust metabolism to be anabolic or catabolic as required. Cellular growth requires anabolic metabolism, and this can be regulated by mTORC1 downstream of PI3K/Akt and growth factor receptors (Fig. 3). Consistent with a role for mTORC1 in DCs, rapamycin, an inhibitor of mTOR, has been shown to selectively inhibit aspects of TLR–driven DC activation in GM-DCs and human monocyte–derived DCs, including the expression of IL-6 and IL-10 and possibly TNF (Cao et al., 2008; Amiel et al., 2012; Boor et al., 2013; Hossaarts et al., 2013), and diminish their immunogenicity (Haidinger et al., 2010). Moreover, deletion of Tsc1, a negative regulator of mTORC1, allows increased basal expression of activation markers (Wang et al., 2013). Nevertheless, in some circumstances, rapamycin may also promote DC immunogenicity by extending cell longevity (Amiel et al., 2012). AMP kinase (AMPK), which is activated by increased AMP relative to ATP concentrations, antagonizes mTORC and promotes catabolic metabolism, in part by inducing the expression of PGC-1α, a key regulator of energy metabolism that promotes mitochondrial biogenesis and therefore the ability of cells to oxidize fatty acids, amino acids, and glucose to fuel the ETC and generate ATP (Fig. 3; Waickman and Powell, 2012; O’Neill and Hardie, 2013). AMPK also promotes autophagy, which in itself is a catabolic process. In DCs, TLR–induced activation is enhanced by the loss of AMPK, and pharmacologic activation of AMPK suppresses TLR–induced glucose consumption and concomitant activation of DCs (Krawczyk et al., 2010; Carroll et al., 2013). Additionally, by promoting autophagy, the activation of AMPK can diminish the ability of cells to produce and present antigenic peptide–MHC complexes to T cells and allow them to become tolerogenic rather than antigenic (Baghdadi et al., 2013). It is particularly intriguing that AMPK can be activated not only by changes in AMP/ATP ratios, but also downstream of surface receptors, indicating again that extracellular signals can induce changes in metabolism that dictate cellular function (O’Neill and Hardie, 2013). This is illustrated in a recent study suggesting that adiponectin is able to inhibit DC activation by promoting production of the antiinflammatory cytokine IL-10 through an AMPK–dependent pathway (Tan et al., 2014). Collectively, these studies indicate that the balance of DC immunogenicity versus tolerogenicity reflects the balance of anabolic versus catabolic
metabolism. In essence, anabolic metabolism might be immunogenic and proinflammatory, whereas catabolic metabolism might be tolerogenic and antiinflammatory (Fig. 3). Because AMPK can antagonize metabolic reprogramming in the face of activation signals, it could represent an excellent target for manipulating DC biology for therapeutic benefits.

**Fatty acid metabolism plays a critical role in the regulation of DC function**

Consistent with the ideas put forward above in the section on macrophage differentiation, there is a growing literature that FAO, an essentially catabolic process, plays a significant role in the development of tolerogenic DCs. This conclusion is based on metabolic analyses of tolerogenic human DCs (Malinarich et al., 2015), as well as the fact that resveratrol, a drug that promotes OXPHOS, and vitamin-D3 and dexamethasone, which promote the expression of genes related to OXPHOS, enhance DC tolerogenicity (Rachamim et al., 1995; Švajger et al., 2010; Ferreira et al., 2015). Recent work has emphasized the complexity of the role of lipid metabolism in the regulation of DC function. DCs from tumors, which inhibit T cell function and thereby facilitate tumor progression rather than regression, accumulate oxidized lipids (Cubillos-Ruiz et al., 2015). These activate the ER stress response through IRE1α, leading to the constitutive activation of XBP1, which plays a critical role in diminishing DC immunogenicity by promoting synthesis and accumulation of fatty acid and triacylglyceride. Remarkably, conditional deletion of XBP1 in DCs renders them more immunogenic and capable of initiating protective immune responses in tumor models, which contrasts significantly with the fact that the same transcription factor normally plays an important role in DC generation, survival, and function (Osorio et al., 2014), and in macrophage activation in response to TLR2 and 4 agonists (Martinon et al., 2010). How the effects of fatty acid synthesis differ so markedly in DCs isolated from tumors compared with those TLR-activated DCs (where it is implicated in ER expansion essential for DC function [Everts et al., 2014]) is an important unanswered question. However, we can speculate that accumulated fatty acids are supporting FAO and therefore tolerogenicity in the cancer setting.

**Signaling pathway activation by metabolites: DCs recognize and respond to changes in extracellular metabolite levels**

As discussed above in the section on IL-1β production, intracellular succinate levels play a critical role in regulating the production of IL-1β in macrophages activated by TLR agonists. However, it is important to recognize that cells can also express receptors, the majority of which are G protein–coupled receptors (GPCRs), that allow them to respond to extracellular metabolites. For example, DCs sense extracellular succinate through the succinate receptor GPR91, and the increase in intracellular Ca²⁺ downstream of this event synergizes with TLR3 or TLR7 (but not TLR2 or TLR4) signaling to promote DC activation and their migratory ability (Rubic et al., 2008). DCs can also respond via specific GPCRs to the short chain fatty acid butyrate (Singh et al., 2014), which is a product of commensal bacteria, to adenosine/ATP (Li et al., 2012), and to lactic acid (Nasi et al., 2013). In contrast to succinate, these metabolites gener-
ally promote IL-10 production by DCs and increase tolerogenicity, although detailed side by side comparisons of the effects of these metabolites alone or with a range of TLR agonists remain to be performed. Nevertheless, these studies are conceptually important because they illustrate that DCs have evolved to integrate signals associated with increased extracellular levels of metabolites with danger signals received through PRRs to regulate immunogenicity.

**Conclusions and future perspectives**

Findings emerging from a renewed research emphasis on metabolism are changing the way we think about the biology of macrophages and DCs. It is now clear that immune system–extrinsic and –intrinsic signals can regulate metabolic pathways and metabolite availability to affect changes in cell function and fate. As we move forward, there is reason to be excited about addressing major unanswered questions in this area of research. We can anticipate interesting findings from comparing the metabolism of resident macrophages from diseased versus healthy tissues, and indeed from comparing the metabolism of resident resting macrophages from different tissues, which have been shown to be quite divergent in terms of core patterns of gene expression (Gautier et al., 2012). Much remains to be understood about the link between metabolic pathways and epigenetic control of gene expression, and this is likely to be critical in both macrophages and DCs. Moreover, the realization that succinate plays important roles outside its prescribed function as an intermediate in the Krebs cycle and that activated macrophages commit significant resources to making itaconic acid, as well as the fact that there are so many GPCRs and poorly defined transporters for metabolites, raise important new questions about the functions of metabolic intermediates in the regulation of immune cell biology. There is also a growing interest in the fact that competition for glucose between T cells and cancer cells within tumors has recently been shown to be critical in terms of determining whether tumors progress or regress (Chang et al., 2015; Ho et al., 2015), and there has been intriguing discussion about the effects on the brain of increased glucose consumption and lactate secretion by LPS-activated microglia, the resident macrophages of this organ (Carpenter et al., 2015). Examining these types of issues further is likely to be important in the future. Also of interest is the effect of microbiome-derived metabolites on immune cell function, which depending on the context could be beneficial or deleterious to the host. Addressing these issues is exciting, not least because it opens up metabolic pathways in macrophages and DCs that could be considered novel therapeutic targets for the regulation of immune responses. It may even be possible for small molecules to reprogram the metabolism of immune cells to treat autoimmune and autoinflammatory diseases. We can look forward to further compelling findings that will hopefully realize the promise of this important area for immunology and immunotherapeutics.

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