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Review

Integrating immunometabolism and macrophage diversity

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ABSTRACT

Macrophages are heterogeneous cells that play a key role in inflammatory and tissue reparative responses. Over the past decade it has become clear that shifts in cellular metabolism are important determinants of macrophage function and phenotype. At the same time, our appreciation of macrophage diversity in vivo has also been increasing. Factors such as cell origin and tissue localization are now recognized as important variables that influence macrophage biology. Whether different macrophage populations also have unique metabolic phenotypes has not been extensively explored. In this article, we will discuss the importance of understanding how macrophage origin can modulate metabolic programming and influence inflammatory responses.

Contents

1. Introduction

1.1. Macrophage heterogeneity and immunometabolism

It is now well accepted that macrophages shift their metabolism in response to environmental cues. In turn, these metabolic adaptations drive specific effector functions in macrophages. Some of the more common events that trigger macrophage metabolic reprogramming include activation of pathogen recognition recep-

Abbreviations: BMDMs, bone marrow derived macrophages; pMACs, elicted peritoneal macrophages; TCA cycle, tricarboxylic acid cycle; CAM, classically activated macrophage; AAM, alternatively activated macrophage; OXPHOS, oxidative phosphorylation; ETC, electron transport chain; TLR, toll like receptor; NO, nitric oxide.

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tors, such as toll-like receptors (TLRs), or nutrient based signals that engage lipid nuclear receptors (PPARγ, ERRγ) and/or kinases (mTOR or AMP kinase). The regulation of metabolism has traditionally been equated with energetics. From this perspective, metabolic shifts occur primarily to maintain the balance of ATP supply and demand. In tissues like heart and skeletal muscle, which have high ATP demand, energy production is indeed the primary job of metabolic pathways. However, the role of metabolic reprogramming clearly extends beyond ATP production and includes regulation of lipid synthesis, nucleotide biosynthesis, cell signaling, and gene expression. Over the past several years the study of metabolism in immune cells has highlighted the importance of the non-ATP generating functions of cellular metabolism. In particular, the ability of specific metabolites and/or metabolic signaling events to regulate cell differentiation and effector function is now appreciated [1,2].

Macrophages have diverse functions in tissue homeostasis and inflammation. Evidence is emerging that the metabolic features of these cells regulate their function, including cytokine release and cell surface receptor expression [3]. One of the clearest examples of this concept comes from the comparison of classically activated "inflammatory" macrophages (CAMs) and alternatively activated "reparative" macrophages (AAM). In general, CAMs are highly glycolytic, whereas AAMs utilize fatty acid metabolism and mitochondrial oxidative phosphorylation (OXPHOS) [4,5]. The distinct metabolic programing of these macrophage subsets is thought to generate unique metabolites that are important for their specific effector functions. At the same time, it has also been recognized that macrophages in vivo are heterogeneous in function based on factors like tissue localization and cell origin [6]. To date, the overlay of immunometabolism with the macrophage diversity has not been explored and represents a critical direction for future research.

In this review we will expand upon established metabolic concepts by exploring how macrophage origin may influence metabolic programming. To accomplish this aim we will take two approaches: (1) review and discuss data comparing the metabolic features of classically activated bone marrow derived macrophages (BMDMs) vs. elicited peritoneal macrophages (pMACs) as a proof of concept that cell origin can influence metabolic behavior; (2) review the data from already existing pools of gene expression profiling to identify metabolic modules that define macrophages from distinct tissues as evidence that these concepts are globally relevant to understanding macrophage biology.

2. Macrophage phenotype and immunometabolism

2.1. Macrophage polarization

Macrophages play important roles in inflammation (cytokine release, phagocytosis) and tissue repair (stem cell proliferation, angiogenesis, fibrosis). The concept that macrophages can be directed towards inflammatory or reparative functions, so called "macrophage polarization" by cues from their microenvironments has been a useful construct to describe macrophage behavior. Activation of TLRs on macrophages by pathogen products or alarmins produces a CAM phenotype whereas IL-4 or efferocytosis promotes an AAM phenotype. CAMs produce inflammatory cytokines and reactive oxygen species, which are important for host defense against infection and the early response to tissue damage. In contrast, AAMs release anti-inflammatory cytokines and are thought to promote angiogenesis and fibrosis. AAMs also mediate host responses to parasites. Over the past decade, several studies have demonstrated that the development of CAMs and AAMs is dependent on distinct modes of metabolic reprogramming (see e.g. [5]). These observations have fueled the concept that metabolic modulation could be used to alter macrophage function in disease states. This topic has been discussed in several recent reviews in detail, so we will only briefly review these established concepts [3,7–9].

2.2. Metabolic phenotype of classically activated macrophages

CAMs are characterized by high rates of aerobic glycolysis, a metabolic feature referred to as Warburg metabolism [10]. In addition to producing ATP, enhanced flux of glucose into glycolysis and the pentose phosphate shunt generates building blocks needed for nucleic acid synthesis, protein synthesis, and lipid synthesis. The other metabolic hallmark of the CAM phenotype observed in bone marrow macrophages is suppression of mitochondrial OXPHOS. This is thought to occur because inflammatory signaling suppresses tricarboxylic acid (TCA) cycle flux at 2 distinct steps [2,5]. One block comes at the level of isocitrate dehydrogenase (IDH) which leads to the accumulation of citrate and the other at the level of succinate dehydrogenase (SDH). Reduced IDH activity correlates with TLR-induced suppression of IDH gene expression and leads to increased shunting of citrate from the mitochondria to the cytosol where it can be converted by acetyl-CoA carboxylase (ACC) to malonyl-CoA or support itaconate synthesis via Irg1[5]. Malonyl-CoA is used for fatty acid synthesis, a key precursor for membrane remodeling and expansion of organelles such the endoplasmic reticulum [11]. Unlike IDH, Irg1 is induced by TLR4 signaling and drives the production of itaconate [12,13]. Itaconate has been described as metabolite possessing both anti-inflammatory and anti-microbial properties [2,14]. While the exact mechanism of action of itaconate is not understood, such duality might stem from its inhibitory properties: being a structural mimetic of succinate, itaconate inhibits both mammalian SDH and microbial Icl enzymes. These two possibilities are not mutually exclusive, however. Strikingly, the amount of itaconate required for microbial killing exceeds the amounts produced by activating macrophages [2,14,15], suggesting that anti-microbial effects of itaconate have to be highly localized to achieve sufficient concentration, e.g. inside phagosomes. Thus, mitochondrial or cytosolic itaconate might play regulatory role while phagosomal itaconate participates in anti-microbial action. The fact that itaconate has roles beyond anti-bacterial/antifungal responses stems from the fact that itaconate and Irg1 are highly induced during anti-viral response as well. Metabo-regulatory roles of itaconate are evident from analysis of the activation of Irg1 knockout (KO) macrophages which show complete absence of succinate accumulation during macrophage activation, and accordingly do not demonstrate SDH breakpoint of the TCA cycle [2]. Thus, itaconate modulates activity of SDH, also known as complex II of the electron transport chain. This places itaconate on the critical intersection of cellular bioenergetics and TCA cycle. Functional importance of this intersection stems from previously reported connection between succinate and Hif1α-IL-1β axis [16,17]. Strikingly, Irg1 KO macrophages are more pro-inflammatory then their wild type counterparts in spite of the fact that succinate does not accumulate. This leads to conclusion that the SDH breakpoint and succinate accumulation per se are not absolutely required for the proinflammatory phenotype of macrophages.

2.3. Macrophage polarization in vivo

The investigation of immunometabolism using ex vivo macrophage systems has led to several key discoveries about the interplay between metabolism and cell function. However, the extent to which these findings translate to the diverse populations of macrophages that exist in vivo remains to be defined. Although the distinction between the CAM and AAM phenotype is black and white in vitro, the in vivo reality is more complicated