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Review

Contribution of metabolic reprogramming to macrophage plasticity and function

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ABSTRACT

Macrophages display a spectrum of functional activation phenotypes depending on the composition of the microenvironment they reside in, including type of tissue/organ and character of injurious challenge they are exposed to. Our understanding of how macrophage plasticity is regulated by the local microenvironment is still limited. Here we review and discuss the recent literature regarding the contribution of cellular metabolic pathways to the ability of the macrophage to sense the microenvironment and to alter its function. We propose that distinct alterations in the microenvironment induce a spectrum of inducible and reversible metabolic programs that might form the basis of the inducible and reversible spectrum of functional macrophage activation/polarization phenotypes. We highlight that metabolic pathways in the bidirectional communication between macrophages and stromals cells are an important component of chronic inflammatory conditions. Recent work demonstrates that inflammatory macrophage activation is tightly associated with metabolic reprogramming to aerobic glycolysis, an altered TCA cycle, and reduced mitochondrial respiration. We review cytosolic and mitochondrial mechanisms that promote initiation and maintenance of macrophage activation as they relate to increased aerobic glycolysis and highlight potential pathways through which anti-inflammatory IL-10 could promote macrophage deactivation. Finally, we propose that in addition to their role in energy generation and regulation of apoptosis, mitochondria reprogram their metabolism to also participate in regulating macrophage activation and plasticity.

1. Sensing of the microenvironment through metabolic adaptation

Macrophages are present in abundant numbers in all tissues of the body where they are regarded as critical in both monitoring and regulating the local tissue microenvironment, including the coordination of organ specific functions of tissue resident cells, such as fibroblasts and parenchymal cells [1,2]. It is increasingly recognized that the composition of the local tissue microenvironment (e.g. the composition of metabolites, cytokines, oxygen tension, inflammatory signals) including signals from other tissue cells are critical determinants of macrophage metabolism and functional plasticity [3–11]. Considering that macrophages are highly sensitive to variations in concentrations of metabolites [3,7,8,10,12–15], substrates [10,12,16], certain lipids [17], oxygen tension [5,18–21], acidification [9], osmolality [22], and other molecular components associated with alterations within the microenvironment (e.g. cytokines) [11,23,24], changes in cellular metabolism in macrophages can function as an important primary indicator of altered tissue homeostasis and thus as a critical regulator of macrophage functional responses [25]. Cellular metabolism in turn may directly affect the microenvironment through generation and/or depletion of metabolites [12]. Furthermore, organ specific differences in availability of substrates, metabolites, or oxygen tension, together with base-line differences in macrophage expression levels of genes that encode for proteins that regulate metabolic and transcriptional processes might account for specificity in macrophage responsiveness across tissues. It follows that the functional phenotype of tissue macrophages may be in near constant flux, continuously changing in response to local environmental cues and local metabolic conditions. This versatility of tissue macrophages (i.e. functional plasticity) is reflected by a vast variety, maybe infinite, number of transcriptional, and

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possibly metabolic phenotypes [4–6,8,26]. For example, during normal homeostasis (e.g. absence of pro-inflammatory stimuli), the resident macrophage must exhibit a functional phenotype that promotes and maintains homeostasis. In contrast, in the presence of tissue stimulation or injury (e.g. pro-inflammatory stimuli), macrophages must detect microenvironmental alterations and actively change from a "base-line" transcriptional and metabolic program that promoted homeostasis into one that is compatible with mounting a pro-inflammatory response, which must return to baseline, once the inciting stimulus has been cleared. Thus, transcriptional and metabolic programs within the macrophage must be inducible and reversible on demand and responsive to environmental cues such that macrophage activation occurs in a regulated fashion with regard to amplitude and duration of activation. These programs must further be tailored to the challenge and to the specific organ/tissue to preserve the integrity and specific organ function [9,27–29]. Thus, a spectrum of inducible and reversible metabolic programs might form the basis of the inducible and reversible spectrum of functional macrophage activation/polarization phenotypes [1,2,30–32]. Here, we review recent evidence that suggests that macrophage function is indeed directly and tightly associated with alterations in cellular metabolism and that macrophage plasticity is directly linked to the ability of the macrophage to alter or reprogram cellular metabolism.

2. Metabolic adaptations associated with inflammatory macrophage activation

ATP production to provide energy for cellular function is essential for cells, including macrophages in both homeostatic conditions and under stress. Glucose is the principal source that can be used for ATP production through two directly linked pathways. The upstream pathway involves metabolism of glucose to pyruvate in the cytosol, where phosphates are transferred from glycolytic intermediates to generate ATP (yielding a net production of 2 ATP molecules). The downstream pathway is the mitochondrial tricarboxylic cycle (TCA cycle, also known as Krebs cycle or citric acid cycle) which is directly linked to glycolysis because pyruvate is converted into acetyl-CoA, which then enters the TCA cycle to generate the reducing equivalents nicotin-amide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2), which donate electrons to the electron transport chain in the mitochondrial oxidative phosphorylation (OXPHOS), in which oxygen serves a electron acceptor to support ATP generation by ATP synthase (yielding a net production of 36 ATP molecules) (Fig. 1). Because complex 2 of the respiratory chain (SDH, succinate dehydrogenase) is part of the TCA cycle, a fully functional TCA cycle is tightly linked to fully functional oxidative phosphorylation, and mitochondrial function. When pyruvate becomes limiting due to reduced glycolysis, cells can also metabolize glutamine or fatty acids to replenish the TCA cycle and maintain OXPHOS. In contrast, when oxygen becomes limiting or the TCA cycle becomes interrupted (see below) cells reprogram metabolism to produce ATP by diverting glycolytic pyruvate to lactate instead of acetyl-CoA. Although glycolysis yields less ATP than OXPHOS (2 vs. 36 ATP molecules), the speed of ATP generation in the former is quicker than in the latter, which is potentially critical to maintain energy levels.

It is believed that under homeostatic conditions macrophages exhibit a metabolic profile (or base line metabolism) consistent with utilizing glucose mainly through the TCA cycle and utilization of oxygen for mitochondrial oxidative phosphorylation to generate ATP [5–7,10,33,34] (Fig. 1). In contrast, the hallmark metabolic adjustment observed in the inflammatory macrophage (macrophages activated with LPS or the combination of LPS and IFNγ that produce pro-inflammatory mediators and cytokines [4,10,35,36]) at least *in vitro*, is decreased utilization of the TCA cycle and decreased OXPHOS together with increased metabolism of glucose to lactate (glycolysis) [4,5,8,33] (Fig. 2). Importantly, this metabolic adaptation occurs without lack of oxygen, and has thus been referred to as "aerobic glycolysis" [4,8,34,37–41]. Reduction in mitochondrial oxidative phosphorylation is associated with accumulation of mitochondrial TCA intermediates, such as citrate, succinate, and fumarate (Fig. 2) and increased consumption of glutamine and arginine [3,8,12,42–45]. Importantly, this metabolic adaptation is required for pro-inflammatory activation (e.g. in response to LPS) and expression of proper effector function [3–8,33,36–41,46,47]. Intriguingly, the anti-inflammatory cytokine IL-10 limits glycolysis and blocks activation of dendritic cells in response to Toll-like receptor (TLR) activation [41].

In contrast, the metabolic phenotype observed in IL-4 activated macrophages (so called alternatively activated, M2 macrophages [48]) exhibits absence of aerobic glycolysis and presence of OXPHOS [35,36]. In addition, it has been demonstrated that IL-4 activated macrophages are very dependent on glutamine together with up-regulated expression of a particular nucleotide sugar, Uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc) [36]. Because UDP-GlcNAc is required for protein glycosylation, the authors hypothesized that this process might be important for functioning of alternatively activated macrophages, because typical M2 macrophage receptors are glycosylated, although the exact functional relevance of UDP-GlcNAc in M2 macrophages remains elusive [4,35,36]. Certain chronic conditions that involve IL-4 signaling (e.g. parasite infestation, allergy, asthma) might be associated with continuous maintenance of macrophages in an OXPHOS state, while on the other hand chronic inflammatory conditions might be associated with macrophages arresting in aerobic glycolysis [29]. The metabolic phenotypes of resident macrophages across tissues under normal homeostatic conditions or under stress conditions and exactly how local metabolic cues promote and regulate distinct metabolic phenotypes of tissue macrophages, especially in vivo, remains unclear [36]. Moreover, whether reprogramming of metabolism can be harnessed to interfere with macrophage function awaits future analysis [4,12,29].

3. Functional consequences of metabolic adaptation in macrophages

An important question is why do inflammatory macrophages switch to aerobic glycolysis in addition to altering mitochondrial metabolism and reducing mitochondrial respiration? This seemingly paradoxical metabolic phenomenon of an increase in glycolysis with increased production of lactate at the cost of repressed mitochondrial respiration (reduced OXPHOS) despite presence of oxygen was first described almost a century ago in cancer cells by the Nobel Laureate Otto Warburg and is now commonly referred to as "Warburg effect" or "Warburg metabolism" [49]. The metabolic adaptations in tumor cells are thought to be driven largely by somatic mutations, whereas those in inflammatory cells likely occur independent of somatic mutations. Therefore, as opposed to cancer cells, metabolic reprogramming in inflammatory macrophages may have evolved as a quickly inducible, adaptable and potentially reversible cellular process that can quickly relay the sensing of the microenvironment to the transcriptional machinery and evoke, as well as terminate, effector functions. Considering that inflammatory macrophages as opposed to cancer cells, are likely not proliferating at all or if so at a very slow rate, metabolic reprogramming to aerobic glycolysis must serve cellular functions other than proliferation. Among those, biosynthetic activities for the