Macrophage heterogeneity and energy metabolism

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ABSTRACT

Macrophages are versatile and multifunctional cell types present in most vertebrate tissues. They are the first line of defense against pathogens through phagocytosis of microbial infections, particles and dead cells. Macrophages harbor additional functions besides immune protection by participating in essential homeostatic and tissue development functions. The immune response requires a concomitant and coordinated regulation of the energetic metabolism. In this review, we will discuss how macrophages influence metabolic tissues and in turn how metabolic pathways, particularly glucose and lipid metabolism, affect macrophage phenotypes.

1. Metabolism of macrophages

Extensive literature describes the paradigm of dual activation of macrophages as pro-inflammatory versus anti-inflammatory also known as classic (M1) versus alternative (M2) activation respectively [1]. In the recent years the M1/M2 concept has been re-evaluated and it is now well accepted that these phenotypes are at the opposite extremes of a spectrum of intermediate phenotypes [2]. Nevertheless, the pro- versus anti-inflammatory activation programs occur in response to different stimuli, which lead to distinctive mediators and biological functions. Microbial infections and associated by-products, such as lipopolysaccharide (LPS) and interferon-γ (IFN-γ), trigger the classic pro-inflammatory response. This leads to the production of cytokines, such as TNFα and IL1β, resulting in a highly bactericidal and phagocytic macrophage capacity. In contrast, alternative anti-inflammatory activation, which mainly defends against parasitic infections, responds to interleukin 4 and 13 (IL-4 and IL-13) and promote tissue repair and wound healing by resolving inflammation [1].

1.1. Signals fueling distinct inflammatory responses in macrophages

The switch between the M1 and M2 extreme phenotypes is known as macrophage polarization. Interestingly, the pro-inflammatory response relies on anaerobic glycolysis, which refers to the breakdown of glucose into pyruvate then conversion to lactate, which yields two molecules of adenosine triphosphate (ATP). On the other hand, the anti-inflammatory action depends on the aerobic respiration, which refers to pyruvate feeding into the TCA cycle and subsequently oxidative phosphorylation to efficiently higher amounts of ATP (30–32 per glucose) than from glycolysis alone [3].

One possible explanation for these key metabolic differences is the distinct dynamics and duration of the inflammatory process (Fig. 1). Classic activation requires the fast generation of ATP through anaerobic glycolysis in order for the macrophages to cope with highly proliferative bacterial infections. On the other hand, sustained inflammation to fight prolonged parasite infections and eventually the resolution of inflammation requires an efficient but slower generation of ATP through fatty acid oxidation and oxidative phosphorylation (Fig. 1).

Although it is not clear how this metabolic rewiring is regulated, toll-like receptor 4 (TLR4) activation by LPS has been shown to induce a range of metabolic changes leading to increased glycolysis and reduced oxidative phosphorylation. Interestingly, high fat feeding in mice has been associated with increased gut permeability leading to higher exposure of macrophages to bacteria-derived factors such as LPS or immunogenic lipids [4]. On the other hand, the anti-inflammatory cytokines, IL-4 and IL-13, have been shown to increase oxidative phosphorylation [5,6].

1.2. Transcriptional regulation of macrophage energy metabolism

Multiple transcription factors have been described as key regulators of macrophage metabolism. Among them, hypoxia-inducible factor alpha (HIF-1α) has been shown as an important regulator of the glycolytic gene program [7]. Two breaks in the Krebs cycle were described in inflammatory macrophages leading to accumulation of citrate, which is then redirected to the production of itaconic acid and inflammatory fatty acid production [7]. The second break leads to the
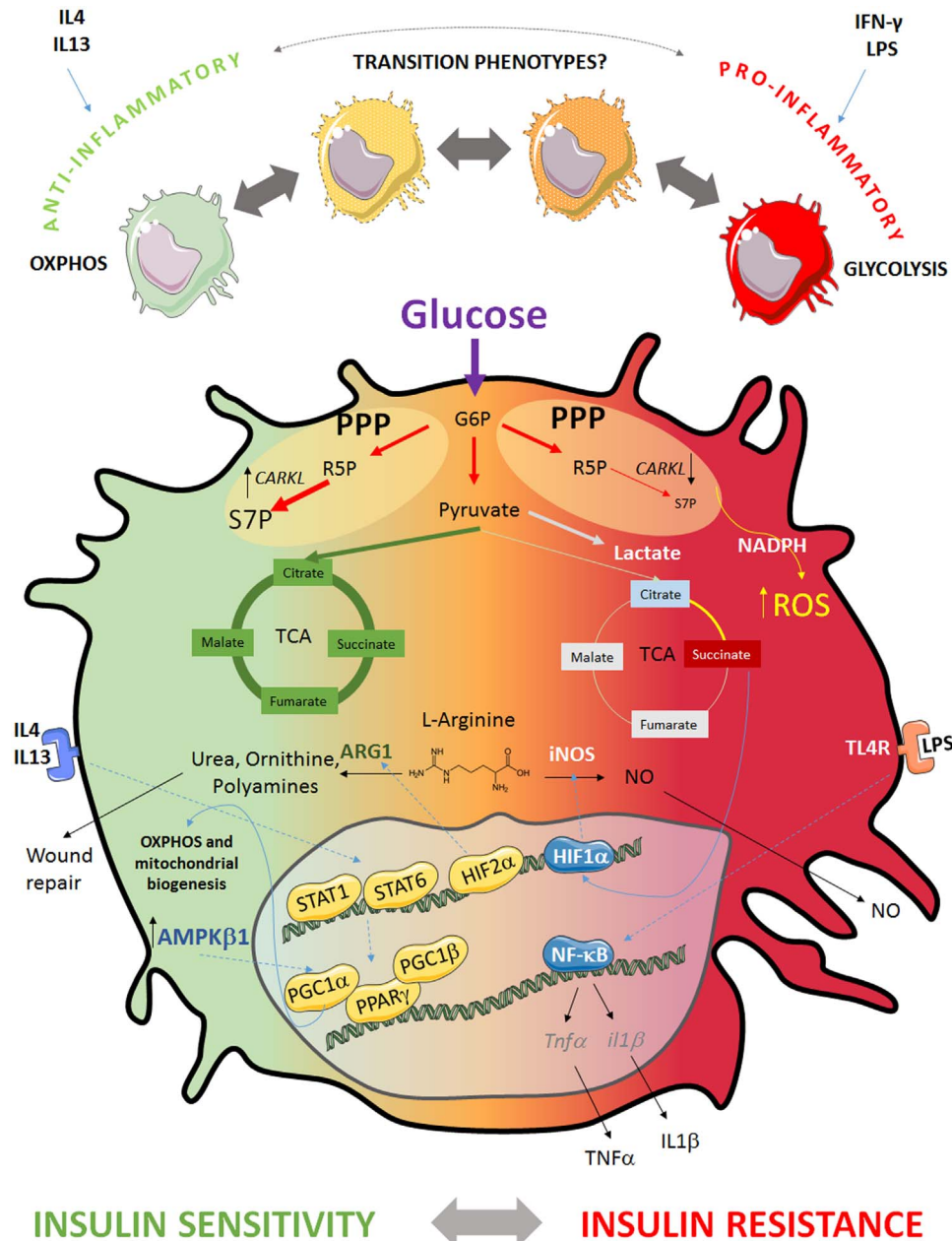

Fig. 1. Macrophage metabolism and polarization. The anti-inflammatory cytokines IL4 and IL13 trigger STAT1 and STAT6 transcriptional responses that lead to enhanced mitochondrial driven energy generation through activation of PPARγ, PGC1α and PGC1β transcription factors. On the other hand, LPS and IFNγ activate NF-kB dependent TNFα and IL1β pro-inflammatory cytokine production. In addition, HIF1α promotes glycolysis which is further sustained by the accumulation of succinate from the TCA. Abbreviations: PPP, Pentose Phosphate Pathway. G6P: Glucose-6-Phosphate. R5P, Ribulose-5-Phosphate. S7P: Sedoheptulose-7-Phosphate. TCA, Tricarboxylic Acid Cycle.

accumulation of succinate, which induces the transcription of HIF-1α. In turn, this factor controls the expression of inducible nitric oxide synthase (iNOS), which is involved the production of the inflammatory factor nitric oxide (NO) [8]. iNOS produces NO by metabolizing its substrate, the amino acid ʟ-arginine [9]. Arginase 1 (ARG1) is highly expressed in anti-inflammatory macrophages and competes with iNOS for their common substrate, ʟ-arginine, to produce ornithine and urea [10]. Therefore, ARG1 activity can decrease NO production via the limitation of arginine availability [11]. HIF-2α is another hypoxia-responsive component of the HIF family that is also expressed in macrophages and induces the expression of *Arg1* [12,13]. HIF-1α and HIF-2α have been shown to play opposite roles in the regulation of macrophage function *in vitro* and *in vivo* [5]. Other evidences have shown that hypoxia, which leads to expression of HIF-1α and HIF-2α,

increases glycolytic flux shifting macrophage polarization towards the pro-inflammatory side [14]. For instance, HIF1α expression is induced in macrophages recruited to hypoxic and acidified (by tumor-derived lactic acid) areas of solid tumors. This leads to the increased expression of *Arg1* and release of Vascular endothelial growth factor (VEGF) which contributes to tumor growth through neovascularization [15,16].

Peroxisome Proliferator Activator Receptor-gamma (PPARγ), a key transcriptional regulator of mitochondrial function and fatty acid oxidation in macrophages can potentiate alternative activation [17]. While disruption of PPARγ in myeloid cells impairs alternative macrophage activation, PPARγ expression by macrophages has been recently shown to reduce inflammation, highlighting the importance of lipid metabolism in macrophage activation [18].