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Medicine in focus

Mitochondria in monocytes and macrophages-implications for translational and basic research

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ABSTRACT

The mitochondrion plays a crucial role in the immune system particularly in regulating the responses of monocytes and macrophages to tissue injury, pathogens, and inflammation. In systemic diseases such as atherosclerosis and chronic kidney disease (CKD), it has been established that disruption of monocyte and macrophage function can lead to chronic inflammation. Polarization of macrophages into the pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes results in distinct metabolic reprograming which corresponds to the progression and resolution of inflammation. In this review, we will discuss the role of the mitochondrion in monocyte and macrophage function and how these cells specifically influence the pathophysiology of atherosclerosis and CKD. We propose that assessing monocyte bioenergetics in different disease states could (1) enhance our understanding of the energetic perturbations occurring in systemic inflammatory conditions and (2) aid in identifying therapeutic interventions to mitigate these disorders in patients.

Organelle facts

- Mitochondrial oxidative phosphorylation and glycolysis support monocyte/macrophage function.
- Macrophages undergo a metabolic switch from glycolysis to oxidative phosphorylation during inflammation.
- Mitochondrial ROS are produced by macrophages following oxidized LDL exposure.
- Monocyte mitochondrial DNA and electron transport chain activity are damaged in mouse models of atherosclerosis.
- Mitochondria in monocytes from patients with chronic kidney disease are impaired.
- Genes involved in mitochondrial biogenesis (PGC-1α and NRF-1) are down-regulated in PBMC's of CKD patients undergoing peritoneal dialysis.

1. Introduction

In the innate immune system, monocytes and macrophages are derived from myeloid progenitor cells and are vital in the resolution of inflammation caused by tissue injury or infection. The early inflammatory signaling-mediated phenotypic changes induce extravasation and differentiation of circulating monocytes to tissue macrophages, the immune cells that are responsible for phagocytosis and tissue repair (Luscinskas et al., 1996; Pardali and Waltenberger, 2012; Davies et al., 2013). These diverse functions are carried out by two distinct classes, the M1 (classically activated) or M2 (alternatively activated) macrophages. M1 macrophages mediate the pro-inflammatory response through TNF-α, IL-1β, reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS) derived nitric oxide (Mills, 2012; Martinez et al., 2008). M2 macrophages are anti-inflammatory in nature and secrete cytokines such as IL-10, IL-4 and TGF-β to aid in wound repair and healing (Martinez et al., 2008; Novak and Koh, 2013). Metabolism, particularly bioenergetics, plays a central role in regulating the physiological roles of the M1 and M2 phenotypes.

In contrast to their physiological function, the monocyte/macrophage system is perturbed in a number of pathologies associated with chronic inflammation such as atherosclerosis and chronic kidney disease (CKD). The role of monocytes and macrophages in the process of atherosclerotic lesion formation has been widely studied and characterized along with dysfunction

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of the M1–M2 transition (Ghattas et al., 2013; Gui et al., 2012). Vascular complications associated with atherosclerosis such as hypertension, tissue ischemia and diabetes can lead to renal injury and result in CKD (Kokubo, 2013; Khatami, 2013; Yamagishi and Imaizumi, 2005). In addition, microvascular complications in patients with CKD can result in cardiovascular complications.

In this review, we will discuss the role of mitochondria in the physiology of monocyte and macrophage function and how this is altered in atherosclerosis and CKD. We will also describe the potential benefits of evaluating monocyte bioenergetics as a translational approach to monitor systemic disease progression and/or identify therapeutic strategies to mitigate disease.

2. Function of monocytes and macrophages in physiology

Monocytes can be divided into three subtypes based on surface receptor expression. There are 3 major populations of circulating monocytes which are classified by the expression of cluster-determinant (CD) antigens. The "so called" classical monocytes are $CD14^{++}CD16^{-}$ and produce the highest levels of IL-10, a cytokine that mediates tissue repair, and reflects the majority of circulating monocytes in healthy individuals (Wong et al., 2011). The non-classical monocytes are $CD14^{+}CD16^{++}$ and have an important role in patrolling the vascular endothelium and produce the highest levels of inflammatory cytokines, TNF-α and IL-1β, in response to pathogens and are thought to be involved in phagocytosis (Wong et al., 2011). The intermediate monocytes are $CD14^{++}CD16^{+}$ and produce the lowest levels of cytokines and chemokines. It is postulated that the classical monocytes mature over time to intermediate then non-classical monocytes (Wong et al., 2011).

Monocytes circulate in the bloodstream and patrol the endothelium for signs of inflammatory distress. In atherosclerosis, inflammation associated with accumulation of oxidized LDL (oxLDL) in the arterial sub-intimal space causes monocytes to infiltrate into the tissue where they mature into macrophages (Imhof and Aurrand-Lions, 2004). The macrophages also can be divided into different sub-types depending on their exposure to the prevailing inflammatory microenvironment. Factors such as the cytokine milieu and pathogens dictate the polarization of the macrophages into either the M1 or M2 phenotype (Fig. 1). Exposure to cytokines such as TNF-α IFN-γ leads to production of M1 macrophages, whereas TGF-β and IL-10 produce M2 macrophages (Martinez et al., 2008). Pathogen associated molecular patterns (PAMPs) such as lipopolysaccharide, flagellin from bacteria and double stranded RNA from viruses can activate the toll like receptor (TLR) pathway to engage the NF-κB system to produce inflammatory cytokines that modulate the M1 macrophage phenotype (Zhang and Wang, 2014). Macrophages can switch their metabolism during inflammation from being dependent on glycolysis for ATP synthesis in the M1 state, to relying on oxidative phosphorylation in the M2 state (Rodriguez-Prados et al., 2010; Vats et al., 2006). Interestingly, M1 and M2 macrophages are dynamic and can convert from one form to another, hence the oxidative phosphorylation capacity remains intact in M1 macrophages and glycolytic machinery remains functional in M2 macrophages, allowing for the pathways to be upregulated based on macrophage polarization (Davis et al., 2013; Lumeng et al., 2007).

Tissue oxygen tension is also a critical modulator of phenotype switching and metabolic alterations in tissue macrophages. HIF1α-mediated differentiation of macrophage to the M1 phenotype and corresponding upregulation of anerobic glycolytic genes in inflamed tissues suggest critical roles for cellular metabolism and tissue oxygen levels in modulating cell function (Nizet and Johnson, 2009; Shapiro et al., 2011). It is important to note that M1 macrophages can transform into M2 macrophages during the

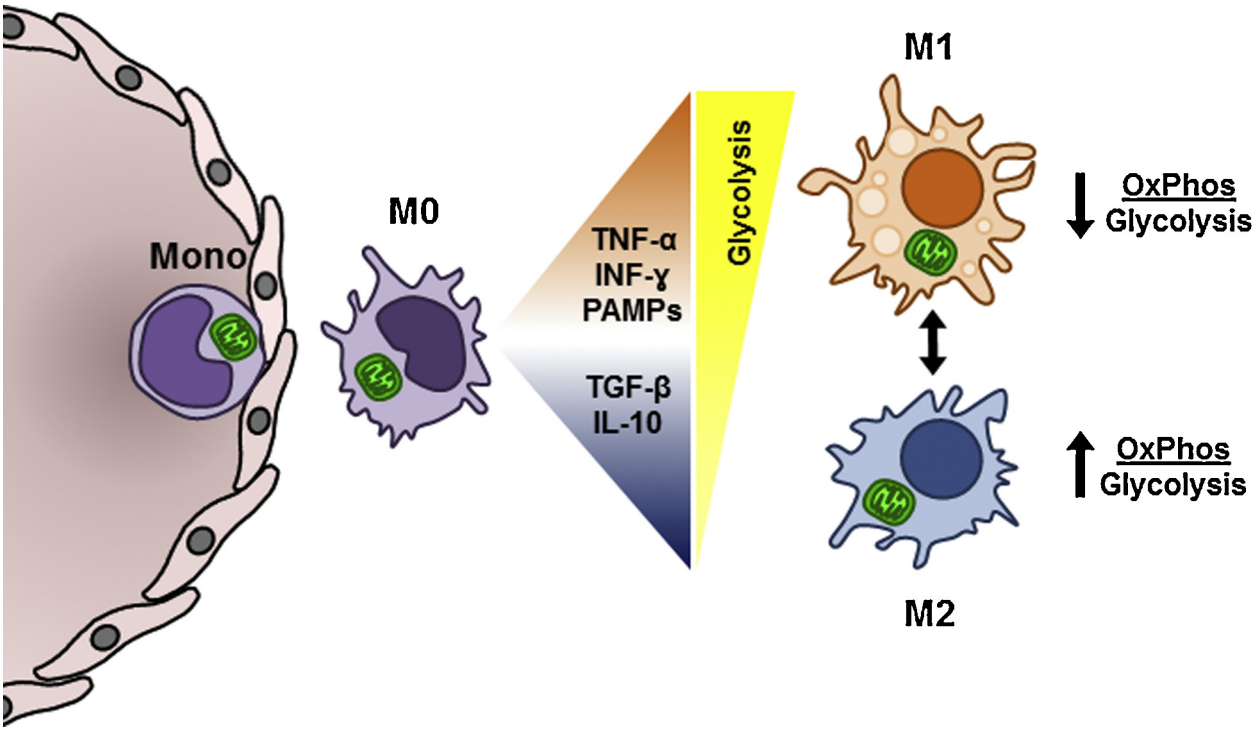

Fig. 1. Differentiation and metabolism of monocytes and tissue macrophages. The circulating monocyte is shown exiting the vasculature and proceeding into the tissue and differentiating into a tissue macrophage (M0). These cells utilize oxidative phosphorylation to meet their energetic demand. Upon differentiation, the cytokine and pathogen environment directs their fate to either the M1 or M2 phenotype in the presence of TNFα, PAMPS, INFγ, or TGFβ and IL-10, respectively. M1 macrophages rely on glycolysis for energy production and as such have a lower ratio of oxidative phosphorylation to glycolysis. On the other hand, M2 macrophages preferentially utilize oxidative phosphorylation, and so have a higher ratio of oxidative phosphorylation to glycolysis.