Maxed Out on Glycolysis: Alveolar Macrophages Rely on Oxidative Phosphorylation for Cytokine Production

Macrophages are a highly versatile population of cells, capable of adopting a complex assortment of behaviors. This ranges from orchestrating pro- and antiinflammatory responses to regulating tissue repair and remodeling, making these innate immune cells important participants in both host defense and tissue homeostasis (1). Although the individual factors that regulate this diverse repertoire of activities are still a focus of intense investigation, an important recent discovery has been the recognition that macrophages use different metabolic fuels and pathways in the transition to individual functional phenotypes (2).

In the lungs, tissue-resident alveolar macrophages (TR-AMs) have long been recognized as a unique subset of immune cells. Originally derived from embryonic progenitor cells that reach the lungs before birth, TR-AMs are extremely long-lived cells that possess a unique self-renewal capacity (3–5). Moreover, unlike other macrophage populations, TR-AMs display an unusual mixture of cell surface markers (e.g., high levels of CD11c) and exhibit reduced phagocytic and antigen-presenting capabilities (6–9). In the alveolar lumen, where there is a constant exposure to allergens, inhaled particulates, and environmental microorganisms, precise control over the activation state of TR-AMs is of paramount importance (10). To date, other than constituents in pulmonary surfactant, the factors important in suppressing TR-AM activation remain poorly understood (9, 10).

Although the role of cellular metabolism in the functional plasticity of macrophages is being increasingly understood, there are limited data dedicated toward the specific metabolic programming of TR-AMs. Much of what we know, especially regarding the importance of glycolysis in macrophage immune effector function, comes from studies using bone marrow–derived macrophages, peritoneal macrophages, or other macrophage cell lines (11–15). For example, the classical paradigm in the immunometabolism field teaches that proinflammatory activation is heavily reliant on upregulating glycolysis, whereas reparative macrophages preferentially use mitochondrial oxidative phosphorylation for their functions (2). That said, emerging evidence suggests that metabolic responses to infectious pathogens or other pulmonary insults in TR-AMs may be distinct from other macrophage subpopulations (9, 16, 17).

In this issue of the *Journal*, Woods and colleagues (pp. 243–255) describe their exploration of the largely unknown metabolic imprint of TR-AMs under steady-state conditions, and, furthermore, they demonstrate how these cells metabolically adapt to stressed conditions (18). In this sophisticated and well-designed study, using both *in vitro* and *in vivo* investigations, these researchers demonstrate that TR-AMs do not rely on glycolysis for activation in response to bacterial LPS and that they have a limited capacity to upregulate glycolysis in response to mitochondrial inhibitors. In addition, they elegantly show that neither the inhibition of glycolysis (via treatment with the lactate dehydrogenase A inhibitor, sodium oxamate) nor the promotion of glycolysis (via stabilization of hypoxia inducible factor-1α) significantly affected the magnitude of the inflammatory response to LPS in TR-AMs. These observations were similarly replicated *in vivo* using a lung injury model of influenza in mice, indicating that the glycolytic reprogramming typical of most other proinflammatory macrophages is not a feature of activated TR-AMs. Importantly, these findings align nicely with several recent reports showing that mitochondrial oxidative phosphorylation is elevated in TR-AMs (9, 16, 17, 19).

Although this study adds significantly to our understanding of the field, many important questions remain. For one thing, it is unclear why TR-AMs have evolved to depend on oxidative phosphorylation for their energy needs. On the surface, this seems to be an awful evolutionary strategy for a long-lived cell, which is constantly exposed to airborne pollutants that can have damaging effects on mitochondria and, more specifically, the electron transport chain (20). However, it is likely that this metabolic adaptation serves some important purpose, such as helping TR-AMs to survive the low-glucose environment of distal airspaces or attenuating the magnitude of inflammatory responses to LPS through limited glycolytic reserves. This study also did not address the potential long-term consequences of a cell depending on mitochondrial oxidation for energy production. Relevant to this, mitochondrial dysfunction has emerged as an important pathogenic player in a variety of age-related lung diseases, such as acute respiratory distress syndrome, infectious pneumonia, and idiopathic pulmonary fibrosis (21). With this in mind, one wonders whether long-term dependence on oxidative phosphorylation might be a contributing factor in the development of these respiratory pathologies.

In summary, findings in this study contribute significantly to our understanding of macrophage biology and delineation of the functional differences between resident and recruited alveolar macrophages. Moreover, this study suggests the novel concept that specific metabolic pathways may be targeted to affect the behavior of individual macrophage subsets in the lung. ■

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