Metabolic reprogramming in inflammatory cells: A new frontier in immunometabolism.

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Introduction

Metabolic reprogramming in inflammatory cells has emerged as a transformative concept in the field of immunometabolism, fundamentally changing our understanding of how immune responses are initiated, sustained, and resolved. Once considered mere background processes providing energy and biosynthetic materials, metabolic pathways are now recognized as central regulators of immune cell function. Inflammatory cells, including macrophages, dendritic cells, neutrophils, and various lymphocyte subsets, undergo dynamic and often profound shifts in their metabolic profiles in response to environmental cues, pathogen encounters, and cytokine signals. These metabolic changes are not simply consequences of activation but are instrumental in shaping the phenotype, effector functions, and fate of immune cells [1].

When immune cells become activated during infection, injury, or autoimmune responses, they must rapidly increase their biosynthetic capacity to support proliferation, cytokine production, and effector mechanisms such as phagocytosis and antigen presentation. This upsurge in activity demands a corresponding adjustment in cellular metabolism. A hallmark of metabolic reprogramming in activated inflammatory cells is the switch from oxidative phosphorylation to aerobic glycolysis, a phenomenon reminiscent of the Warburg effect observed in cancer cells. Despite being less efficient in terms of ATP yield, glycolysis provides rapid energy production and generates intermediates required for nucleotide, amino acid, and lipid biosynthesis. This metabolic shift supports the robust functional demands of activated cells [2].

Macrophages exemplify the metabolic plasticity of immune cells. Upon activation by microbial products such as lipopolysaccharide (LPS) or cytokines like interferon-gamma (IFN-γ), macrophages differentiate into a classically activated, or M1, phenotype characterized by high pro-inflammatory activity. M1 macrophages upregulate glycolysis and exhibit a disrupted tricarboxylic acid (TCA) cycle, with accumulation of intermediates such as succinate and citrate [3]. These metabolites are not only byproducts but also have signaling roles; for instance, succinate stabilizes hypoxia-inducible factor-1 alpha (HIF-1α), promoting the transcription of glycolytic genes and pro-inflammatory cytokines like interleukin-1β (IL-1β). Citrate, on the other hand, serves as a precursor for fatty acid synthesis and the production of inflammatory mediators like prostaglandins and nitric oxide. Thus, metabolic intermediates become key regulators of the inflammatory response [4].

In contrast, alternatively activated, or M2, macrophages induced by signals like interleukin-4 (IL-4) and interleukin-13 (IL-13) adopt a distinct metabolic profile dominated by oxidative phosphorylation and fatty acid oxidation. These cells are associated with anti-inflammatory functions, tissue repair, and resolution of inflammation. The reliance on oxidative metabolism in M2 macrophages is supported by mitochondrial biogenesis and increased expression of enzymes involved in fatty acid metabolism. The metabolic divergence between M1 and M2 macrophages illustrates how metabolic programs align with distinct functional phenotypes, revealing potential targets for therapeutic modulation [5].

Dendritic cells (DCs), the key antigen-presenting cells bridging innate and adaptive immunity, also undergo metabolic reprogramming upon activation. Immature DCs primarily utilize oxidative phosphorylation to meet their basal energy needs. However, upon encountering pathogens, they rapidly shift to glycolysis, which supports their maturation and migration to lymphoid organs. Glycolysis fuels the synthesis of membrane components required for dendrite expansion and antigen processing machinery. Inhibition of glycolysis impairs DC maturation and limits their ability to activate T cells, demonstrating the essential role of metabolic reprogramming in initiating adaptive immunity [6].

Neutrophils, another major class of inflammatory cells, are highly dependent on glycolysis, even under normoxic conditions. This metabolic preference allows them to function effectively in hypoxic and inflamed tissues, where oxygen is scarce. Upon activation, neutrophils increase glucose uptake and enhance glycolytic flux to generate ATP for processes like chemotaxis, phagocytosis, and the formation of neutrophil extracellular traps (NETs). Inflammatory signals such as tumor necrosis factor-alpha (TNF-α) and granulocyte colony-stimulating factor (G-CSF) further promote this glycolytic state, amplifying neutrophil responses during acute inflammation [7].

In adaptive immunity, metabolic reprogramming also dictates T cell fate and function. Naïve T cells rely on oxidative phosphorylation for their low-energy requirements, but upon activation, they switch to glycolysis and glutaminolysis to support proliferation and effector function. Effector T cells,

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such as Th1, Th2, and Th17 subsets, exhibit high glycolytic activity, which is necessary for their differentiation and cytokine production. In contrast, regulatory T cells (Tregs), which suppress immune responses and maintain tolerance, rely more on oxidative phosphorylation and lipid oxidation. This metabolic dichotomy between effector and regulatory T cells influences immune balance and offers opportunities for selective immunomodulation [8].

The metabolic pathways activated in T cells are regulated by key signaling molecules and transcription factors. The mechanistic target of rapamycin (mTOR) pathway plays a pivotal role in promoting glycolysis and anabolic metabolism in effector T cells, whereas AMP-activated protein kinase (AMPK) and sirtuins support catabolic pathways in Tregs and memory T cells. Modulation of these pathways can tilt the balance between pro-inflammatory and anti-inflammatory responses, providing a framework for therapeutic interventions in autoimmune diseases, infections, and cancer [9].

B cells also undergo metabolic changes during activation and differentiation. Activated B cells increase glycolysis and mitochondrial respiration to support antibody production. Germinal center B cells, involved in affinity maturation and memory formation, show unique metabolic characteristics, balancing energy production with reactive oxygen species (ROS) management. The metabolic needs of plasma cells and memory B cells further reflect their specialized functions and longevity [10].

Conclusion

In conclusion, metabolic reprogramming in inflammatory cells is a fundamental aspect of immune function that bridges immunology and metabolism. The ability of immune cells to dynamically adjust their metabolic pathways enables them to respond effectively to diverse challenges, from infections to tissue injury and malignancy. Understanding the molecular mechanisms that govern these metabolic shifts provides a new lens through which to view immunity and offers exciting opportunities for therapeutic innovation. As the field of immunometabolism continues to evolve, it holds the potential to unlock novel strategies for treating a wide array of immune-mediated and metabolic disorders.

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