Glycolysis beyond energy production: Metabolic rewiring in immune cell function.

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Introduction

Glycolysis, traditionally viewed as a central pathway for ATP production through the breakdown of glucose into pyruvate, has emerged as a key metabolic axis regulating immune cell function. While its canonical role involves generating energy rapidly, especially under anaerobic conditions, recent research has revealed that glycolysis plays a far more complex and dynamic role in shaping immune responses. Immune cells undergo extensive metabolic rewiring during activation, differentiation, and effector function, and glycolysis stands at the heart of this transformation [1, 2].

In resting immune cells, such as naïve T cells and macrophages, oxidative phosphorylation in mitochondria is the predominant energy source, supporting their relatively low metabolic demands. However, upon activation, these cells shift dramatically toward aerobic glycolysis—a phenomenon similar to the Warburg effect observed in cancer cells. This shift allows immune cells to rapidly generate not only ATP but also biosynthetic intermediates necessary for cell proliferation, cytokine production, and effector functionsm [3, 4].

For activated T cells, glycolysis is essential for clonal expansion and the execution of their immune roles. Effector T cells (such as Th1, Th17, and cytotoxic T cells) show increased glucose uptake and glycolytic flux, which supports their high energy demands and production of inflammatory mediators. Inhibition of glycolysis impairs their ability to produce cytokines like IFN-γ and TNF-α, underscoring the pathway's role beyond simple energy supply [5, 6].

Macrophages also exhibit distinct metabolic profiles depending on their polarization. Classically activated M1 macrophages, which are pro-inflammatory, rely heavily on glycolysis to support their rapid response to pathogens and tissue damage. In contrast, alternatively activated M2 macrophages, associated with tissue repair and anti-inflammatory functions, prefer oxidative metabolism. This metabolic dichotomy reflects how glycolysis not only supports but actively shapes immune phenotypes and responses [7].

Glycolytic intermediates further contribute to immune regulation. Metabolites such as phosphoenolpyruvate and lactate are not merely byproducts but function as signaling molecules that modulate gene expression, enzyme activity, and immune cell fate. For instance, lactate accumulation in the tumor microenvironment has immunosuppressive effects, inhibiting cytotoxic T cell function and promoting the differentiation of regulatory T cells (Tregs), which dampen immune responses. This highlights how altered glycolytic metabolism can influence immune escape in cancer and chronic infections [8].

Dendritic cells (DCs), the professional antigen-presenting cells, also undergo a glycolytic shift upon encountering pathogens. This metabolic reprogramming is crucial for their maturation, cytokine production, and ability to prime T cells. Blocking glycolysis in DCs disrupts their ability to activate adaptive immune responses, suggesting that metabolic regulation is a prerequisite for effective immunity [9].

The regulation of glycolysis in immune cells is tightly controlled by signaling pathways such as PI3K/Akt/mTOR and HIF-1α, which link environmental cues to metabolic adaptation. These pathways respond to changes in oxygen, nutrients, and inflammatory signals, orchestrating a coordinated metabolic response that tailors immune function to specific contexts.

Understanding the role of glycolysis in immune cell function has therapeutic implications. Modulating glycolytic pathways offers a strategy to enhance or suppress immune responses, depending on the clinical need. In cancer, promoting oxidative metabolism while inhibiting glycolysis in tumor-associated immune cells may restore their anti-tumor activity. Conversely, enhancing glycolysis might boost vaccine efficacy or improve host defense during infections [10].

Conclusion

In conclusion, glycolysis extends far beyond its classical role in energy production, acting as a central regulator of immune cell metabolism, activation, and function. The dynamic rewiring of glycolytic pathways enables immune cells to adapt to environmental and functional demands, shaping the outcome of immune responses. Targeting glycolytic metabolism holds great potential for therapeutic interventions in cancer, autoimmune diseases, infections, and inflammatory disorders.

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