Series titles:
The Immunometabolism of Infection

Title for this editorial:
Metabolic mediators: how immunometabolism directs the immune response to infection

The immune system in action is an impressive piece of choreography. Exquisite balance is essential, maintaining protection against a diverse array of pathogens while preventing immune-mediated pathologies. Understanding the mechanisms behind such balance is a high priority for research and clinical communities. In the last decade, there has been growing interest in immune cell nutrition and metabolism, giving rise to the emerging field of "immunometabolism" and casting new light on the regulation of immune cell activity. Here we present an exciting new series of review articles that consider immunometabolism in the context of infection, discussing new insights in immune cell migration, function, and persistence, and new perspectives on how metabolites can mediate the fraught dialogue between invading pathogens and their host.

The field of immunometabolism rests upon the foundation that immune cells show distinct states of nutrient and energy metabolism during activation compared to their inactivated state(1). Superficially, it may be no surprise that an activated cell consumes and uses energy differently than a cell at rest. Nevertheless, this simple premise has resulted in an explosion of inquiry into how nutrient usage and cellular energetics are regulated during an immune response, and how these processes direct downstream cellular function(2–4). The study of immunometabolism has been revolutionary in immunology, opening another "lens" through which to view the nuanced complexity of immune response regulation.

Early studies in immunometabolism focused on the gross characterization of shifts in cellular metabolism that occur during immune cell activation(5–7). In most contexts, both myeloid and lymphoid cells upregulate their consumption of glucose to fuel their effector functions(8,9). However, immune cell activation is not a simple "on/off" metabolic switch, but rather a qualitative engagement and prioritisation of distinct metabolic pathways that can specifically support unique effector outcomes, such as polarization of T helper cells or specification of macrophage effector responses. This review series highlights recent advances in understanding the links between metabolism and function in immune cells, using the context of microbial infection to illuminate immunometabolism in action. The series illustrates the convergence of metabolism with other forms of cellular regulation, including epigenetics, post-translational modifications, and nutrient competition. The reviews emphasize the role of immunometabolism in the beauty of the immune orchestration required to eradicate pathogens and yet maintain balance throughout the immune responses to infection.

We are publishing the review series in two parts. The first half of this series, presented here, focuses on metabolic mechanisms and discusses their influence on immune cell activity and protection from infection. Topics in this part of the series include the influence of cellular metabolism on epigenetic regulation, post-translational protein modification, immune cell trafficking, and intestinal homeostasis. The second half of the series which will be published in early 2021, provides specific examples of immunometabolism in action in particular infections,

illustrating its ability to mediate the conversations between host and pathogen and to influence disease outcome.

In the first article of this series, Lio and Huang address emerging evidence of the connection between metabolic processes and epigenetic regulation of gene expression(10). The authors introduce one-carbon metabolism and highlight the key metabolites S-adenosylmethionine (SAM) and α-ketoglutarate (αKG) as important contributors to the DNA methylation cycle in both innate and adaptive immune cells. They discuss the critical role of the TCA cycle intermediate αKG as a cofactor for a family of dioxygenase enzymes which play fundamental roles in the epigenetic regulation of inflammation-associated genes(11). These dioxygenases include the ten-eleven translocation (TET) methylcytosine oxidases which are required for proper lymphocyte development and activation, neatly illustrating the importance of metabolic regulation of gene expression.

TET methylcytosine oxidases are also iron-dependent(11,12), and Geros and colleagues discuss the central importance of iron as a metabolic regulator of both host and pathogen. Iron is essential to every living cell, being a required cofactor for enzymes involved in DNA synthesis and mitochondrial function. Tight regulation of iron availability is a key immune defense against bacterial pathogens, and the human gut is a dynamic frontline of a battle for access to iron. Host defense mechanisms that capture iron and prevent accessibility to microbes affect the intestinal microbiota as well as unwanted pathogens, and Geros et al highlight the metabolic dialogues between host, pathogen and commensal that determine health and dysbiosis. The authors also provide valuable perspectives on the therapeutic potential of targeting iron metabolism and iron availability, considering the impact on both host and pathogen.

Building on the conversation between host and pathogen, Quik, Hokke and Everts introduce us to a novel mechanism of metabolic control over immune defenses (13). They describe an emerging connection between the hexosamine biosynthesis pathway (HBP) and a specific form of post-translational glycosylation termed O-GlcNAcylation. O-GlcNAcylation can alter functional properties of the proteins that it modifies(14,15) and the pathway particularly targets transcription factors and epigenetic regulators. This review dovetails beautifully with the work presented by Lio and Huang, both describing the multi-faceted ways in which cellular metabolism can influence genetic regulation. Quik and colleagues comprehensively address the existing evidence for HBP-mediated O-GlcNAcylation in regulating immune cell function in responses to bacterial, viral, fungal, and parasitic infections, providing exciting new insight into metabolic control across the broad diversity of antimicrobial responses. Their work highlights the therapeutic promise of targeting HBP metabolism and O-GlcNAcylation as a mechanism of host-protective immunological intervention.

Our final mechanistic article is a thought-provoking piece by Guak and Krawczyk, in which the authors consider how shifts in nutrient usage and energy production support the motility and location of both innate and adaptive immune cells (16). One of the highlights of this article is in its discussion of the exciting finding that metabolic enzyme activity and energy production can be geospatially compartmentalized within the cell to support the unique energetic demands of directional chemotaxis(17). This pertains not only to the compartmentalization of glycolytic enzyme machinery in the cytoplasm, but also to specific regional location of mitochondria in

areas of the cell that support high-energy demands, such as the leading edge of a migrating cell. Guak and Krawczyk discuss nuanced metabolic contexts such as hypoxia and dyslipidemia, and describe the impact of these pathophysiological states on cellular metabolism and consequently cell motility. Such metabolic restrictions are decisive components of pathological microenvironments and understanding their significance is an essential step towards therapeutic intervention in disease states associated with altered nutrient microenvironments, including infection and cancer.

Together our four groups of authors presented here provide a fantastic discussion of the metabolic pressures and potential in the dynamic interaction between the mammalian host and diverse microbial pathogens. We hope you enjoy this collection of articles, and we also look forward to sharing the next installment: the influence of immunometabolism during specific pathogenic infections.

Authors:
Eyal Amiel and Georgia Perona-Wright

Published in *Immunology* (2020) v161, p163-164.

References

1. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. 2016. Nature Reviews Immunology. Vol 16, p. 553–65.
2. Ganeshan K, Chawla A. Metabolic regulation of immune responses. 2014. Annual Review of Immunology. Vol 32, p. 609–34.
3. Klein Geltink RI, Kyle RL, Pearce EL. Unraveling the Complex Interplay Between T Cell Metabolism and Function. 2018. Annual Review of Immunology. 36(1):461–88.
4. Teijlingen Bakker N, Pearce EJ. Cell-intrinsic metabolic regulation of mononuclear phagocyte activation: Findings from the tip of the iceberg. 2020. Immunological Reviews 295(1):54–67.
5. OREN R, FARNHAM AE, SAITO K, MILOFSKY E, KARNOVSKY ML. Metabolic patterns in three types of phagocytizing cells. 1963. The Journal of Cell Biology 17(3):487–501.
6. Newsholme P, Curi R, Gordon S, Newsholme EA. Metabolism of glucose, glutamine, long-chain fatty acids and ketone bodies by murine macrophages. 1986. Biochemical Journal. 239(1):121–5.
7. Fukuzumi M, Shinomiya H, Shimizu Y, Ohishi K, Utsumi S. Endotoxin-induced enhancement of glucose influx into murine peritoneal macrophages via GLUT 1. 1996. Infection and Immunity 64(1):108–12.
8. Krawczyk CM, Holowka T, Sun J, Blagih J, Amiel E, DeBerardinis RJ, et al. 2010. Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. Blood 115(23):4742–9.
9. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, et al. Cutting Edge: Distinct Glycolytic and Lipid Oxidative Metabolic Programs Are Essential

for Effector and Regulatory CD4 + T Cell Subsets. 2011. The Journal of Immunology 186(6):3299–303.
10. Lio CJ, Huang SC. Circles of Life: linking metabolic and epigenetic cycles to immunity. 2020. Immunology ; imm.13207.
11. Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. 2009. Science 324(5929):930–5.
12. Sousa Gerós A, Simmons A, Drakesmith H, Aulicino A, Frost JN. The battle for iron in enteric infections. 2020. Immunology ; imm.13236.
13. Quik M, Hokke CH, Everts B. The role of O-GlcNAcylation in immunity against infections. 2020. Immunology ; imm.13245.
14. Wang X, Lin Y, Liu S, Zhu Y, Lu K, Broering R, et al. *O* -GlcNAcylation modulates HBV replication through regulating cellular autophagy at multiple levels. 2020. The FASEB Journal ; fj.202001168RR.
15. Zhu Y, Hart GW. Targeting O-GlcNAcylation to develop novel therapeutics. 2020. Molecular Aspects of Medicine. p. 100885.
16. Guak H, Krawczyk C. Implications of cellular metabolism for immune cell migration. 2020. Immunology ; imm.13260.
17. Hu H, Juvekar A, Lyssiotis CA, Lien EC, Albeck JG, Oh D, et al. Phosphoinositide 3-Kinase Regulates Glycolysis through Mobilization of Aldolase from the Actin Cytoskeleton. 2016. Cell 164(3):433–46.