Series title:
The Immunometabolism of Infection

Title for this editorial:
Sweet talk: metabolic conversations between host and microbe during infection

Summary

In this issue, we introduce the second part of a series of reviews focusing on how immunometabolism influences host and pathogen interactions during infection. This part of the collection addresses the interface between metabolism and specific types of infection, including immunometabolism in macrophages during helminth infection, the role of metabolism in T cell exhaustion during chronic viral infections, and host immunometabolism in the defense against Mycobacterium tuberculosis infection. These reviews, together with their four sister articles published in November 2020, offer new insights into the complex interactions between mammalian hosts and microbial pathogens through the lens of cellular metabolic regulation.

Main text

The immune response to infection is a dynamic interaction whose outcome is life or death for both the host and the pathogen. The field of immunometabolism has recently given new perspective to our understanding of immune activity, and in this review series we are highlighting the contribution of metabolites and metabolism to the dynamic conversation between host and pathogen. The regulation of metabolism can control the size, speed, quality and location of an immune response, and a wily pathogen can manipulate host cell metabolism as part of its strategy of immune evasion. Understanding these metabolic interactions offers hope of new therapies and new strategies for controlling infection.

Our review series illustrates an exciting range of mechanisms by which immunometabolism can influence the outcome of infection. We have published the series in two parts. The first four reviews were included in the November 2020 issue of this journal. They provide an overview of metabolic mechanisms for regulating immune activity and defense against infection, including the influence of cellular metabolism on epigenetic regulation, post-translational protein modification, immune cell trafficking, and intestinal homeostasis. This second half of the series provides specific examples of immunometabolism in action during particular infections, highlighting metabolic regulation in macrophages during helminth infection, T cells during chronic viral infections, and at the interface of innate and adaptive immunity to Mycobacterium tuberculosis infection.

In the first article in this issue, Cortes-Selva and Fairfax discuss the elegance of macrophage metabolic regulation during helminth infection, with a particular emphasis on their expertise in *Schistosoma mansoni* infection. Readers who enjoyed the review by Geros et al. in the first part of this series will appreciate Cortes-Selva and Fairfax's discussion of the central role of macrophages in iron regulation. Infections with helminth parasites are typically chronic by

nature, often at least in part due to immune suppression by the parasite. Metabolic mechanisms for reprogramming the immunological microenvironment can therefore be an important aspect of the replicative success of these pathogens. This review describes how helminth-derived molecules are able to modulate both glycolytic and mitochondrial metabolism to condition macrophage responses to a less inflammatory state, closely associated with macrophage "alternative activation". The authors discuss the impact of *S. mansoni* infection on the metabolism of perivascular macrophages and Kupffer cells in the liver, both of which play particularly important roles in this infection. Excitingly, the authors describe recent evidence that helminth infection can modulate systemic metabolic parameters, potentially providing protection against metabolic disease. Such protection may be sex-dependent, as *S. mansoni* infection protects against metabolic disease in male but not female mice.

Cortes-Selva and Fairfax also evaluate similarities and differences between metabolic regulation in infections with different helminths, comparing the impact of soil transmitted helminths with that of *S. mansoni* infection. Their review handles the complexity of macrophage lineages and immune plasticity adeptly, providing readers with a comprehensive overview of macrophage metabolic regulation during helminth-mediated disease. Continuing the theme of chronic infection and the associated immune cell metabolism, our second review by Sears et al. addresses the metabolic underpinnings of $CD8^+$ T cell exhaustion during chronic viral infections (CVIs). The authors discuss the metabolic shifts associated with T cell activation and memory formation, and describe how persistent T cell receptor (TCR) stimulation during chronic infection results in less glycolysis and more fatty acid oxidation and TCA cycle usage. Sears et al explain that such metabolic remodeling of T cells during CVIs is thought to be caused by epigenetic modulation, inhibitory receptor regulation (PD-1 and LAG-3), IL-10 signalling, and virus-stimulated increases in regulatory micro-RNA expression. A major strength of this review is its emphasis on therapy. The authors provides a detailed assessment of the ability of metabolic mediators to reverse chronic T cell exhaustion and reignite cytotoxic lmyphocyte responses. Their work outlines the therapeutic promise of directly targeting immune cell metabolism, especially by re-enabling the glycolytic machinery typically suppressed in exhausted lymphocytes during chronic viral infection.

The final review article of the series by Sheedy and Divangahi nicely bridges the conceptual framework of the previous two, considering innate and adaptive immunometabolism in another chronic infection context, Mycobacterium tuberculosis (*Mtb*). The authors characterize the unique features of the lung microenvironment (including low glucose levels compared to serum) that foster a permissive space for *Mtb* infection characterized by a nutrient environment that favors fatty acid oxidation and TCA cycle activity, which in turn supports the attenuated inflammatory potential of lung alveolar macrophages compared to classic inflammatory macrophages. The authors discuss the enhanced glycolytic profiles of macrophages recruited to the lung during *Mtb* infection, compared to alveolar macrophages, and argue that these macropahges and their distinct metabolism are important for pathogen control. They also provide a nuanced discussion of other risk factors and comorbidities, such as smoking and hyperlipidemia, that impact the inflammatory potential of cells recruited to lung tissue during infection. The authors highlight disease tolerance rather than pathogen elimination in *Mtb* infection, and discuss how the regulation of T cell glycolysis influences the balance between Th17 and T regulatory cells, with important implication for disease control and

immunopathology. The authors conclude with a thought-provoking discussion of the therapeutic potential of harnessing "trained immunity", an epigenetic and perhaps metabolic reprogramming of innate immune cells, to provide better vaccination strategies against *Mtb* infection.

The three reviews here each provide exciting examples of immunometabolism "in action", in three very different infection contexts. They highlight the elegant biology involved, and they suggest new routes for therapeutic and preventative strategies. Together with the first part of our series, we provide a platform to engage with some of the latest findings in the fields of immunometabolism and infection biology. We hope you enjoy diving in.

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References

1. Ma EH, Verway MJ, Johnson RM, Roy DG, Steadman M, Hayes S, et al. Metabolic profiling using stable isotope tracing reveals distinct patterns of glucose utilization by physiologically activated CD8+ T cells. *Immunity* 2019; 51: 856– 70.e5.
2. Chang CH, Pearce EL. Emerging concepts of T cell metabolism as a target of immunotherapy. *Nat Immunol.* 2016; 17: 364– 8.
3. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol.* 2016; 16: 553– 65.
4. Cumming BM, Addicott KW, Adamson JH, Steyn AJC. *Mycobacterium tuberculosis* induces decelerated bioenergetic metabolism in human macrophages. *eLife.* 2018; 7:e39169.
5. Duette G, Pereyra Gerber P, Rubione J, Perez PS, Landay AL, Crowe SM, et al. Induction of HIF-1α by HIV-1 infection in CD4 + T cells promotes viral replication and drives extracellular vesicle-mediated inflammation. *MBio*. 2018; 9:e00757-18.
6. Amiel E, Perona-Wright G. Metabolic mediators: how immunometabolism directs the immune response to infection. *Immunology* 2020; 161: 163– 4.
7. Lio CJ, Huang SC. Circles of Life: linking metabolic and epigenetic cycles to immunity. *Immunology* 2020; 161: 165– 74.
8. Quik M, Hokke CH, Everts B. The role of O-GlcNAcylation in immunity against infections. *Immunology* 2020; 161: 175– 85.
9. Guak H, Krawczyk CM. Implications of cellular metabolism for immune cell migration. *Immunology* 2020; 161: 200– 8.
10. Sousa Gerós A, Simmons A, Drakesmith H, Aulicino A, Frost JN. The battle for iron in enteric infections. *Immunology* 2020; 161: 186– 99.
11. Cortes-Selva D, Fairfax K. Schistosome and intestinal helminth modulation of macrophage immunometabolism. *Immunology* 2021; 162: 123– 34.

12. Sears JD, Waldron KJ, Wei J, Chang C. Targeting metabolism to reverse T-cell exhaustion in chronic viral infections. *Immunology* 2021; 162: 135– 44.
13. Sheedy FJ, Divangahi M. Targeting immunometabolism in host defence against *Mycobacterium tuberculosis*. *Immunology* 2021; 162: 145– 59.