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Where do plasmacytoid dendritic cells find the energy?

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Immunometabolism has entered center stage over the last decade as a critical component of understanding the immune response to pathogens and self-antigens.¹ A clearer understanding of the metabolic reprogramming that occurs in innate and adaptive cell types to impact activation state, cytokine and chemokine production, and differentiation is emerging. However, plasmacytoid dendritic cells (pDCs) have been highly understudied in this regard and it is not clear that the developing framework of immunometabolism can be generalized to this cell type. Reports to date have not come to a consensus regarding the metabolic pathways that are at play in regulating the primary role of pDCs: production of type I IFN. In this report, Hurley et al. bring pDC biology into the newly developing field of immunometabolism. Specifically, they identify the metabolic reprogramming that facilitates rapid type I IFN production following activation via viral genomic material.

Plasmacytoid dendritic cells are a specialized sentinel cell type that can respond to pathogen-associated molecular patterns (PAMPs), for example, nucleic acids with rapid and massive production of IFN-I.² Over the last several decades, this relatively understudied cell type has been highlighted as an innate antiviral powerhouse thanks to high level production of type I IFNs, and the primary pathogen recognition receptors it utilizes—namely TLR7, TLR9, and retinoic acid-inducible gene-I (RIG-I)—have been identified.^{2,3} Additionally, pDCs are thought to play an important role in chronic viral infections, autoimmune disease, and cancer, though these are areas of open investigation and their most well-defined function remains that of antiviral IFN-I production.^{4–6}

Now more than ever immunometabolism is revolutionizing immunology, as investigators begin to examine how we can manipulate metabolic pathways to promote favorable immune responses.⁷ Although the field is quite complex (reviewed thoroughly elsewhere), some advances have emphasized a role for glycolysis in activated inflammatory cells (M1 macrophages) and rapidly proliferating cell types (activated effector T cells) as cells prioritize synthesis and replication, suggesting that oxidative phosphorylation (OXPHOS) may be prominent in quiescent cells (memory T cells) or anti-inflammatory cells favoring longevity and energy production.^{1,8} In broad strokes, one of the developing tenets of immunometabolism is that glycolysis is indispensable for highly activated cells. But can this generalized principle be applied to the highly activated IFN-producing pDC?

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DISCLOSURES

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Several groups have attempted to define the metabolic pathways relevant for regulation of IFN-I production by pDCs. As early as 2008, Cao et al.⁹ suggested that mTORC signaling was required for TLR7/9-mediated activation of IFN-I production, both using in vitro culture of murine and human pDC and in vivo murine modeling. In 2016, Bajwa et al.¹⁰ showed that primary human pDCs responded to TLR7 agonists by up-regulating HIF1 α and glycolytic flux in both in vitro and in vivo models. Fekete et al.¹¹ used primary human pDCs and the Gen2.2 cell line in 2018 to propose that pDCs activated via TLR9 rely on glycolysis, whereas those activated through RIG-I require OXPHOS for downstream IFN-I signaling. In vitro murine work by Wu et al.¹² suggested that fatty acid oxidation (FAO) and fatty acid synthesis are required for the autocrine loop that occurs via IFN- α/β receptor signaling to promote continued type I IFN production in TLR-activated pDCs. In contrast, Basit et al.'s 2018 manuscript¹³ suggests that TLR activation in pDCs favors glutaminolysis and OXPHOS in cells derived from healthy donors.

There are several points throughout Hurley et al.'s work that merit highlighting. The manuscript uses in vitro manipulation of isolated primary human pDCs to convincingly argue for a mechanism that is in contrast to the existing literature and proposes a new mechanism for metabolic regulation of IFN-I production. Despite how few studies have explored metabolic reprogramming associated with pDC activation, Hurley et al.'s work challenges each of these studies in turn, proposing an alternative mechanism that conflicts with several studies, convincingly arguing for their model at each step. Finally, their work not only challenges the existing literature surrounding pDC activation and metabolic reprogramming, but also challenges the dogma in immunometabolism that largely highlights the role of AG in supporting highly activated inflammatory or effector cells and the tricarboxylic acid cycle (TCA) cycle and OXPHOS in favoring long-lasting or quiescent immune cells. Here, the authors demonstrate instead a highly productive and highly inflammatory cell type, which at its most active seems to be reliant on the TCA cycle and OXPHOS instead of AG as others had suggested.^{10,11}

The authors take an approach that broadly explores the role of FAO (suggested to be critical by Wu et al.¹²), glutaminolysis, AG (implicated by Bajwa et al.¹⁰ and Fekete et al.¹¹), and OXPHOS (emphasized by Basit et al.¹³) each by several different methods before narrowing in on the role of 5' AMP-activated protein kinase (AMPK) signaling and OXPHOS (see Figure 1 for summary of model). In examining the use of OXPHOS as a primary regulator of IFN-I production in the pDC, the authors also examine several possible metabolic inputs. They argue that the TCA cycle, glycolysis, and FAO all have an impact on IFN-I production, but demonstrate that pyruvate is the most critical metabolite for pDC activation. Their findings, in direct contrast to that of Basit et al., suggest that glutaminolysis plays no role in pDC activation. The authors argue that their data do not match to that of the preexisting literature in this regard due to different culture methods of pDCs and use of distinct TLR ligands. Specifically, the current manuscript uses viral genomic material as the primary TLR agonist, whereas Basit et al.'s work uses pRNA from the chromatin remodeling complex. This generates additional compelling questions about the possibility that alternative metabolic pathways might be required given different PAMPs. However, in best trying to understand the antiviral response, the choice made by Hurley et al. is the most appropriate choice and is a strength of their model.

Hurley et al. go beyond identifying mitochondrial oxidation as the primary metabolic pathway at play by demonstrating that pyruvate is an essential input for the full activation of a TLR-stimulated pDC. They go on to identify major players in the signaling required to generate a metabolic shift on the scale required for the massive output of IFN which a pDC is capable of generating. Specifically, the authors identify AMPK as a master regulator at play via measurement of phospho-Raptor (a downstream target of AMPK), assessment of transcript levels of downstream PPAR pathways, and analysis of RNA seq data demonstrating increased relative activation of PPAR pathways in TLR-stimulated cells. They further demonstrate that inhibition of AMPK abolishes mitochondrial oxidation and thus IFN-I production in stimulated pDCs.

Overall, Hurley et al. use a compelling model—primary human pDCs are the most appropriate model system in which to do the current work—to undertake a robust experimental vetting of previously proposed theories and to generate their own model that they explore at several levels. Worthy of additional emphasis is the thorough experimental undertaking presented in this manuscript. The investigator's expertise shows in their extensive use of several difficult methods to analyze a very rare cell type, including RNASeq on stimulated pDCs. This is a feat on its own, lending weight to several of their findings and distinguishing their work when compared with the existing literature.

As the authors highlight in their discussion, there is compelling work that remains to be done but is outside the scope of the current manuscript. We hope to see more from Hurley et al. as they explore the signaling events that tie TLR7/9 activation to AMPK signaling, closing the loop on the compelling mechanism they propose here. Their current work is limited in its applicability beyond viral activation given the choice of PAMP. Future work to address differences in metabolic regulation of activation downstream of different PAMPs would be interesting. In vivo confirmation would lend additional weight to their proposed model. Further, we find that the distinction between type I IFN and type III IFN production, both requiring OXPHOS but diverging at the level of AMPK regulation, generates compelling questions regarding distinct regulatory mechanisms for production of these cytokines.

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FIGURE 1.

(1) Recognition of viral nucleic acids by TLR7 or TLR9 activates a signaling cascade in pDC, which leads to IRF7 phosphorylation, transcription, and translation of type I IFN. (2) Other contributors to the field have argued for essential roles for anaerobic glycolysis, fatty acid oxidation, glutaminolysis, and the TCA cycle in generating the energy required for IFN production. (3) However, Hurley et al. demonstrate that the energy burst needed for pDC to produce significant quantities of type I IFN rapidly comes from the recruitment of AMPK to increase ATP production through the TCA cycle and oxidative phosphorylation. Increased ATP allows more rapid translation of IFN mRNA and the subsequent release of large amounts of IFN. Created with [BioRender.com](https://www.biorender.com)