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Journal club

IMMUNOMETABOLISM AND THE LAND OF MILK AND HONEY

In 2010, my laboratory submitted a paper to *Nature Immunology* (Masters *et al.*, 2010) describing how islet amyloid polypeptide (IAPP), which is deposited in the pancreas in type 2 diabetes (T2D), induces interleukin-1β (IL-1β) production via the NLRP3 inflammasome. IL-1β had for some time been implicated in T2D pathogenesis, and a role for NLRP3 had been indicated by Jurg Tschopp and colleagues (Zhou *et al.*, 2010). Soon after our paper was accepted for publication, I came across a study by Connie Krawczyk, Ed Pearce and colleagues, published earlier in 2010, that introduced us to metabolic reprogramming as an important component of these responses.

In response to a peer-review comment about the role of glucose in our study, we found that 2-deoxyglucose (2-DG), which blocks glucose uptake in cells treated with IL-1 (Bird *et al.*, 1990), inhibited IL-1β induction in macrophages by lipopolysaccharide (LPS). This result confirmed a role for glucose metabolism in this process. Vince Kelly, a biochemistry colleague at Trinity College Dublin, described this process as the Warburg effect, of which I had never heard.

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The paper by Krawczyk *et al.* that I read soon afterwards described how LPS signalling causes a metabolic shift in dendritic cells (DCs) from oxidative phosphorylation to aerobic glycolysis, which defines the Warburg effect. They showed that just like IL-1, LPS could increase glucose consumption in DCs by inducing expression of the glucose transporter GLUT1. Furthermore, they treated cells with 2-DG and saw inhibition of the induction of key genes associated with DC activation. They interpreted the shift to glycolysis as being required for the enhanced biosynthetic activity in activated DCs. We concluded that glycolysis was needed for LPS to induce IL-1β production.

Krawczyk *et al.* inspired us to continue working on the metabolic effect of activating macrophages with LPS. My laboratory and many others have since made fascinating observations regarding roles for metabolites and metabolic enzymes in the immune processes of diverse cell types. Who would have thought that the simple experiment of adding 2-DG to immune cells would lead to the land of milk and honey that is metabolic reprogramming in immunity?

Luke O'Neill
School of Biochemistry and Immunology, Trinity College Dublin, Ireland.
laoneill@tcd.ie

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ORIGINAL ARTICLE Krawczyk, C. M. *et al.* Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. *Blood* **115**, 4742–4749 (2010)
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