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Translating glycolytic metabolism to innate immunity in dendritic cells

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Abstract

Growing evidence supports a role for glycolysis in immune activation. Everts et al. (2014) now show that TLR-mediated stimulation of dendritic cells rapidly induces glycolysis, which regenerates NADPH and TCA intermediates to support fatty acid production. This enhances ER and Golgi membrane synthesis and innate activation of dendritic cells.

For over a century, the study of immunity to infections has been the exclusive province of immunologists. Delineatingthemyriad cell types and receptors that orchestrate immune responses to infectious agents has provided an overarching framework of how the immune system can sense and fight infections. Recent advances, however, reveal an intricate interplay between ancient biochemical mechanisms that govern cellular metabolism and mechanisms of immunity to infections. In particular, recent studies highlightthat major glycolytic reprogramming occurs in dendritic cells (DCs) and macrophages activated with Toll-like receptor (TLR) ligands (Krawczyk et al., 2010; Tannahill et al., 2013). Now, Everts et al. provide key mechanistic insights into the molecular pathways that drive TLR-induced glycolysis in DCs andthe functional consequences on innate and adaptive immunity(Everts et al., 2014).

DCs play a central role in sensing pathogens via an array of pathogen recognition receptors such as TLRs,and stimulating antigen-specific T cells to proliferate and differentiate into effector and memory cells. Ligand binding by TLRs results in DC activation and anincreased ability to stimulate T cells. Previous studies have shown that TLR activation of DCs results in enhanced glycolysis, whereas inhibition of glycolysis impairs DC activation and survival (Jantsch et al., 2008; Krawczyk et al., 2010). Late commitment to TLR-induced glycolysis occurs via the induction of nitric oxide (NO)after 24h of stimulation, partly as a compensatory mechanism from the direct inhibition of mitochondrial OXPHOS by NO(Everts et al., 2012).

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In their latest study, Pearce and colleagues focusedon the earlierNO-independent stages of glycolytic induction that occur in bone marrow derived DCs within minutes of activation by TLR ligands (Everts et al., 2014). Early glycolysis was controlled bythe rate-limiting glycolytic enzyme HK-II, whichfacilitatesutilization of citrate to support *de novo* synthesis of fatty acids and accommodates increased ER and Golgi membrane synthesis - essential for effector cytokine production. Consistent with this, TLR-induced glycolysis enhanced expression of co-stimulatory molecules such as CD86, the pro-inflammatory cytokines IL-12, IL-6 and TNF, and improvedDC capacity to stimulate T cells. Interestingly, inhibition of glycolysis did not result in reduced expression of mRNA encoding these cytokines, suggesting that glycolysis regulates innate activation of DCs at the post transcriptional level.

To investigate how glycolytic metabolism directly promoted cytokine secretion,Everts*et al.* analyzed metabolic flux using ^{13}C glucose. This approach revealed enhanced labeling of TCA intermediates and the depletion of citrate from the mitochondria, as a consequence of its transportto the cytosol via the citrate shuttle Slc25a1,towardsfatty acid synthetic pathways. In addition, these experiments revealed considerable alterations in pentose phosphate pathway (PPP) intermediates, a pathway that rechargesthe crucial fatty acid-synthetic cofactor, NADPH(Figure 1). Transmission electron microscopy experiments revealed that *de novo* synthesis of fatty-acids promotedER and Golgi expansion, whereas inhibition of either glycolysis or fatty acid synthesis abrogated this phenomenon. Thus,glycolysisdrives lipogenesis, serving the generation of additional organelle membranesand fulfilling cellular activation requirements, such as the synthesis and production ofpro-inflammatory cytokines. Together, these results mechanistically dissect a metabolic checkpoint during the early activation of DCs.

Finally, Everts and colleaguesaddressed the question of how TLR stimulationdirectly signalsa change in cellular metabolism. Here, the authors demonstrated a role for non-canonical Akt signaling. A complex of Tbk1-IKKε activated Akt downstream of TLRs. This was unexpected given that canonical PI(3)K-dependent Akt signaling was implicatedduringlate-stagemaintenance of aerobic glycolysis in TLR stimulated BMDCs(Krawczyk et al., 2010). The authors further showed that Akt directly phosphorylates the rate-limiting glycolytic enzyme hexokinase II (HK-II), promoting its association withvoltage-dependent anion channels (VDACs) located in the outer mitochondrial membrane. This physical relocation has been described to expose HK-II toincreased mitochondrial-derived ATP concentrations,enhancingitsenzymatic activity to drive glycolysis (Figure 1)(Miyamoto et al., 2008; Stiles, 2009). Thus,the authors reveal the signaling pathway linking TLR signaling to control glycolytic machinery.

The study by Everts et al. provides new mechanistic insightsinto the role ofaerobic glycolysisduring DC activation and also raises several questions. First,it will be necessary todetermine the relative importance of this innate activation pathwayin the context of other well-described innate activation pathways downstream of TLRs and other innate receptors, in response to infections in vivo. Second, can alterations in the concentration of glucose within the cell, (caused either by changes in the nutritional status of the cell or individual, or by direct appropriation of such nutrients by pathogens), act as a trigger for this glycolytic

mechanism of immune regulation? In this context, recent evidence suggests that immune cells can indeed sense changes in intracellular nutrient concentration, leading to their activation. Infection of DCs with the live attenuated yellow fever virus resulted in a striking decline in the concentration of free cytosolic amino acids, which activated the general control nonderepressible 2 kinase (GCN2) and the integrated stress response pathway(Ravindran et al., 2014). GCN2 in turn programs DCs to undergo enhanced autophagy and antigen presentation to CD8+ T cells. Thus, it is possible that pathogens may cause changes in the concentrations of glucose and other nutrients, which act as a trigger for innate activation. Third, whilst this study identifies aerobic glycolysis as essential for DC maturation, to what extent is this a common mechanism during activation of additional immune cell-types? Recently, Chang et al. reported that a switch to glycolytic metabolism similarly programs T-cell cytokine production, albeit via a distinct biochemical mechanism(Chang et al., 2013). Given that activated DCs utilize anabolically synthesized fatty acids for the expansion of the ER and Golgi, it will be interesting to address what role organelle enlargement plays during B-cell antibody production and antibody affinity maturation – processes that are heavily dependent on these organelles. Finally, whether components of this glycolytic pathway could be exploited to pharmacologically reprogram dysfunctional immune systems in the therapeutic control of infections, autoimmunity or transplantation needs to be explored.

Taken together, the study of Everts and colleagues casts new light on the intimate communication between cellular metabolism and immune activation, emphasizing the importance of thisemerging research field.

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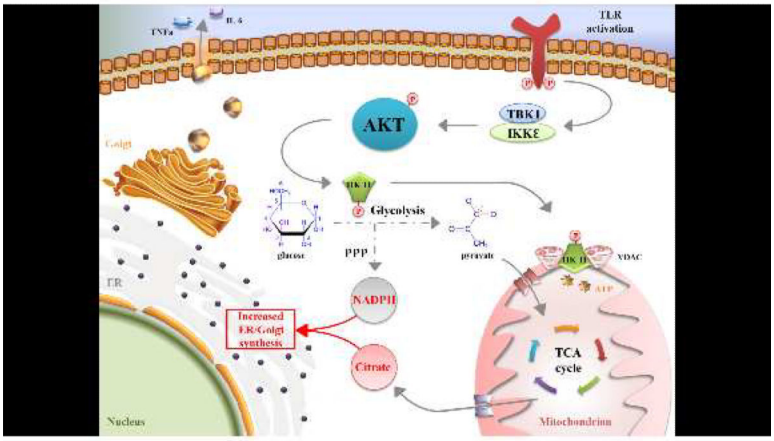

Figure 1.

TLR-mediated reprogramming of cellular metabolism is a requirement for DC effector functions.

TLR signaling via the kinases Tbk1-IKKε and Aktrapidly increases glycolysis by promoting juxtaposition of the rate-limiting glycolytic enzyme HK-II to the outer mitochondrial membrane. Upon translocation,HK-II gains direct access to high concentrations of ATP, which enhances its enzymatic activity. Increased glycolytic flux: a) recharges NADPH through the PPP; b) promotes utilization of citrate and isocitrate for lipogenesis. Together, increased fatty acid synthesis induces ER and Golgi expansion, accommodating cellular demand for the translation, transport and secretion of early activation markers and pro-inflammatory cytokines TNFa and IL-6.