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DISSERTATION

"The mechanism of metabolic reprogramming in activated plasmacytoid dendritic cells"

by

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M.D./Ph.D. Program

B.A. 2014, Kenyon College, Gambier, OH

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Friday, April 10th, 2020
10:00 A.M.
Webex TBD

Abstract

Plasmacytoid dendritic cells (pDCs) play a crucial role in innate viral immunity as the most potent producers of type I interferons (IFN) in the human body. They sense viral ssRNA through toll-like receptor (TLR) 7 and CpG motifs abundant in viral DNA through TLR9. These pattern recognition receptors (PRRs) signal downstream through two MyD88 dependent pathways that culminate in translocation of NF-κB and interferon regulatory factor (IRF) 7. This cascade of events is commonly referred to as “activation”. This activation leads to the production of vast quantities of IFN-α by pDCs. While evidence of pDC metabolic reprogramming is present in the literature, the cellular mechanisms of metabolic regulation of IFN production in such vast quantity remains poorly understood. In this thesis, we strongly implicate AMP-activated protein kinase (AMPK) as a driver of metabolic reprogramming that we and others have observed in pDCs after activation via toll-like receptor (TLR)7/9. Oxygen consumption and mitochondrial membrane potential (MMP) were elevated following stimulation of pDCs with influenza or herpes simplex virus. Blocking these changes using mitochondrial inhibitors abrogated IFN-α production. While it appears that multiple carbon sources can be used by pDCs, blocking pyruvate metabolism had the strongest effect on IFN-α production. Furthermore, we saw no evidence of aerobic glycolysis (AG) during pDC activation, blocking lactate dehydrogenase activity did not inhibit IFN-α, nor did we see evidence of increased glucose uptake during activation. Dorsomorphin, an AMPK inhibitor, inhibited both IFN-α production and MMP in a dose-dependent manner. Meanwhile, rapamycin had no significant effect on OXPHOS or IFN-α production. Resveratrol similarly had no effect on OXPHOS or IFN-α production. Finally, we demonstrated that TLR7/9 ligation induces a post-translational modification in Raptor that is catalyzed by AMPK, and that blocking TLR7/9 before virus introduction prevents this change. Taken together, these data reveal a potential cellular mechanism for metabolic reprogramming in TLR 7/9-activated pDCs that supports activation and IFN-α production.