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A sweet alternative: maintaining M2 macrophage polarization

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One-Sentence Summary:

Glycolytic metabolism functions as a backup mechanism for M2 macrophage polarization when oxidative phosphorylation is disrupted.

Whereas LPS-associated "classical" M1 macrophage polarization is driven mainly by glycolysis, IL-4-driven "alternative" M2a polarization in macrophages relies on oxidative phosphorylation (OXPHOS) and fatty acid oxidation. This so-called "glycolytic switch" driving macrophage toward either M1 or M2 phenotypes has recently been challenged by data suggesting that glycolysis may also be important for M2a polarization. Wang and colleagues definitively address this conundrum by delineating complementary metabolic pathways driving macrophage M2a polarization under distinct conditions. The authors confirmed that the traceable glucose analog 2-deoxy-D-glucose (2-DG), known to block glycolysis, inhibits IL-4-induced M2a polarization, indicating that glycolysis indeed may be associated with M2a development. Though galactose treatment or glucose depletion also inhibits glycolysis, M2a polarization is remarkably unimpeded in this setting. What explains this apparent discrepancy? The authors show that inhibiting glycolysis via galactose addition or glucose depletion increased $^{13}C_5$-glutamine-labelled Krebs cycle metabolites, indicating that in macrophages glutamine can also fuel Krebs cycle metabolism. By contrast, 2-DG treatment reduced Krebs cycle function via OXPHOS inhibition. The JAK-STAT6 pathway, normally activated upon IL-4 stimulation, plays a key role in M2a polarization. The authors found that only combined inhibition of glycolysis and Krebs cycle by 2-DG treatment, and not specific inhibition of glycolysis via galactose treatment or glucose depletion, inhibited IL-4-induced STAT6 phosphorylation. How does blocking both glycolysis and OXPHOS metabolism lead to inhibition of M2a polarization? Data presented by Wang *et al* demonstrates that this may be due to the marked reduction in ATP production caused by combined inhibition of glycolysis and Krebs cycle-associated OXPHOS metabolism. These findings delineate that M2a macrophages possess metabolic plasticity, allowing them to use

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either glucose (glycolysis) or glutamate (Krebs cycle) as energy sources to fuel ATP production and maintain M2a polarization under different environmental conditions. This work advances our understanding of metabolic programming and phenotypic plasticity in macrophages and points to novel strategies for macrophage metabolic reprogramming as a potential means to treat macrophage-associated inflammatory diseases.

Full Citation:

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