Getting Started in Immunometabolism

Literature Resources

Lymphocytes – An Army Marches on Its Metabolism

Lymphocytes migrate between wildly different microenvironments in vivo. Metabolic pathways, integrating cell-specific and site-specific factors, are intimately tied to activation, proliferation, and differentiation of lymphocytes. A circulating naïve lymphocyte may use Oxidative Phosphorylation (OxPhos) for energy, but it is non-proliferative. Blasting lymphocytes utilize glycolysis to meet high demands for metabolites for building biomass. Memory lymphocytes, often in low oxygen niches, favor glycolysis. Competition with other lymphocytes, tumor cells and microbes as well as the physiology of local nutrient and oxygen are environmental influences. Importantly, key control molecules in lymphocyte activation, such as mTOR, HIF, and NF-kappa B, are exquisitely sensitive to pericellular oxygen. As Immunometabolism coalesces as a new field, it brings a picture of comprehensive metabolic control of immunity.

T Cell Activation, Proliferation, and Differentiation is Tied to Metabolism

- T cell metabolism is intimately tied to activation and proliferation through multiple signaling pathways including Notch/PI3K/mTOR (reviewed in [1] [2])
- mTORC1 and 2 differentially regulate anabolic and catabolic pathways in response to O2 changes and mTORC1 induces HIF-1a production [2]
- NF-kappa B, central to cytokine signals like TNF, is affected by O2 levels [3]

T Cell Phenotype and Function is Shifted by mTOR, HIF-1a and Oxygen

- Low O2 and stabilization of HIF-1 favors differentiation of Th9, Th17, and Th22 phenotypes over Th1 and Treg (reviewed in [2] [4]) [5]
- Foxp3 upregulates OxPhos and downregulates glycolytic enzymes [6]
- HIF and mTOR activity are needed for CTL effector function [7]
- Lymphnode O2 (5%) rather than 21% increased IL-10, 4-1BB and CD25 in CTL [8]

B Cells, the Germinal Center, and Tolerance are Affected by a Metabolic Milieu

- B cells proliferating in the GC light zone are hypoxic (reviewed in [9] [10])
- B cells cultured in low O2 exhibit reduced proliferation, AID expression, and CSR to IgG1, but not IgA, which may accomodate microbial competition for GI O2 [10]
- HIF stabilization induces CXCR4 expression, affecting B cell homing [9]
- Mice with HIF1a-deficient T and B cells exhibit increased autoimmunity [11]
- Low O2 promotes T follicular regulatory cell differentiation and these cells in turn, help limit proliferation of autoreactive GC B cells [12].

Appropriate In Vitro Oxygen is Critical for Immune Cell Studies

- Room air oxygen dramatically reduces HSC isolation yields [13] and increased intracellular ROS affect HSC generation and differentiation [14] [15]
- Culture under physiologic oxygen in vitro reduces T cell proliferation [4] [16]

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