

Immune cells use the well-known metabolic pathways of oxidative phosphorylation, glycolysis, and fatty acid oxidation to different extents to accomplish different immune functions. Many, many factors affect metabolic state of any particular cell. These include cell-specific factors like cell type and cell state (activation, differentiation, proliferation, migration). They also include site-specific factors such as tissue site and state (normal, disease, injury, infection). Any cell's metabolic state can be affected by the relative availability of nutrients and oxygen. However, the immune cell microenvironment provides a new context in which to connect specific functions in immunity with physiologic conditions such as blood delivery and competition for oxygen by nearby cells or microbes. Most importantly, these new connections give us a better picture of physiologically relevant in vitro assay conditions for translatability and reproducibility.

A Few Recent Reviews on Metabolism as Immunomodulator [1] [2] [3] [4]

Hematopoietic Stem Cell Metabolism and Microenvironment

- The physiology of the blood, nutrient, and oxygen delivery in the bone marrow hematopoietic stem cell niche favors very low oxygen levels (Reviewed in [5]) [6]
- HSC yields from cord blood or marrow are higher when isolated in physioxia [7]
- Elevated intracellular ROS levels reduce engraftment [8]

Pathologic Hypoxia and Inflammation (reviewed in [9])

- High altitude exposure can result in inflammation of tissues [9]
- Wounds and sites of inflammation are hypoxic [10] [11] [12] [13] [14]
- Ischemia/reperfusion (embolism or grafts) is followed by inflammation [15]

The Tumor Microenvironment

- Tumor infiltrating lymphocytes (TIL) compete with highly glycolytic tumor cells for glucose and oxygen in poorly vascularized tumors (reviewed in [16])
- Lung may be immunologically permissive for metastasis due to higher O₂ [17]
- CAR-T that express the CAR protein only upon HIF-1 α induction, may increase anti-tumor cytotoxicity and specificity in solid tumors [18]

Controlled In Vitro O₂ is Critical for Translatability and Reproducibility in Immunology

- Even lung cell cultures experience oxygen artifact cultured in room air [19]
- Hypoxic Pre-conditioning in vitro may improve immune cell function in vivo [20]
- Isolation of HSC in room air O₂ cuts yields and engraftment [7]
- The proper oxygen level in vitro is critical for physiologically relevant findings in lymphocyte assays [21] [22]

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