

Innate Immunometabolism

Myeloid cells are subjected to highly variable environments in vivo and in vitro. Integrating environmental and cell-specific factors, the emerging field of Immunometabolism is making new connections between well-known metabolic mechanisms and specific innate immune functions. It is becoming increasingly clear that metabolic processes do more than just provide material support cell functions, but also contain key control points to innate immunity.

Key Control Points - mTOR, HIF, and Oxygen

Macrophage, granulocytes and DC, primarily use glycolysis for generating energy and metabolites for use (reviewed in [1]). mTOR and HIF-1, well known for their ability to change cell function in response to oxygen and other environmental stimuli, are key regulators of metabolic programs as well as specific myeloid functions. HIF-1a and mTOR activity in myeloid cells have been implicated in disease states such as infection [2], sepsis [3], and autoimmunity [4]. Transcription factors such as NF- κ B that are central to the cytokine response are linked to these signaling pathways as well [5].

Macrophage

- mTORC1 is a key controller of metabolic programming, proliferation, migration, polarization, and antigen presentation (reviewed in [6] [7] [8])
- Oxygen-sensitive HIF proteins are central in innate immune cell regulation [9] [10]
- Myeloid cells of the airway system may be suppressed by systemic hypoxia [11]

Neutrophils

- ROS are a critical secondary signal for formation of the NLRP3 inflammasome in response to TLR signaling (reviewed in [12])
- Low O₂ levels due to microbial competition and disrupted vasculature may limit neutrophil recruitment to a wound and affect duration of the response [13]
- Low O₂ pre-conditioning via HIF and glycolysis reduces neutrophil-mediated Staph mortality. [14]

Dendritic Cells

- HIF-1a is essential for DC maturation (reviewed in [15])
- Through HIF-1a, in vitro oxygen levels can alter DC LPS-responses, CD80 and CD86 expression, and stimulation of allo T cell responses (reviewed in [16])
- Low O₂ may favor DC migration over recruitment functions ([16])

Physiologically relevant O₂ control in vitro is essential for translatable myeloid studies.

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