SnapShot: Immunometabolism

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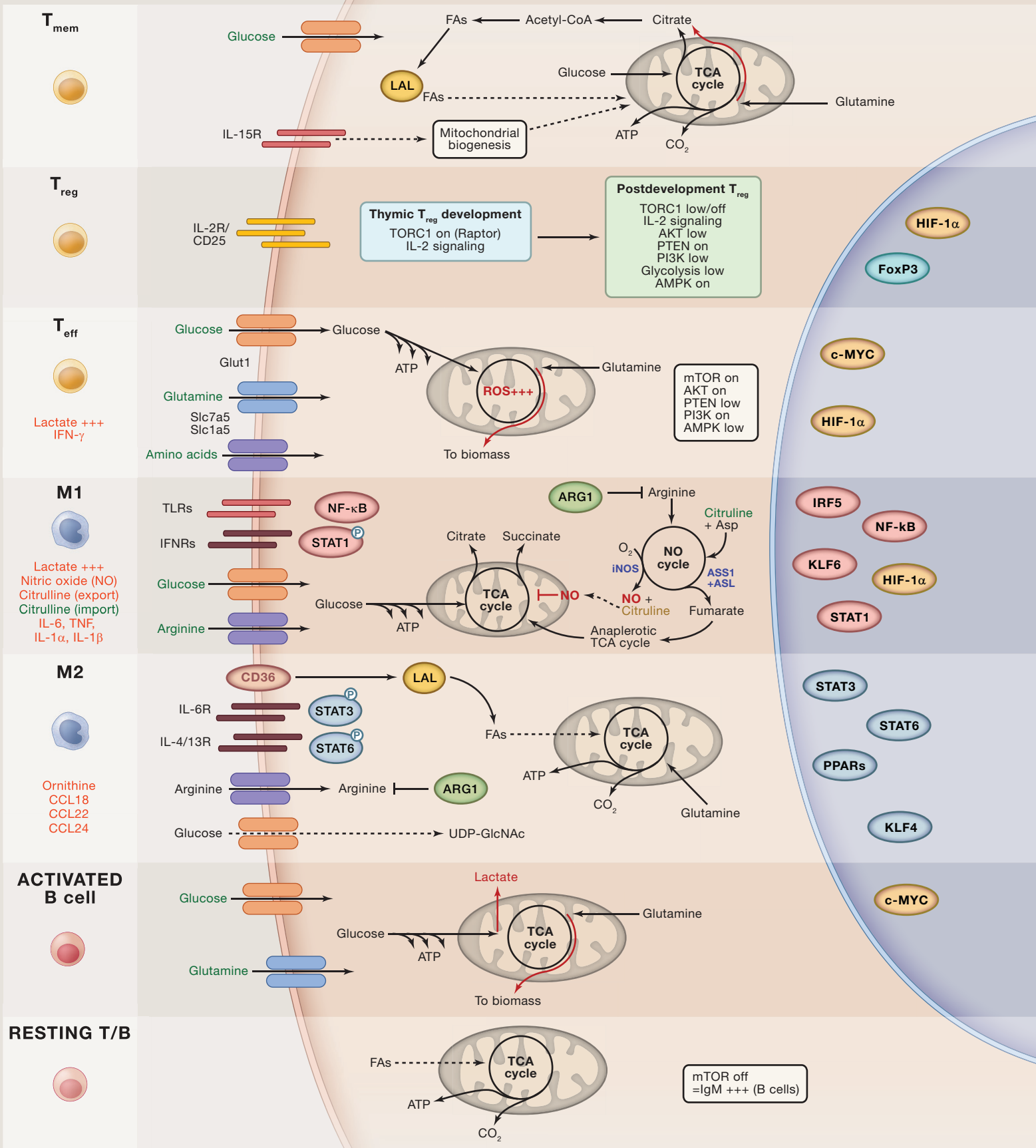
Cell Metabolism



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Cell Metabolism

The vast and fast-moving field of immunometabolism deciphers the contribution of biochemistry to immune cell development, fate, and behavior. An advantage of using the immune system to uncover fundamental aspects of intermediary metabolism lies in the fact that the majority of immune cell populations are (i) dispensable for normal organismal development (with the exception of tissue macrophages that populate, monitor, and modify most of the tissues of the body), (ii) can often be produced in large amounts or highly purified, (iii) are amenable to exquisitely specific genetic ablation strategies, and (iv) can be isolated and transferred between animals. A major theme of immunometabolism concerns distinctions between cells requiring rapid division cycles or activation, and cells destined for quiescent or surveillance roles. Characteristics of the former are closely related to oncogenically transformed malignant cells and embryonic stem cells, which import and burn massive amounts of glucose to generate biomass (Warburg-type metabolism). By contrast, the latter generally use fatty acid oxidation and the Krebs cycle to generate energy. Manipulating specific pathway components of immunometabolic cycles (TORC1, TORC2, PTEN, AMPK, PI3K) via genetic or pharmacological approaches is a useful tool to alter cell behavior and switch fates. Biochemical strategies help further uncover specific metabolic requirements for immune responses, globally, and address specific questions about how metabolites are made and metabolized.

Lymphocytes and T Cells

Quiescent lymphocytes rely primarily on fatty acid and glucose metabolism.

T effectors (T_{eff}) emerge from quiescence following activation by antigen through the T cell receptor and costimulation through an mTOR-dependent process that involves an increase in aerobic glycolysis (Warburg-type metabolism). Activated T_{eff} cells undergo multiple cellular divisions and convert glucose and glutamine into biomass, require substantial supplies of amino acids imported from the local environment, and are dependent on TORC1, PI3K, and AKT. In terms of metabolic requirements, therefore, T_{eff} cells are similar to oncogenically transformed cells. Glycolysis also allows the efficient translation of mRNAs encoding effector cytokines, such as IFN-γ, by preventing GAPDH moonlighting as an mRNA-binding protein.

To persist for long periods as quiescent cells, memory T (T_{mem}) cells maintain healthy mitochondria by synthesizing and then oxidizing FA to support OXPHOS. $CD8^+$ cytotoxic T cells treated with the TORC1 inhibitor rapamycin exhibit features of T_{mem} cells. TORC1 signaling is required for exit from quiescence.

Regulatory T (T_{reg}) cells are dependent on FoxP3, allowing highly specific genetic tests of T_{reg} metabolic requirements. Mice lacking mTOR in all T cells have a phenotype similar to T_{reg}, arguing that mTOR signaling counters the T_{reg} phenotype. Similarly, AKT activation blocks T_{reg}. However, ablation of Raptor (a component of TORC1) using FoxP3-Cre causes defects in T_{reg} number and function. T_{reg} development and function thus appear strongly dependent on specific metabolic cues at specific times: T_{reg} expansion likely requires TORC1 and glycolysis, though this pathway must be suppressed for T_{reg} to become fully functional. Further metabolic pathways impinging on T_{reg} function include withdrawal of essential amino acids such as arginine, which is thought to help T_{eff} convert to a more regulatory state.

Activated B Cells

Once triggered to make antibodies, B cells are glycolytic and must construct an expanded endoplasmic reticulum to secrete antibodies. The metabolic requirements for antibody production and then return to the memory state are just being uncovered. Blocking mTOR in an ongoing B cell response biases antibody production to IgM, suggesting that metabolism is interlaced with antibody class.

Macrophages M1 and M2

M1 macrophages activated by pathogen products and type I IFNs are glycolytic and anti-microbial and have tissue-destructive potential. Most M1-like macrophages in inflammatory sites originate from bone marrow inflammatory monocytes and are thus replaceable without requiring self-renewal. A major product of M1 macrophages is NO, which requires the importation of arginine and oxygen. The product of the nitric oxide synthase reaction (mediated by iNOS) is citrulline and NO. Remarkably, citrulline is exported and then re-imported as needed to re-generate arginine and sustain NO production; this cycle forms part of the anaplerotic TCA cycle of M1 cells, which can also lead to poisoning of mitochondrial respiratory activity (in monocyte-derived dendritic cells). ARG1, induced by a complex TLR-dependent indirect mechanism, blocks this reaction by hydrolyzing arginine. In addition to NO, major products of M1 macrophages are cytokines, chemokines, metalloproteases, and the anti-microbial metabolite itaconate. The TCA cycle is fragmented in M1 macrophages, and this is associated with an accumulation of succinate, which has proinflammatory effects by stabilizing HIF1α. In related dendritic cells, citrate derived from glucose is used to support increased fatty acid synthesis, which is essential for activation.

M2 macrophages do not make NO and instead use ARG1 to hydrolyze massive amounts of imported arginine. While the products of this reaction are ornithine and urea, the main function of arginine consumption by M2 macrophages is to restrict supply to neighboring arginine auxotrophs: M2 macrophages are therefore immunoregulatory and can suppress T_{eff} by blocking their supply of arginine. M2 macrophages use FA primarily derived from acquired triacyglycerols to support OXPHOS, have an intact TCA cycle, and make large amounts of glycosylated proteins, which require UDP-GlcNac from glucose.

The metabolic status of the tissue macrophages that expand and seed growing organs in the early embryo (e.g., microglia) remains unclear and may be dependent on the tissue context. However, like monocyte-derived macrophages, tissue macrophages can be M1 or M2 polarized, depending on the inflammatory microenvironment.

ABBREVIATIONS

ARG1, arginase 1; ASL, argininosuccinate lyase; ASS1, argininosuccinate synthase 1; FA, fatty acid; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HIF1-α, hypoxia-inducible factor 1-α; IFN, interferon; IL, interleukin; KLF, Kruppel-like factor; NO, nitric oxide; iNOS, inducible NO synthase; LAL, lysosomal acid lipase; ROS, reactive oxygen species; TLR, Toll-like receptor; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine.

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