Immuno-biology

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Basic and translational aspects of lymphocyte function and its metabolic basis

T cells belong to the adaptive arm of the immune system and play key roles in protecting the host from invading pathogens. The metabolic repertoire of T cells – which encompasses metabolic enzymes/pathways, the available nutrient sensors and metabolic checkpoint kinases, and the epigenetic programming of metabolic genes – directly enables and modulates specific immune functions (Gubser/Bantug *et al.*; Dimeloe *et al.*; Jones and Thompson; MacIver *et al.*; O'Sullivan *et al.*; van der Windt *et al.*).

The signaling pathways that are shaping the metabolic repertoire of T cells *in vivo* remain poorly defined, particularly in humans. We established a critical link between the complement system and immunometabolic adaptations driving CD4+ T cell effector function. In activated human T cells, autocrine stimulation of the complement receptor CD46 was found to be required for enhanced expression of the glucose transporter GLUT1 and induction of the amino acid transporter LAT1. Furthermore, CD46 activation simultaneously drives expression of LAMTOR5, which mediates assembly of the amino acid-sensing Ragulator-Rag-mTORC1 complex, and increases glycolysis and oxidative phosphorylation required for cytokine production (Kolev/Dimeloe *et al.*).

The cell-intrinsic metabolic repertoire is also subject to modification by extracellular local and systemic metabolic alterations – driven e. g. by malignancies or infection, respectively. In that regard, depletion of glucose from the tumor-microenvironment by malignant cells has been shown to impair effector-functions of tumor-infiltrating T cells (Zhao, E. *et al.*, 2016). Systemic metabolic alterations, such as increased abundance of the short-chain fatty acid acetate during bacterial infections (i.e. acetate stress-levels), likewise impact immune cell metabolism and function. Specifically, we found that acetate is taken up by memory CD8+ T cells, metabolized and utilized to acetylate GAPDH, which in turn increases glycolytic flux and thereby the memory T cell recall capacity (Balmer *et al.*, 2016).

Our ongoing goal is to delineate the molecular basis of how cellular metabolism is regulated, and itself regulates, immune-function in health and disease states, and to define how environmental cues are integrated at the cellular level by immune cells to shape cellular metabolism and function.

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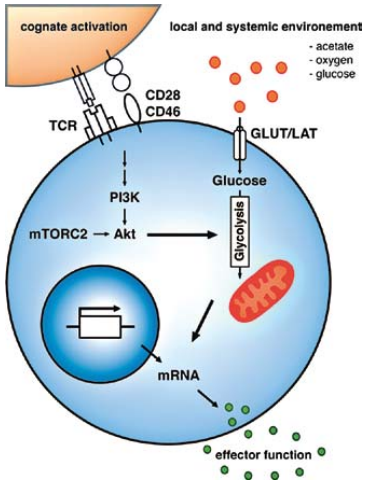

Fig. 1: T cell metabolism defines cellular function – and is, itself, influenced by the extracellular metabolic environment. Glucose metabolism and mitochondrial function are central to the immune function of T cells, critically regulated through PI3K–Akt–mTOR signaling. Activation of T cells initiates rapid metabolic reprogramming (increased glycolysis and oxidative phosphorylation) and changes the expression of key nutrient channels, such as glucose and amino acid transporters. TCR=T cell receptor; CD28 and CD46 (a complement receptor) represent co-stimulatory molecules; GLUT=glucose transporter; LAT=amino acid transporter

Selected Publications

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