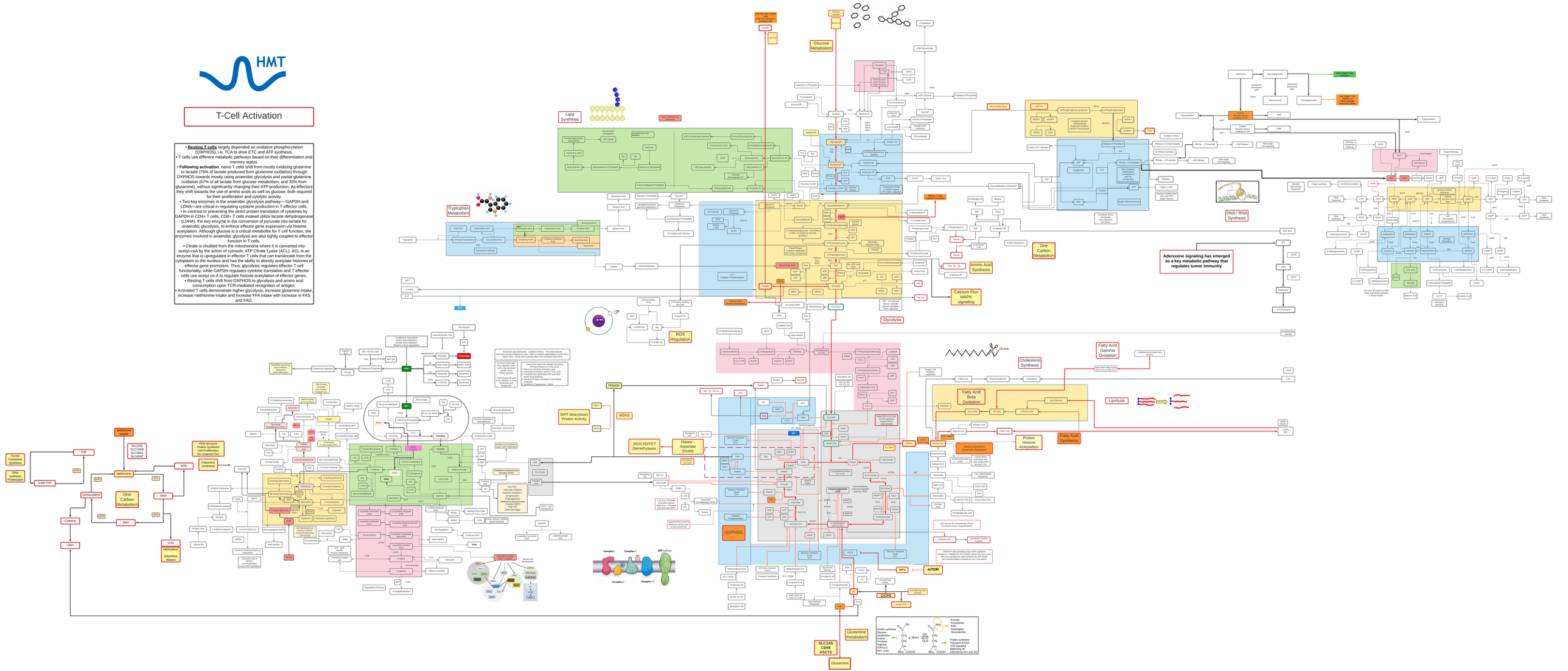
HMT

T-Cell Activation

- **Resting T cells** largely depended on oxidative phosphorylation (OXPHOS), i.e. TCA to drive ETC and ATP synthesis,
- T cells use different metabolic pathways based on their differentiation and memory status.
- **Following activation**, naïve T cells shift from mostly oxidizing glutamine to lactate (75% of lactate produced from glutamine oxidation) through OXPHOS towards mostly using anaerobic glycolysis and partial glutamine oxidation (67% of all lactate from glucose metabolism, and 33% from glutamine), without significantly changing their ATP production. As effectors they shift towards the use of amino acids as well as glucose, both required for their proliferation and cytolytic activity.
- Two key enzymes in the anaerobic glycolysis pathway— GAPDH and LDHA—are critical in regulating cytokine production in T effector cells.
- In contrast to preventing the direct protein translation of cytokines by GAPDH in CD4+ T cells, CD8+ T cells instead utilize lactate dehydrogenase (LDHA), the key enzyme in the conversion of pyruvate into lactate for anaerobic glycolysis, to enforce effector gene expression via histone acetylation. Although glucose is a critical metabolite for T cell function, the enzymes involved in anaerobic glycolysis are also tightly coupled to effector function in T cells.
- Citrate is shuttled from the mitochondria where it is converted into acetyl-coA by the action of cytosolic ATP Citrate Lyase (ACL). ACL is an enzyme that is upregulated in effector T cells that can translocate from the cytoplasm to the nucleus and has the ability to directly acetylate histones of effector gene promoters. Thus, glycolysis regulates effector T cell functionality; while GAPDH regulates cytokine translation and T effector cells use acetyl co-A to regulate histone acetylation of effector genes.
- Resting T cells shift from OXPHOS to glycolysis and amino acid consumption upon TCR-mediated recognition of antigen.
- Activated T cells demonstrate higher glycolysis, increase glutamine intake, increase methionine intake and increase FFA intake with increase in FAS and FAO.