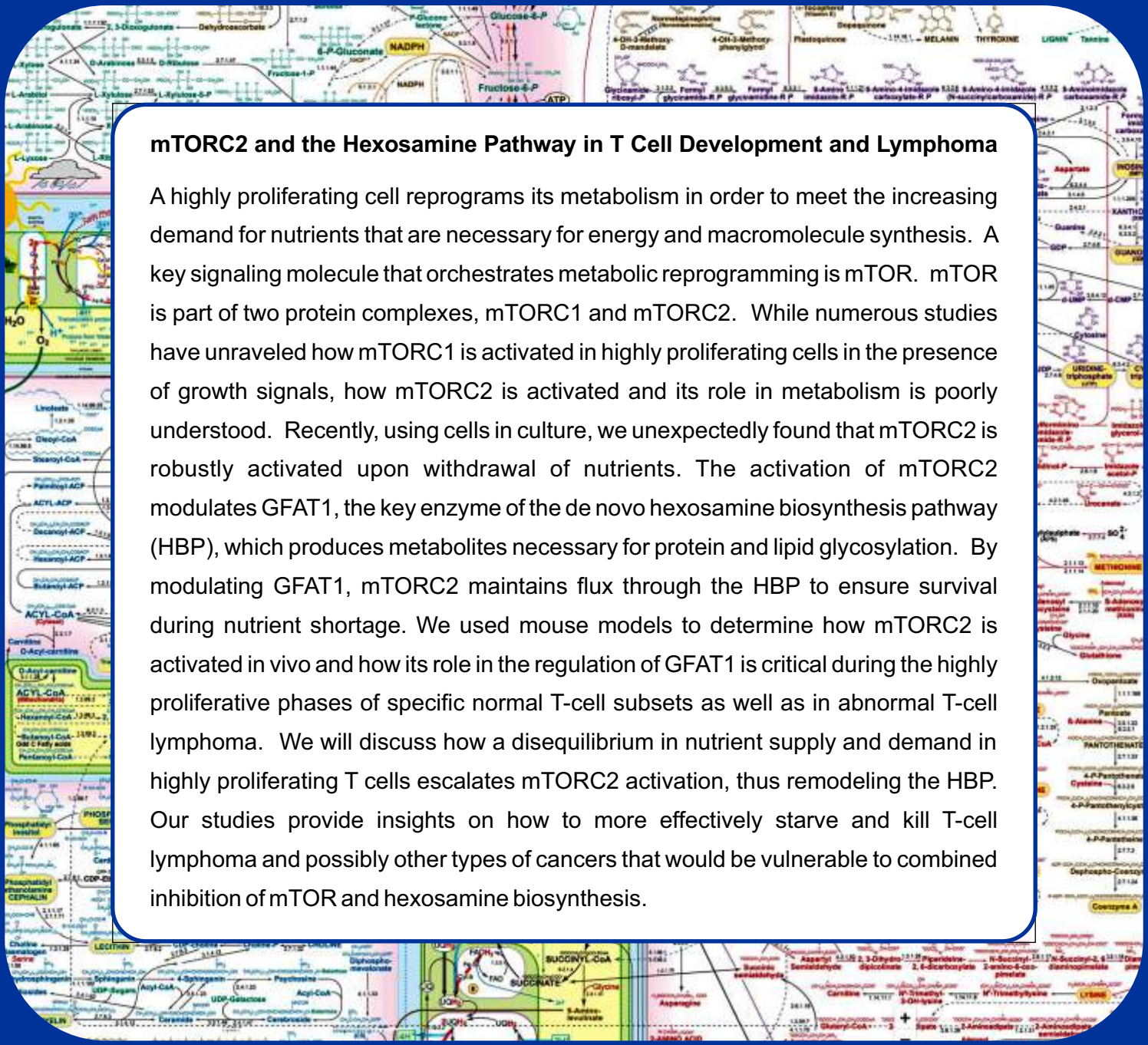

mTORC2 and the Hexosamine Pathway in T Cell Development and Lymphoma

A highly proliferating cell reprograms its metabolism in order to meet the increasing demand for nutrients that are necessary for energy and macromolecule synthesis. A key signaling molecule that orchestrates metabolic reprogramming is mTOR. mTOR is part of two protein complexes, mTORC1 and mTORC2. While numerous studies have unraveled how mTORC1 is activated in highly proliferating cells in the presence of growth signals, how mTORC2 is activated and its role in metabolism is poorly understood. Recently, using cells in culture, we unexpectedly found that mTORC2 is robustly activated upon withdrawal of nutrients. The activation of mTORC2 modulates GFAT1, the key enzyme of the de novo hexosamine biosynthesis pathway (HBP), which produces metabolites necessary for protein and lipid glycosylation. By modulating GFAT1, mTORC2 maintains flux through the HBP to ensure survival during nutrient shortage. We used mouse models to determine how mTORC2 is activated in vivo and how its role in the regulation of GFAT1 is critical during the highly proliferative phases of specific normal T-cell subsets as well as in abnormal T-cell lymphoma. We will discuss how a disequilibrium in nutrient supply and demand in highly proliferating T cells escalates mTORC2 activation, thus remodeling the HBP. Our studies provide insights on how to more effectively starve and kill T-cell lymphoma and possibly other types of cancers that would be vulnerable to combined inhibition of mTOR and hexosamine biosynthesis.