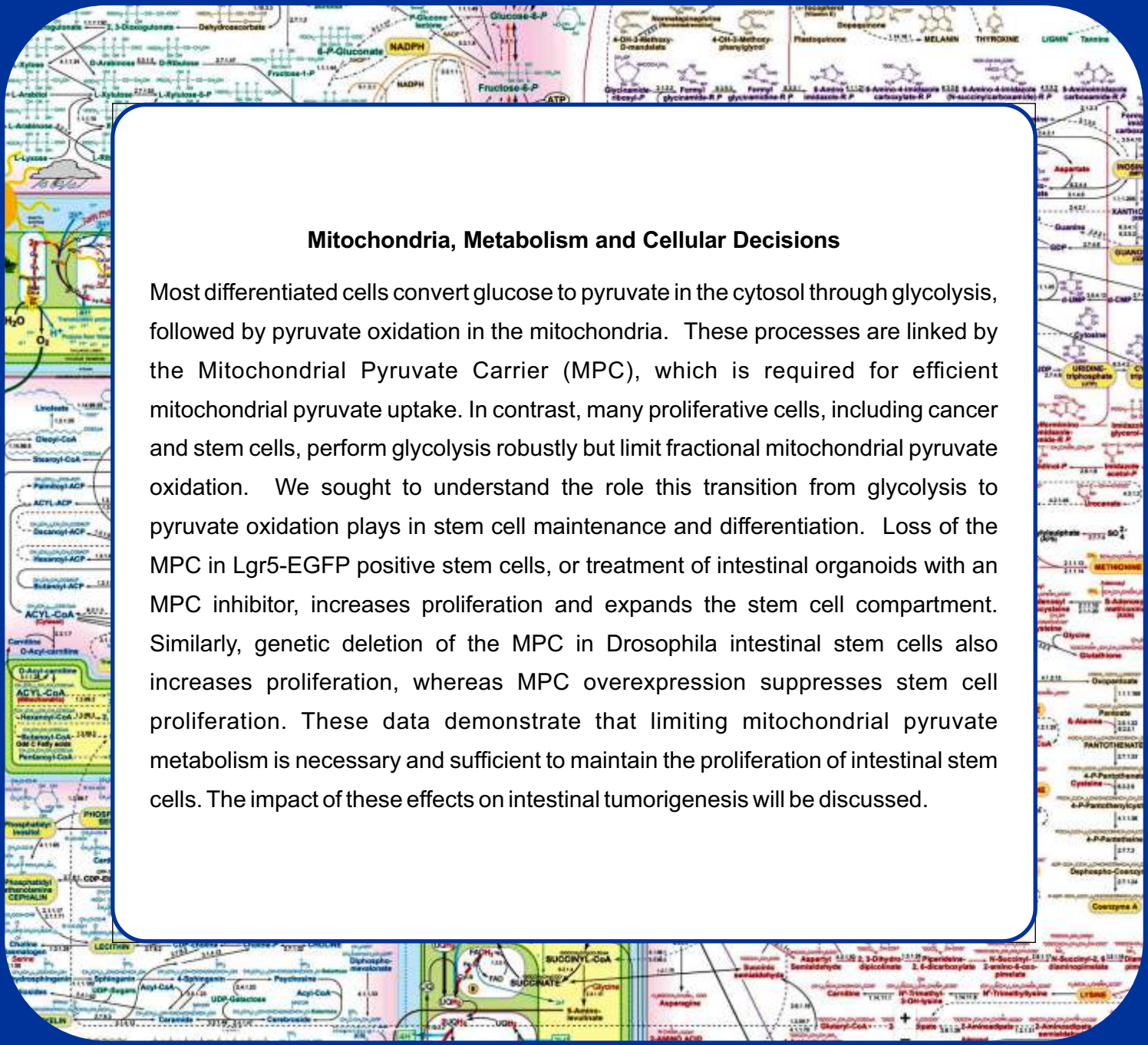

Mitochondria, Metabolism and Cellular Decisions

Most differentiated cells convert glucose to pyruvate in the cytosol through glycolysis, followed by pyruvate oxidation in the mitochondria. These processes are linked by the Mitochondrial Pyruvate Carrier (MPC), which is required for efficient mitochondrial pyruvate uptake. In contrast, many proliferative cells, including cancer and stem cells, perform glycolysis robustly but limit fractional mitochondrial pyruvate oxidation. We sought to understand the role this transition from glycolysis to pyruvate oxidation plays in stem cell maintenance and differentiation. Loss of the MPC in Lgr5-EGFP positive stem cells, or treatment of intestinal organoids with an MPC inhibitor, increases proliferation and expands the stem cell compartment. Similarly, genetic deletion of the MPC in Drosophila intestinal stem cells also increases proliferation, whereas MPC overexpression suppresses stem cell proliferation. These data demonstrate that limiting mitochondrial pyruvate metabolism is necessary and sufficient to maintain the proliferation of intestinal stem cells. The impact of these effects on intestinal tumorigenesis will be discussed.