Control of intestinal stem cell function and proliferation by mitochondrial pyruvate metabolism.

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Public Summary:
Most adult cells perform metabolism to produce energy in a manner using oxygen. Most cancer cells and stem cells perform metabolism to produce energy in a specific manner that does not use oxygen. Our study provides evidence of how these cancer and stem cells perform their specialized metabolism without oxygen. Our results point to new ways of fighting cancer by targeting this specialized metabolism to block their ability to make the energy they need to survive.

Scientific Abstract:
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, proliferative cells, including many 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.