

Cancer-Associated Metabolic Changes Evolve Prior to Malignancy

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Cancer cells undergo dramatic metabolic changes during the course of the disease which are believed to be adaptive, protecting them from low oxygen conditions in the tumor. Despite its importance for cancer biology, the timing of these metabolic changes is still unclear. In a recent paper published in *PLOS One*, Drs. Martin T. Suchorolski, David Hockenbery, and Brian J. Reid demonstrate that these metabolic changes occur in later stages of Barrett's esophagus (BE), a premalignant condition.

In normal cellular metabolism, energy is produced through oxidative phosphorylation at the mitochondrial membrane. Many cancer cells, however, produce energy preferentially through less efficient glycolytic and lactic acid fermentation pathways, a condition known as the Warburg effect. Many cancer cells also down-regulate oxygen consumption in the presence of high glucose concentrations, promoting glycolysis, a phenomenon known as the Crabtree effect.

Barrett's esophagus is a condition in which epithelial cells of the esophagus undergo changes characteristic of cell types commonly found in the intestine, such as mucus-producing goblet cells. These changes occur in response to chronic tissue damage by recurrent acid-reflux from the stomach, and are associated with an increased risk of esophageal adenocarcinoma. Because BE is a pre-malignant condition, it is an informative model for studying the timing of metabolic changes that arise during progression to cancer.

The team employed 4 cell lines (A-D) representing early, middle, and late stages of BE disease, respectively, to define the metabolic changes occurring over time. They found that the cell lines C and D had significantly higher extracellular acidification rates (ECAR) than either normal control or early BE cell lines. Inhibiting glycolysis resulted in a significant decrease to the ECAR of the C and D cell lines. These two cell lines were also the least sensitive to inhibition of oxidative phosphorylation through mitochondrial uncoupling, suggesting that these cells are deriving energy via the Warburg effect. To determine the role of the Crabtree effect in BE, the team exposed the four cell lines to increasing concentrations of glucose, and found that the two latest stage cell lines significantly decreased their oxygen consumption rate (OCR). Importantly, ECAR and OCR did not correlate,

suggesting that these metabolic changes evolve separately. Finally, array analysis of copy number changes identified genetic instability and changes in metabolic pathways, particularly in later stage cell lines.

Taken together, the data suggest a progression of metabolic changes in BE, with increased glycolytic metabolism beginning in the middle stages of the disease and the Crabtree effect arising later. However, the mechanism driving these metabolic changes still remains unclear. The underlying cause is likely multifactorial, including pressure from low oxygen conditions and increased proliferation secondary to tissue damage from acid reflux and genetic changes as the cells progress towards cancer. Future studies will focus on defining the mechanism(s) driving these metabolic changes.

[Suchorolski MT, Paulson TG, Sanchez CA, Hockenbery D, Reid BJ](#). 2013. Warburg and Crabtree Effects in Premalignant Barrett's Esophagus Cell Lines with Active Mitochondria. *PLoS One*. Epub ahead of print, doi: 10.1371/journal.pone.0056884.

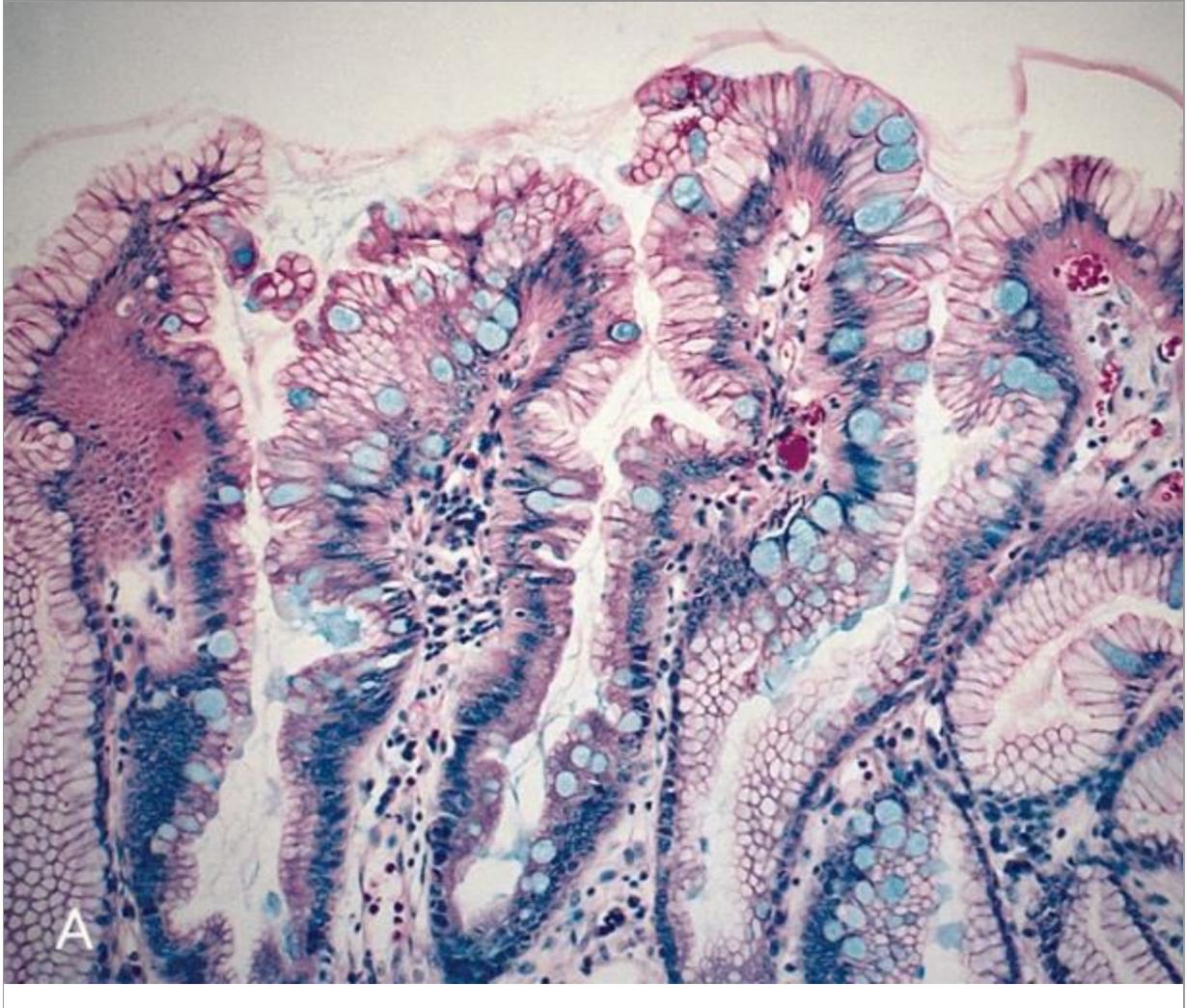


Image courtesy AFIP Atlas of Tumor Pathology, via Wiki Commons.

Image of Barrett's esophagus demonstrating the characteristic cryptic epithelium and the presence of goblet cells (blue), which are normally only found in the intestine.