May 27, 2015

RE: Cure Breast Cancer Foundation
Progress Report 2015
Laboratory of Richard Kolesnick, MD and Philip Paty, MD

Philip B. Paty, MD
Colorectal Service

Dear Andy and CBCF supporters:

It is my pleasure to update the CBCF on our progress studying the role of stem cells in colon cancer.

In a mouse model, we have learned that pre-malignant polyps of the colon develop due to a massive expansion of stem cells. Colon polyps are composed of 60-85% stem cells, compared to only 6% in the normal colon. We have validated this finding in human tumors, demonstrating that colon polyps and colon cancers are indeed diseases caused by dysregulated growth of colon stem cells. By intensive study of early polyp formation in mice, we have learned that oncogenic outgrowth of stem cells requires : 1) the acquisition of an activating mutation in a colon stem cell, and 2) the suppression of the adjacent normal, non-mutated stem cells by a toxic molecule that disrupts the physical contact of stem cells with their neighboring cells, or "niche." We believe this two step model of colon tumor formation – cancer stem cell activation by gene mutation + normal stem cell suppression by niche disruption – is a fundamental mechanism that has broad implications for both colon cancer prevention and colon cancer screening. For example, we are developing an in vitro assay for "niche disrupting molecules" as a way of identifying compounds that have the potential to promote colon cancer formation. If successful, such an assay might be used to screen and eliminate food additives that contribute to cancer risk.

Because cancer stem cells are resistant to chemotherapy and radiation and are therefore a major barrier to cure of cancer, we are studying how to selectively target and kill cancer stem cells with radiation therapy. Using special culture conditions we are now able to propagate stem cells from surgical specimens either as pure stem cell colonies or as mini-glands known as organoids. We are testing whether stem cells grown in culture retain or modify their biologic sensitivity to radiation. Our data show that a hierarchy of radiosensitivity is retained in cultured organoids (small intestine > colon > colon tumor) but not in pure stem cell colonies (small intestine = colon = colon tumor). This surprising data indicates that sensitivity to radiation is not an entirely cell autonomous trait, but instead depends on growth conditions of the stem cell. Using these techniques we can now study radiation sensitivity of colon cancer stem cells under a variety of conditions using high throughput, in vitro assays that were not previously possible. Our goal is to identify compounds and growth conditions that selectively enhance radiation killing of cancer stem cells while not affecting normal intestinal stem cells.

We greatly admire and appreciate the generosity of CBCF, which makes this work possible.

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