SIRT1 Inactivation Reduces Tumor Growth in Colon Cancer Model

August 19, 2013

VA Morris

Colon cancer, the third most common cancer in the world, develops through the accumulation of genetic and epigenetic changes in cells of the intestine. These changes result in the disruption of several oncogenic signaling pathways. In most colon cancer cases, tumor formation is initiated by mutations that turn on the Wnt signaling pathway. Additional mutations and epigenetic changes then drive the progression of benign intestinal polyps to malignant tumors. Identifying these changes and understanding how they contribute to tumor growth can identify new therapeutic targets. New research from the laboratory of Dr. Antonio Bedalov (Clinical Research Division) led by lead author and postdoctoral fellow Dr. Vid Leko clarifies the role that one gene, SIRT1, plays in colon tumor growth and suggests that SIRT1 inhibition may be useful in treating colon cancer.

The sirtuin family of proteins was originally linked to lifespan, based on the role of the founding member SIR2 in yeast. One of the seven human homologs of yeast SIR2, SIRT1 functions as a protein deacetylase, removing acetyl groups from histones and other proteins to regulate ageing, metabolism, and development. SIRT1 deacetylates and inhibits tumor suppressor proteins, including p53, which promotes survival of cells with DNA damage and accumulation of oncogenic mutations. Depending on the tumor type or cancer model system, SIRT1 activity has opposing roles, either promoting or inhibiting tumor growth. In some cancers, including colon cancer, SIRT1 expression is increased and is associated with poor prognosis. Furthermore, small molecule inhibitors of SIRT1 can inhibit tumorigenesis of certain cancers, including B-cell lymphomas.

In the current study, Leko *et al*. more precisely defined the role of SIRT1 in colon cancer through specific deletion of SIRT1 in enterocyte cells, the epithelial cells of the small intestine and colon. Mice with this deletion were crossed with a commonly used mouse model of colon cancer, harboring a mutation in one copy of the APC gene (APC+/min) in the intestine. The APC protein normally functions to suppress Wnt signaling, and inactivating mutations of the APC gene are the most common in colon cancers. After birth, these mice lose their remaining normal copy of APC and develop numerous polyps or tumors in the intestine. Previous studies examined SIRT1 activity in this mouse model with conflicting results. SIRT1 overexpression in the intestines resulted in mice

developing fewer tumors, while SIRT1 deletion in the entire mouse resulted in decreased tumor size. Leko *et al*. resolved these results and demonstrated that SIRT1 deficiency reduced overall tumor cell size and the number of larger tumors (see figure), however very tiny polyps are more numerous in SIRT1 deficient mice that so the difference in total polyp number in not different from control tumors. These results suggests that SIRT1 influences tumor cell growth and progression but not initial tumor formation.

By examining the tumors in the SIRT1-inactivated mice with proliferation and apoptosis markers, the researchers showed that SIRT1 deficiency increased cell death without altering cell proliferation. This *in vivo* result suggests that SIRT1 activity promotes tumor cell survival in colon cancer. The effect of SIRT1 deletion on the oncogenic Wnt signaling pathway was then examined. The SIRT1-inactivated tumors had decreased nuclear accumulation of β-catenin, a transcription factor activated by the Wnt pathway. *In vitro*, the researchers inhibited SIRT1 activity with small molecule inhibitors or knocked down expression with small hairpin RNAs and also decreased Wnt signaling in colon cancer cell lines. These results suggest SIRT1 activates Wnt signaling to promote colon tumor growth. In addition, SIRT1 deleted tumors had increased p53 acetylation, indicating that SIRT1 inhibition of the tumor suppressor p53 also contributes to colon tumor growth.

According to Dr. Bedalov, "Since the discovery that expression of SIR2 in yeast extends yeast lifespan there has been an intense interest in sirtuin activation as a way to promote "youthfulness" and health in people. However, our result that loss of SIRT1 slows down polyp growth in mice suggests that inhibition, rather than activation, of SIRT1 may be used as a preventive or therapeutic modality in colon cancer." Future studies will evaluate the utility and the mechanisms by which sirtuin inhibitors exert anticancer activity in colon cancer.

Leko V, Park GJ, Lao U, Simon JA, Bedalov A. 2013. Enterocyte-Specific Inactivation of SIRT1 Reduces Tumor Load in the APC(+/min) Mouse Model. *PLoS One* 8:e66283

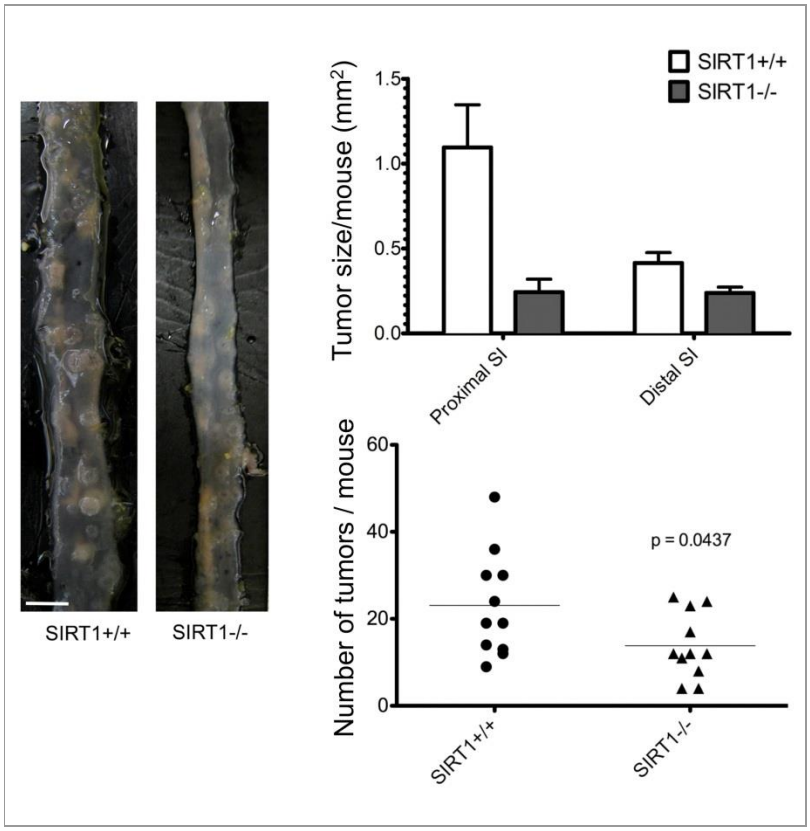

Image modified from the manuscript, published in the open access journal PLoS One.

SIRT1 inactivation decreases the size of polyps in a mouse model of colon cancer. Representative image of the polyps in the small intestines from SIRT1 inactivated (SIRT1-/-) compared to control mice (SIRT1+/+) with an APC mutation to initiate colon tumor formation. SIRT1 inactivation reduces tumor size (top graph) and the number of larger tumors (> 0.5 mm) that develop (bottom graph).