RET Is A Potential Tumor Suppressor in Colon Cancer

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RET is a receptor tyrosine kinase that is normally involved in signaling processes during embryonic development and contributes to normal function in several types of adult cells. Aberrant activity of the *RET* gene, which results from activating mutations, can contribute to the growth of several types of human cancers, demonstrating that *RET* can be an oncogene. However, Dr. William Grady's lab in the Clinical Research Division has recently suggested that *RET* may also have a role as a tumor suppressor in colorectal cancer. The authors show that the expression of*RET* is decreased in colon cancer samples relative to normal colon epithelium as a result of aberrant and excessive DNA methylation. In addition, they show that some tumors have inactivating mutations in the gene, which inhibit *RET*'s ability to promote apoptosis.

RET is a well-characterized oncogene. Genetic rearrangements of *RET* with a variety of activating genes results in inappropriate expression patterns and the creation of fusion proteins that are constitutively active. Furthermore, germline mutations resulting in a constitutively active *RET* have been found to drive certain types of inherited endocrine cancers. Thus, lead authors Drs. Yanxin Luo and Karen Tsuchiya were surprised to identify *RET* as a gene that is hypermethylated, and whose expression is downregulated, in colorectal cancer.

Using a genome-wide screen to identify genes that are abnormally methylated in colorectal cancer, Luo *et al.* identified DNA hypermethylation of *RET* in colon cancer cell lines. The authors also verified the frequency of its methylation in advanced benign adenomas (27%) and pathogenic adenocarcinomas (63%). *RET* expression was significantly decreased in cell lines and tumors that had methylated *RET* compared to those that did not, and this expression could be restored by treatment of the cells with a DNA-demethylating agent.

The authors suggest that RET may function as a tumor suppressor in colorectal cancer by inducing apoptosis when this receptor tyrosine kinase is not bound to one of its four ligands. One of these ligands, GDNF, is expressed in normal colon epithelia, but not in colon cancer.
Ectopic *RET* expression was sufficient to induce cell death by apoptosis, but this could be blocked by treating the cancer cell lines with the RET ligand GDNF. Introduction of *RET* variants that

contained inactivating mutations that are often observed in human colorectal cancers was unable to induce apoptosis. Finally, knockdown of endogenous *RET* in cell lines promoted colony formation on soft agar, a method for assessing tumorigenecity *in vitro*.

Thus, the role of *RET* in tumor development appears to be complex and highly dependent on the cellular context in which it is expressed. In colon epithelia, *RET* appears to serve as a tumor suppressor by promoting apoptosis. However, normal colon epithelia expresses the RET ligand GDNF, preventing aberrant apoptosis. To overcome the apoptotic effects of RET in the absence of GDNF, this study suggests that colon cancer cells block the expression or function of *RET* through DNA hypermethylation or inactivating mutations.

Luo Y, Tsuchiya KD, Il Park D, Fausel R, Kanngurn S, Welcsh P, Dzieciatkowski S, Wang J, Grady WM. 2012. RET is a potential tumor suppressor gene in colorectal cancer. *Oncogene*, Epub ahead of print, doi: 10.1038/onc.2012.225.

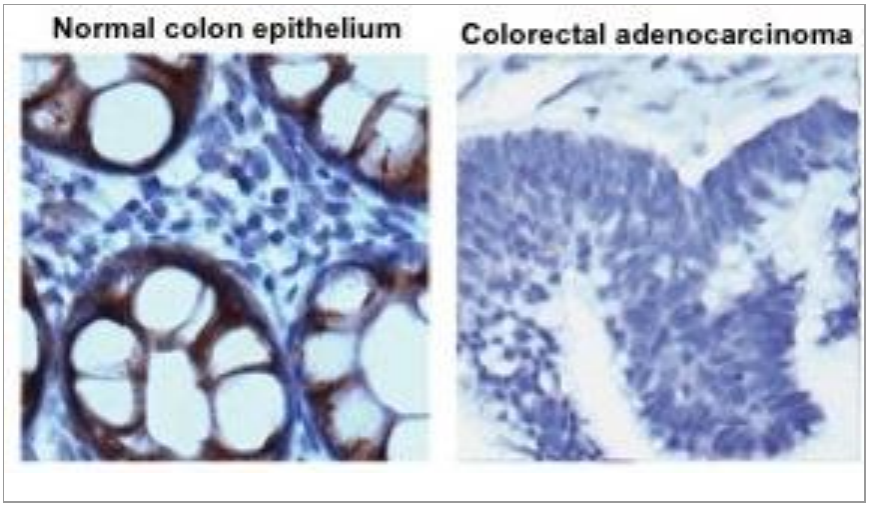

Image courtesy of the authors

Expression of RET in normal colon epithelium (brown staining areas) and colon cancer.