Gastrointestinal Stem Cells and Cancer Bridging the Molecular Gap

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Abstract
Cancer is believed to be a disease involving stem cells. The digestive tract has a very high cancer prevalence partly owing to rapid epithelial cell turnover and exposure to dietary toxins. Work on the hereditary cancer syndromes including famalial adenomatous polyposis (FAP) has led to significant advances, including the adenoma-carcinoma sequence. The initial mutation involved in this stepwise progression is in the “gatekeeper” tumor suppressor gene adenomatous polyposis coli (APC). In FAP somatic, second hits in this gene are nonrandom events, selected for by the position of the germline mutation. Extensive work in both the mouse and human has shown that crypts are clonal units and mutated stem cells may develop a selective advantage, eventually forming a clonal crypt population by a process called “niche succession.” Aberrant crypt foci are then formed by the longitudinal division of crypts into two daughter units—crypt fission. The early growth of adenomas is contentious with two main theories, the “topdown” and “bottom-up” hypotheses, attempting to explain the spread of dysplastic tissue in the bowel. Initial X chromosome inactivation studies suggested that colorectal tumors were monoclonal; however, work on a rare XO/XY human patient with FAP and chimeric Min mice showed that 76% of adenomas were polyclonal. A reduction in tumor multiplicity in the chimeric mouse model has been achieved by the introduction of a homozygous tumor resistance allele. This model has been used to suggest that shortrange interaction between adjacent initiated crypts, not random polyp collision, is responsible for tumor polyclonality.
Key words: APC, stem cells, clonality, niche succession, crypt fission, top down, bottom up