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 familial 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 germ-line 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 “top-down” 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 short-range interaction between adjacent initiated crypts, not random polyp collision, is responsible for tumor polyclonality.

Index Entries: APC; stem cells; clonality; niche succession; crypt fission; top down; bottom up.

Introduction

The cells that line the gastrointestinal tract are among the most rapidly proliferating cells in the body with differentiated cells undergoing continual replacement. They are also exposed to a hostile environment as they come into close contact with numerous toxins and carcinogens contained in digested food. Thus it is of little surprise that cancer of the digestive system is common, with 255,640 new cases in the US alone in 2004 (1). The gastrointestinal epithelium is an important tissue in the understanding of cancer biology partly owing to its rapid cell turnover and high cancer prevalence. Colonic polyposis syndromes were first recognized 200 yr ago, and it has been 100 yr since inflammatory and adenomatous polyps were characterized (2). The observation of familial cancer syndromes led to the establishment of polyposis registries, with one of the largest starting at St. Marks Hospital in London in 1925. Work on the familial colon cancer syndromes including familial adenomatous polyposis (FAP) has led to a number of advances in the
understanding of intestinal tumor initiation including the recognition that many colonic adenocarcinomas arise from adenomas (3). The adenoma-carcinoma sequence has subsequently become established as a stepwise pattern of mutational activation of oncogenes and inactivation of tumor suppressor genes that result in cancer (4). Malignant cells share a number of characteristics with stem cells, such as the ability to self-replicate and proliferate, and it is widely believed that the gastrointestinal stem cell is the target of the mutational changes. This review will summarize the molecular and cellular events involving the stem cell, which occur at the birth of the adenoma, the spread of dysplastic tissue around the bowel, and the development of malignancy.

Gastrointestinal Stem Cells

The immature, relatively undifferentiated nature of gastrointestinal epithelial stem cells means that they are not directly identifiable and researchers in this field in the past have had to rely on ingenious indirect methods to identify their position and track their progeny (5). Recent work on molecules uniquely involved in the biochemical pathways of the stem cell may provide useful tools for cell identification. One such protein is Mushashi-1, the mammalian equivalent of a Drosophila protein. It is responsible for the upregulation of expression of the transcriptional repressor Hes-1, a protein involved in neural stem cell self-renewal (6). Both these proteins are coexpressed in cells superior to the Paneth cells in the mouse intestine, but Hes-1 alone is only seen in differentiating cells, thus it is hypothesized that the colocalization of these two markers may denote the small bowel stem cell population (7). The putative stem cell compartment position varies according to the location in the digestive tract. In the stomach, the epithelial lining is formed into long tubular glands, each subdivided into foveolae, isthmus, neck, and base regions. The foveolae and mucosal surface is made up of gastric foveolar mucous cells. The acid-secreting parietal (oxyntic) cells and the pepsinogen-secreting peptic/chief (zymogenic) cells are found in the base of the gastric glands, and in the body and the fundus/body of the stomach, respectively (8). Within the gastric glands cell migration is bidirectional, with the differentiating mucous cells migrating upward and the developing parietal and chief cells moving down toward the gland base. The putative stem cell compartment is thus believed to lie in the neck/isthmus region of the gastric gland. Throughout the small and large intestine the luminal surface is composed of a columnar epithelial mucosa, with glandular invaginations called crypts. Several of these crypts contribute epithelium to finger-like projections called villi in the small bowel. The cells of the intestinal epithelium are arranged hierarchically, becoming progressively more differentiated as they age and pass along the crypt-to-villus axis. The stem cell compartment is believed to be at the origin of this axis, the base of the colonic crypt, and at cell position 4–5 in the small bowel (reviewed in ref. 9). The number of stem cells within this compartment is debated but is generally believed to be between 4 and 6 (10,11). Stem cells themselves divide infrequently and it is the first few generations of stem cell daughters, known as transit amplifying cells, which proliferate in the lower part of the crypt (12). Stem cells reside within a stem cell compartment or “niche.” This is a group of epithelial and mesenchymal cells and extracellular substrates, which provide an optimal microenvironment for stem cells to give rise to their differentiated progeny. In the intestinal crypts this is formed by a fenestrated sheath of surrounding mesenchymal cells that regulate differentiating progeny. In the intestinal crypts, this is formed by a fenestrated sheath of surrounding mesenchymal cells that regulate differentiating progeny. In the intestinal crypts this is formed by a fenestrated sheath of surrounding mesenchymal cells that regulate differentiating progeny.

Genetic Pathways Leading to Tumorigenesis

Numerous steps are involved in the progression of normal tissue from dysplasia to malignancy and it is estimated that a typical colorectal tumor contains at least 11,000 genomic alterations (17). Some tumor suppressor genes such as p53 and DCC are predominantly mutated in carcinomas rather than early adenomas, suggesting a late role in the transition from adenoma to carcinoma (reviewed in ref. 18). Other genes such as SMAD2 and SMAD4 are seen in 50% of adenomas as well, and their role in tumorigenesis is unclear (19). Mutations also occur in proto-oncogenes, such as K-RAS, which are seen in 50% of large adenomas and tumors; however, similar changes are also seen in nondysplastic lesions such as hyperplastic polyps (20). Based on the observation that the accumulation of molecular alterations seemed to parallel the clinical progression of tumors, Vogelstein et al. (4) proposed a stepwise model of colorectal tumorigenesis. The molecular pathogenesis of FAP has shed much light on the initial mutations required in this step, like progression. FAP results in the formation of multiple bowel adenomas in the second and third decades of life. Colonic cancer is inevitable in these patients who therefore require prophylactic colectomy. The heritable nature of FAP was first recognized at the end of the nineteenth century, however, not until 1986 was observed an interstitial deletion of chromosome 5q in an FAP patient (21). This prompted linkage analysis studies which codemonstrated tight linkage of the condition to markers on chromosome 5q21 (22,23). The gene responsible was adenomatous polyposis coli (APC) (24,25) which encodes a large (approx 2800 amino acids) multifunctional cytoplasmic protein (26). This important protein binds and downregulates β-catenin and is vital in the regulation of Wnt signaling, as well as maintenance of apoptosis, cell-cycle progression, and chromosomal stability (reviewed in refs. 27–30). Subsequent work revealed that mutations in APC are also found in 65% of sporadic adenomas (31) and up to 80% of sporadic colorectal cancers (32). This led Kinzler and Vogelstein to propose that APC acts as a “gatekeeper” gene—a gene involved in the control of normal epithelial cell proliferation required for cellular homeostasis. Mutation of a gatekeeper gene results in an imbalance of cell division over death, thus FAP is a disease of accelerated tumor initiation (33). Other hereditary bowel cancer syndromes have been used in the identification of alternative pathogenetic mechanisms. Hereditary nonpolyposis coli is a condition that predisposes to cancers of the colon, endometrium, and several other extracolonic sites, notably...