COLON CANCER PATHWAYS TO CURE

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INTERNAL MEDICINE GRAND ROUNDS
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This is to acknowledge that Dr. Willson has disclosed financial interests or other relationships with commercial concerns related directly to this program. Dr. Willson will be discussing off-label uses in his/her presentation.

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Key Points

- Cancers of the colon and rectum are the second leading cause of cancer incidence and cancer death among adult Americans, with 148,000 new cases and 55,000 deaths expected in 2007.
- Encouraging declines in the death rate from colorectal cancer in the last decade provide evidence of the effectiveness of recent advances in prevention, screening, and therapy of colorectal cancers.
- Colon cancer is a genetic disease that can be eliminated through recognition of risk factors and the application of screening methods particularly colonoscopy.
- Colon cancer is a genetic disease with the earliest event a loss of Wnt pathway regulation and subsequent mutation of additional oncogenes and tumor suppressors. A hallmark of colon cancer as these mutations accumulate is increased genetic instability that contributes to further mutations contribution to tumor progress and drug resistance.

Learning Objectives

After this lecture, the participant should be able to:

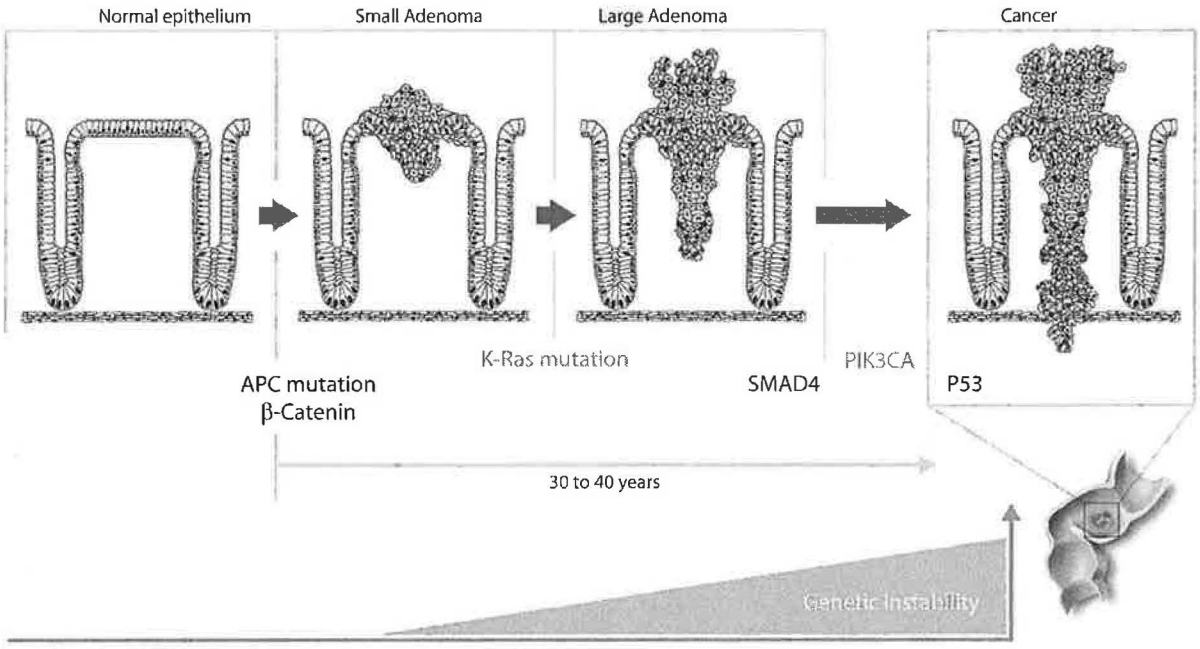
1. Understand the adenoma to cancer sequence and how interruption of this pathway can prevent colon cancers.
2. Describe how the loss of a tumor suppressor signaling pathway, TGFB, contributes to colon cancer progression.
3. Describe how somatic gene mutations acquired by colon cancers can alter normal growth control pathways, contribute to cancer progression, and are promising targets for new cancer therapies.

I. Colon Cancer etiology – understanding the adenoma to cancer sequence.

- Cancers of the colon arise from colon epithelial cells that line the lumen of the organ. These colon epithelial cells are replaced every five days from a stem cell population located at the base of colonic epithelial cell crypts. Daughter cells undergo several divisions and then differentiate and migrate to the top of the crypt where they are shed. Disruption of this growth control leads to development of adenomas and cancer.
- Colon cancers arise from the colon epithelial cells and are the end result of a multi-step process of carcinogenesis that extends over several years. This is known as the **adenoma-cancer sequence**.
- The APC gene is a tumor suppressor gene whose product inhibits colon cell growth and promotes terminal differentiation and cell death as the colon cell migrates to the top of the mucosal crypt. Normal colorectal epithelial cells are transformed into benign tumors called adenomas through the acquisition of a mutation in APC that disrupts its tumor suppressor activity. **Loss of APC function is the first step in the adenoma to cancer sequence**.

- Loss of APC function leads to further genetic changes in colon cells and over time, adenomas acquire increasingly disordered villous histology and dysplastic cellular cytology, and are recognized as frank cancers when cells breach the underlying epithelial basement membrane.
  Acquisition of additional mutations leads to cells with the capability of migrating to distant sites, establishing a blood supply and growing into a metastatic cancer.
- Shown below are the tumor suppressor genes (APC; TGFB, SMAD4, P53) and oncogenes (*K-Ras*, PIK3CA) whose mutation or abnormal expression drives the adenoma to cancer progression.

Genetic Model for Colorectal Tumorigenesis



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Colon cancers are the end result of a multi-step process of carcinogenesis that extends over several years. First, loss of APC tumor suppressor function leads to increased cell proliferation and resistance to apoptosis. As a consequence an adenoma forms as a pedunculated polypoid structure growing into the colon lumen. With time, adenomas acquire additional genetic changes that lead to cells that breach the underlying epithelial basement membrane. Further genetic instability leads to cells with the capability of migrating to distant sites, establishing a blood supply and growing into a metastatic cancer.

II. Colonoscopy screening – an effective strategy for eliminating death and suffering from colon cancer.

- Colon cancers can be prevented by detection and removal of premalignant colon adenomas. Removal of an adenomatous polyp interrupts the adenoma to cancer sequence and prevents development of colon cancer.

- Likewise, colonoscopy screening can detect colon cancers at early stages when the disease is amenable to cure by surgical excision.

- These considerations have lead to recommendations for mass screening starting at age 50 for the average risk adult population, and earlier for individuals at higher risk due to family history or other predisposing factors.

- CT based screening (virtual colonoscopy) and stool based screening for genetic changes associated with colon cancer are promising new screening strategies to identify individuals for colonoscopy and are likely in the near future to become the preferred first line for colon cancer screening.

III. Familial colon cancer – hereditary factors lead to early development of colon cancer.

- Approximately 20% of colon cancers are related to hereditary factors.
  - Typically familial colon cancers develop earlier than sporadic cancer.
  - Colon cancer in a first degree relative increases an individual's lifetime risk of developing colon cancer by 3-fold and 8-fold if two first degree relatives have colon cancer.
  - Colonoscopy is recommended to begin 20 years earlier than a family member's diagnosis.
- Familial adenomatous polyposis (FAP)
  - Germ line mutations in the APC gene cause the familial adenomatous polyposis.
  - FAP patients inherit a defected APC allele from one parent. Early in life these individuals lose the second APC allele and this leads to further disruption of the genes that control proliferation and differentiation in the colon cell resulting in formation of hundreds to thousands of colonic adenomas develop during the second and third decade of life.
  - Individuals who inherit a mutation in the APC gene have 100% lifetime risk for colon cancer.
  - FAP accounts for 1% of colon cancers.
  - A child of a FAP patient has a 50% chance of inheriting the defected APC gene which can be detected through genetic testing and prophylactic colectomy improves survival in carriers.
- Hereditary Non polyposis colon cancer (HNPCC)
  - HNPCC is another inherited form of colon cancer that accounts for 5% of colon cancers.
  - These individuals inherit an abnormality in a DNA repair gene that leads to mutational loss of tumor suppressor gene function and the adenoma to cancer sequence.
  - A key feature of this syndrome is that the formation of adenomas and cancers is accelerated compared to sporadic colon cancers and as a consequence cancers develop in young adults and susceptible individuals require earlier and more frequent screening.
  - Colonoscopy screening should begin in the twenties as well as screening for uterine cancer.

IV. Colon cancer staging and treatment.

- TNM stage of colon cancer is based on the surgical pathology review of the tumor penetration through the colonic wall (T), the number of lymph nodes involved (N), and the presence of metastatic disease (M).

Stage I cancer has grown through the mucosa and invaded the muscularis.
Stage II cancer has grown beyond the muscularis of the colon or rectum.
Stage III any depth of penetration with spread to the regional lymph nodes.
Stage IV any depth of penetration with spread outside the colon to other areas of the body.

- **Survival and treatment based on stage at the time of surgery.**

Diagnosed Classification	5-Year Survival	Percent at this Stage
Local (Stage I & II)	91%	38%
Regional (Stage III)	61%	37%
Distant (Stage IV)	8.5%	25%

- Primary treatment includes resection of the tumor and a surrounding portion of the colon and regional lymph nodes. When the rectum is involved, preoperative chemoradiation is advised prior to surgical resection.

- The use of adjuvant chemotherapy following surgery has increased the likelihood of cure by 30 percent among patients with stage III disease and increasingly patients with high-risk Stage II disease are treated with adjuvant chemotherapy.

V. Additional reading:

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