Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology, Fall 2005
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Gastrointestinal Neoplasms

Neoplastic Diseases of the Stomach

- Mucosal polyps
  - Hyperplastic (regenerative) polyps
  - Cystic fundic gland polyp
  - Inflammatory fibroid polyp
  - Polyposis syndromes
  - Adenomas
- Gastric adenocarcinoma
  - Variants: Adenosquamous; lymphoepithelial; hepatoid; parietal cell
- Neuroendocrine tumors
- Stromal tumors
- Lymphomas

Overview of the Lecture

- Epithelial tumors
  - Epithelial polyps
  - Colorectal ACA
  - Gastric ACA
  - Esophageal ACA
  - Esophageal SCC
- Neuroendocrine tumors
- Lymphomas
- Gastrointestinal stromal tumors

The Art of Terminology!

- A tumor is a mass lesion without reference to tissue composition or malignant potential
- GI tumors typically present as protrusions of mucosal tissue into the lumen (polyps); Polyps may have a broad base (sessile polyps) or be attached to the wall by a stalk (pedunculated polyps)
- Over the years, the term tumor has *almost* become synonymous with a neoplastic growth

The Art of Terminology

- A neoplasm is the new (new onset) growth (overgrowth) of a specific cell or tissue type, which may or may not form a tumor
- Based on their natural history, neoplasms may be benign, malignant, or locally aggressive
- If the new growth consists of benign indigenous cell or tissue elements, it may be called a hamartoma or a hyperplasia

The Art of Terminology

- **In the GI tract, dysplasia implies the presence of pre-malignant epithelial abnormalities (this is not necessarily true for other organs)**
- **Dysplasia has a cytological spectrum from mild to severe (or from low-grade to high-grade)**
- **Carcinoma indicates the presence of severe dysplasia, which may be confined by the basement membrane (carcinoma-in-situ) or invade through the basement membrane (invasive carcinoma)**

Epithelial Polyps

- Inflammatory polyps
  - Inflammatory (pseudo)polyps
  - Sporadic juvenile polyps
- Hamartomatous polyps
  - Juvenile polyposis syndrome
  - Peutz-Jeghers syndrome
- Hyperplastic polyps
- Adenomas

Juvenile Polyps and Polyposis

- Juvenile polyps consist of abnormal epithelial glands nested in an inflammatory background
- Sporadic polyps (also called retention polyps) are typically found in the rectosigmoid of children presenting with blood in stools
- Juvenile polyposis syndrome may be sporadic or familial (AD) and is associated with an increased risk of ACA and extraintestinal manifestations

Hamartomatous Polyps

- Polyps consist of indigenous epithelial elements with an arborizing muscular framework and little to no inflammation
- Peutz-Jeghers syndrome is an AD disease with gastrointestinal hamartomatous polyps and mucocutaneous pigmented macules
- Molecular defect: STK11/LKB1 gene (serine-threonine kinase)
- PJS patients have an increased risk of gastro-intestinal neoplasms and neoplasms of many other organs including ovaries, testes, cervix, breast, thyroid, biliary tree, and urogenital tract

Hyperplastic Polyps

- The most common type of colorectal polyp
- Hyperplastic polyps are typically small and sessile protrusions of “hypermature” colonic epithelium with little inflammation and no muscular component
- Large hyperplastic polyps are much less common, but may be associated with an increased risk of dysplasia and ACA
- “Serrated neoplasia pathway”- methylation silencing of tumor suppressor genes

Adenomas

- Adenomas are benign but dysplastic epithelial neoplasms of the GI tract
- Adenomas are common lesions, occuring in 25-50% of individuals over the age of 60
- Most adenomas (~90%) are colonic
- Most colonic adenomas (~75%) are in the rectosigmoid
- Most adenomas (~75%) are single

Classification of Adenomas

- Adenomas are divided into three types based on their glandular architecture
  - Tubular (most common)
  - Villous (least common)
  - Tubulovillous
- The above three types are histological variants of the same neoplastic process

Familial Adenomatous Polyposis

- AD disease characterized by progressive development of hundreds of adenomatous polyps (primarily colonic)
- Incidence of 1 in 10,000 live births
- Inherited in 80% of cases
- Associated with 100% risk of ACA
- Associated with mutations of APC gene (5q21)

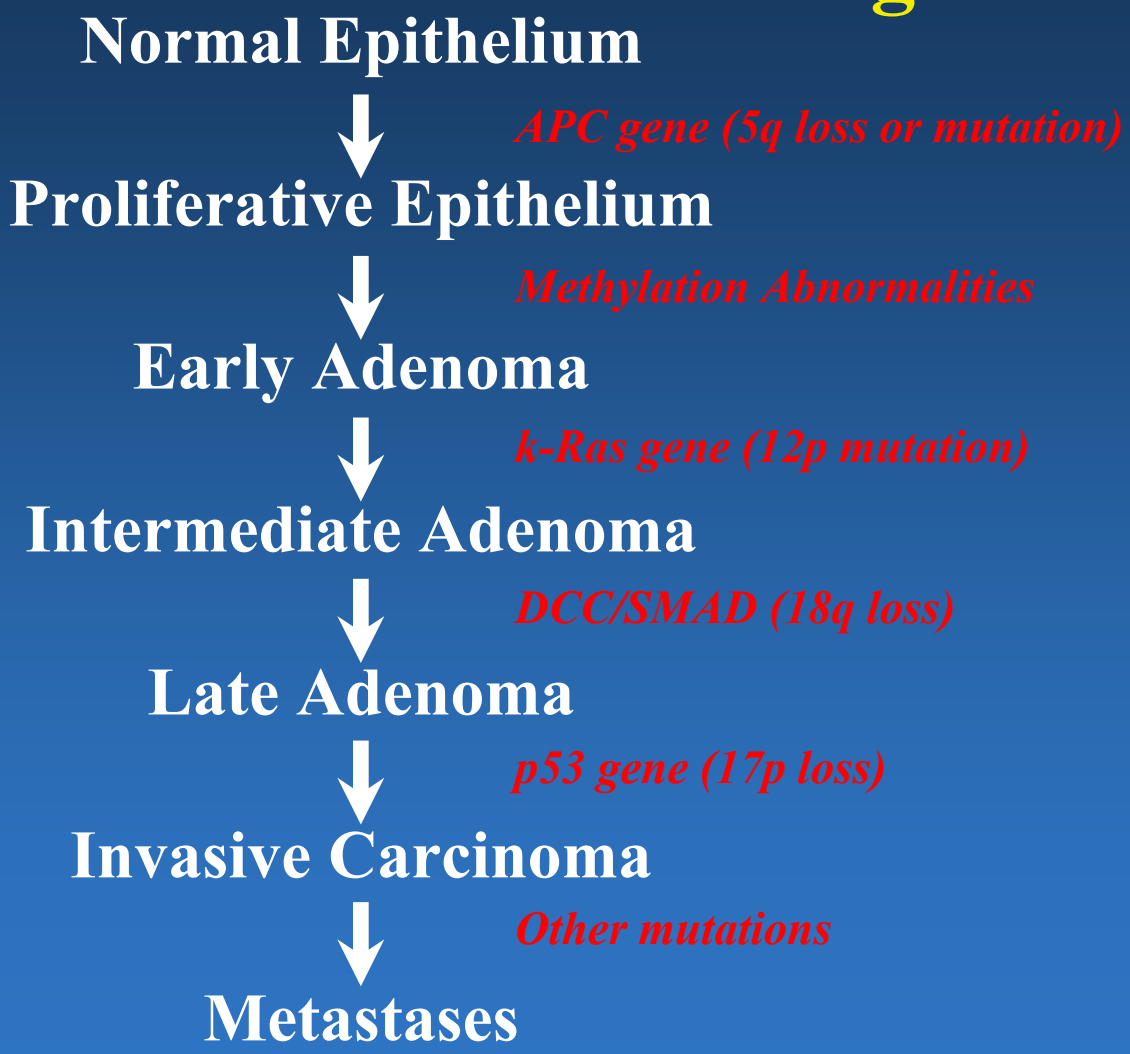
APC Genotype-FAP Phenotype Associations

- Mutations in exons 3, 4, and distal 15 are associated with Attenuated FAP (also known as Flat Adenoma Syndrome)
- Mutations in codons 1309/1328 of exon 15 are associated with an early aggressive FAP
- Mutations in distal portion of exon 15 are weakly associated with Gardner's Syndrome (FAP + desmoids + osteomas + other)
- Mutations between exons 9 and 15 are associated with CHRPE

The APC Gene

- APC is a basolateral membrane protein that functions as a tumor suppressor protein presumably through interactions with β-catenin (a cytoskeletal protein that can exert a suppressive effect on cellular proliferation through the Wnt signaling pathway)
- Numerous mutations of the APC gene have been described in FAP; Somatic APC mutations are critical in sporadic colorectal carcinogenesis

APC Gene in Colorectal Carcinogenesis

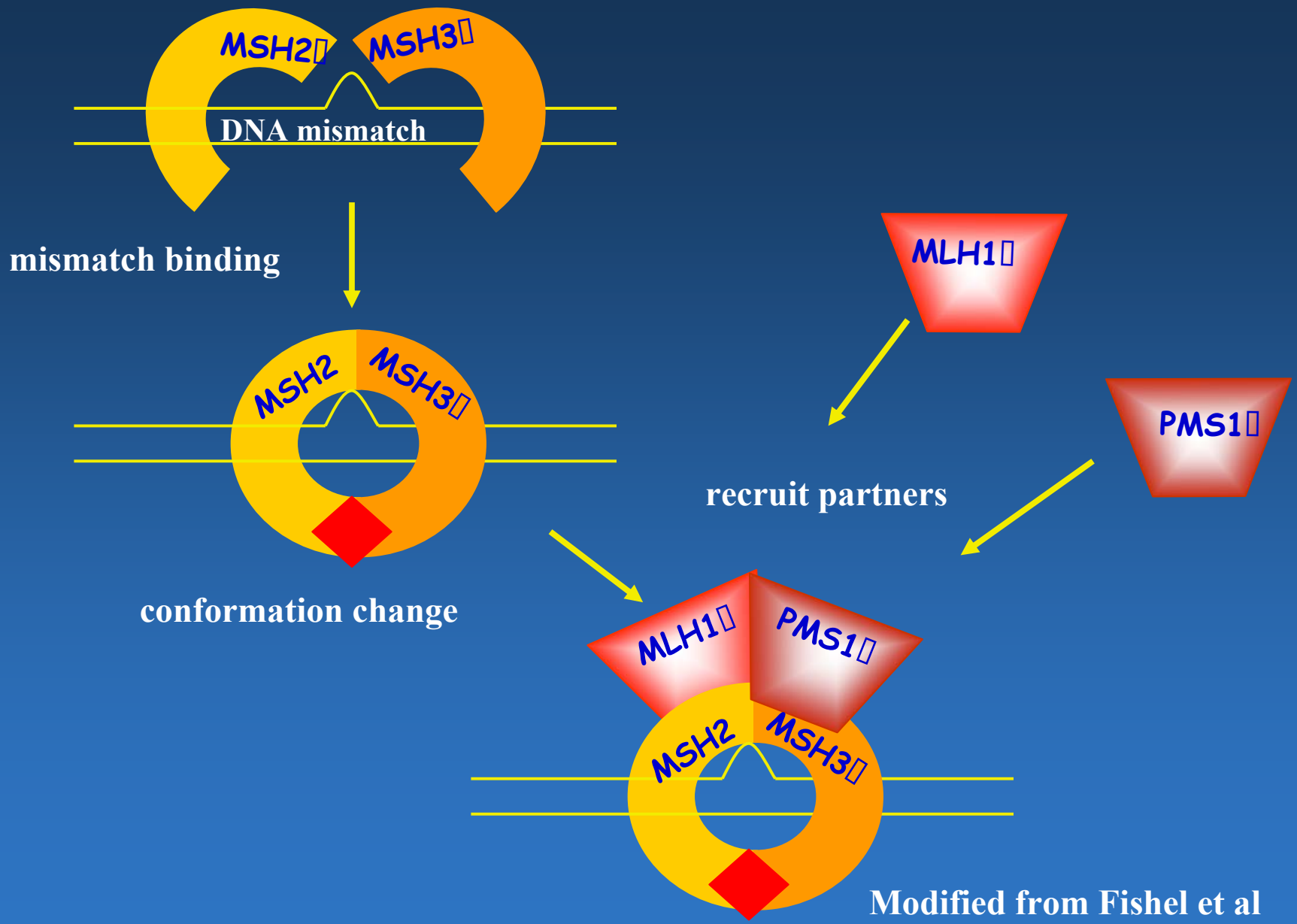


Genomic Instability in CRC

- **Chromosomal instability (majority of CRCs): Allelic losses, translocations, and other gross chromosomal abnormalities in key regulatory proteins**
- **Microsatellite instability (minority of CRCs): Increased intragenic mutations due to instability of short tandemly repeated DNA sequences (microsatellites)**

Microsatellite Instability (MSI)

- Nucleotide mismatches that "normally" occur when DNA polymerase inserts the wrong base in the newly synthesized DNA are typically repaired by mismatch repair enzymes
- Defects in the process of mismatch repair lead to MSI (instability in >40% of loci)
- Mutations in DNA mismatch repair (MMR) genes (primarily MSH2 & MLH1) are found in sporadic CRCs with MSI and in families with HNPCC



Modified from Fishel et al
Cancer Research 61:7369;2001

Herediatry Non-Polyposis Colorectal Cancer

Original International Collaborative Group criteria (the Amsterdam Criteria)	1. Three relatives with colorectal cancer (CRC), one a first-degree relative of the other two 2. CRC involving at least 2 generations 3. ≥1 CRC diagnosed before the age of 50y
Modified Amsterdam Criteria	• In very small families: 1. Two CRC's in first-degree relatives 2. CRC involving at least 2 generations 3. ≥1 CRC diagnosed before the age of 50y • In families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusually early onset of CRC or endometrial cancer
NCI Workshop (Bethesda Guidelines)	• Cancer in families that fulfill Amsterdam criteria • Two HNPCC-related cancers • CRC or endometrial cancer before the age of 45 • CRC and a first-degree relative with CRC and/or HNPCC-related cancer and/or colorectal adenoma; one of the cancers before the age of 45 and adenoma before the age of 40 • Right-sided CRC with "undifferentiated" histology before the age of 45 • Signet-ring-cell-type CRC before the age of 45 • Adenomas before the age of 40

Colorectal Adenocarcinoma (CRC)

- In 1999, CRC was the third most common carcinoma and the third leading cause of cancer deaths in the US
- Greater than 130,000 new cases per year
- Rare before the age of 40
- M:F ratio of 1 (but ~2 for rectal cancers)
- Risk factors: ? environmental, ? diet
- Five-year survival ~65% in 1994

Pathology of CRC

- Most CRCs are in the rectosigmoid
- Left-sided tumors tend to produce "napkin-ring" lesions and present with obstruction
- Right-sided tumors tend to be large and centrally necrotic polypoid masses
- Most tumors are gland-forming and well- to moderately-differentiated; ~10% are mucinous
- Survival generally related to depth of invasion, nodal status, and metastases

Gastric adenocarcinoma

- Worldwide variation in incidence (e.g. high in Japan)
- Incidence falling in U.S. over last 50 years
- Most common 50-70 years, M>F
- Causative factors:
  - dietary carcinogens
  - familial
  - chronic inflammatory conditions
- Aggressive tumors with poor prognosis (15% 5 year survival

Genetic Progression in Gastric Neoplasia

- •5q21 deletion/APC inactivation
- •17p13 deletion/p53 mutation
- •MLH1 methylation

- •C-met/HGF amplification/ overexpression
- •9p21 deletion/p16 inactivation
- •19q12 amplification/Cyclin E overexpression
- •18q deletion
- •16q22 deletion/E-cadherin loss
- •chromosomal deletions (1p, 1q, 7q, 13q)

Gastric carcinoma- pathology

- Location: antrum (70%)>lesser curvature, cardia (25%)>diffuse (5%)
- Gross configuration: polypoid, ulcerating, or infiltrating
- **Intestinal type:** gland formation, associated with intestinal metaplasia, dysplasia
- **Diffuse type:** signet ring cells, arises directly from surface foveolar cells, not associated with environmental factors

Esophageal carcinomas

- Two major types
  - Squamous cell carcinoma
  - Adenocarcinoma
- Squamous cell carcinoma more common worldwide
- Incidence of adenocarcinomas rising in U.S., Western Europe, now accounts for 50% of esophageal malignancies in those regions

Esophageal adenocarcinoma

- Peak age 60-70 years, M>>F
- Symptoms: dysphagia, weight loss
- Arises in setting of Barrett's esophagus (columnar metaplasia with goblet cells) in distal esophagus
- Proceeds through dysplasia-carcinoma sequence
- Microscopically similar to adenocarcinomas elsewhere in GI tract
- Aggressive tumors; key to survival is early detection

Esophageal squamous cell carcinoma

- Incidence highest in Africa, Iran, China
- Peak age: 55-65 years, M>F
- Causative factors
  - Alcohol, tobacco
  - Corrosive esophagitis
  - Achalasia
  - ?HPV
- Symptoms: dysphagia, weight loss
- Aggressive tumors (10% 5 year survival)

Neuroendocrine (carcinoid) tumors

- Arise from neuroendocrine cells of gastrointestinal mucosa and its derivatives (e.g. lung, pancreas)
- Variable clinical behavior but often slow-growing
- Appendix most common site (35%) followed by ileum (20%)
- Pathology: uniform cells with round nuclei, “salt and pepper” chromatin
- Extra-appendiceal carcinoids frequently invade wall, metastasize

Carcinoid syndrome

- Only develops in patients with liver metastases
- Tumors elaborate serotonin, plus histamine, others
- Flushing, diarrhea, bronchoconstriction, valvular changes in right heart
- Treatment: removal or ablation of metastasis or antagonism/suppression of circulating serotonin

GI tract lymphomas

- Nearly all non-Hodgkin's lymphomas (NHL)
- GI tract involved in 70% of patients with NHL
- Stomach most common site, followed by intestine and colon
- Nearly all B cell type, except for enteropathy associated T cell lymphoma (a/w celiac diseae)
- **MALT lymphoma:** gastric lymphomas develop in setting of H. pylori infection (potentially treatable by H, pylori eradication)

Gastrointestinal stromal tumors (GISTs)

- Spindle cell neoplasms arising from interstitial cells of Cajal (pacemaker cells)
- Most associated with activating mutations in c-kit tyrosine kinase; sensitive to treatment with inhibitor (Gleevec)
- Variable aggressiveness
- Prognostic factors: size, location, histologic grade
- Distinguish leiomyomas (true neoplasms of smooth muscle)

Other tumors

- Adenocarcinoma of small intestine, appendix
- Anal squamous cell carcinoma
- Mesotheliomas od peritoneum
- Melanoma (rectum, anus, esophagus)
- Lipoma (colon, stomach)
- Kaposi's sarcoma