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The Molecular Biology of Gastrointestinal Cancer: Implications for Diagnosis and Therapy

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Abstract

Cancers are caused by the sequential accumulation of alterations in genes that control the growth, differentiation, and other behaviors of cells. It has long been recognized that cancers are very heterogeneous pathologically, which is a reflection of the variable genetic lesions that give rise to the variety of lesions present in the gastrointestinal tract. In spite of this complexity, certain types of genetic alterations are linked to specific pathological lesions. This review summarizes our current understanding of the molecular pathogenesis of gastrointestinal neoplasia, and provides explanations for some of the pathological variability of lesions encountered by the endoscopist.

The molecular basis of gastrointestinal carcinogenesis

In the mid-1980s, the techniques of molecular biology were brought to the field of cancer research. It became clear that cancers occur as a consequence of alterations to genes that control growth and differentiation. In most instances, multiple genes were altered, and the genes involved were different between neoplasms, which helped explain the pathological heterogeneity observed in neoplasia. Various combinations of altered genes occurred, and if these accumulated at different rates, it might explain the unpredictability of premalignant lesions[1].

Classes of genes involved in carcinogenesis

There are different types of genes involved in neoplastic growth. Oncogenes typically promote cellular proliferation. In almost all instances, there are copies of these genes in the normal human genome, which are involved in regulating ordinary growth. The key to carcinogenesis is that the proto-oncogene becomes an oncogene when mutated, amplified, or dysregulated in such a way that it is overactive, and no longer controlled by usual feedback mechanisms. For example, the K-RAS gene can be activated by a point mutation that permits it to continue to stimulate cell proliferation even when the counter-regulatory signals are trying to halt the process. The c-MYC oncogene can be active in a tumor by gene amplification, so, even though each copy is potentially regulatable, the excessive copy number fosters neoplastic growth. Oncogenes are considered to act “dominantly”, since a single mutated copy will dominate over

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Important genes involved in gastrointestinal carcinogenesis: APC, K-RAS, p53, C-MYC, Rb, p16, SMAD, PTEN, STK11/LKB1, TGRβ1RII, EGF receptor, MAP kinase, MEK, BRAF, DPC, MLH1, WNT, MYH, MSH2, MSH6, PMS2, BMPR1A, BRCA1, BRCA2,

the normal ("wild type") copy of the gene, and only one mutation is sufficient to drive cell growth.

Tumor suppressor genes (TSGs) are present in all cells, and serve to regulate normal proliferation, or mediate cell-specific differentiation. These genes become involved in carcinogenesis through their inactivation. We inherit two copies of every gene – one from each parent – and both copies of a TSG must be inactivated to participate in carcinogenesis. There are multiple ways to inactivate TSGs, including point mutations, deletions (which may be called "loss of heterozygosity", or LOH), and silencing of the promoter by methylation of the cytosine residues at C-G sequences, which are preferentially present in promoters (in what are called "CpG islands"). When a sufficient number of the C-G's in a promoter become methylated, the gene is silenced. Importantly, the methylation is passed on to the progeny of that cell, keeping that gene "permanently" silenced[2].

The TSG story can become a bit more complex. In some instances, a mutation in one copy of a TSG creates an altered protein that functionally inactivates the other copy (from the wild type allele), causing a "dominant negative" effect, which removes the tumor suppressor activity from that cell by a single mutation.

TSGs have several different functions. Some are involved in regulating the cell cycle, such as the p53, p16, and the retinoblastoma (Rb) genes. Others are involved in cell signaling, and transmit signals to stop growing, such as the APC gene, the TGF-β receptor II gene, and the SMAD genes. Others (i.e., PTEN, STK11) are involved in regulating or controlling the phosphorylation of proteins that stimulate cellular proliferation, so their loss permits unregulated growth signals.

The DNA repair genes include several different classes of housekeeping genes that can be involved in carcinogenesis. One group is the nucleotide excision repair (NER) system, which is especially critical for the repair of DNA damage caused by exposure to UV light. The NER genes are responsible for the inherited disease xeroderma pigmentosa when both copies are mutated. Base excision repair (BER) genes are important in repairing injury caused by oxidative damage and adducts created by chemical carcinogens. The DNA mismatch repair (DNA MMR) genes, which are involved in Lynch syndrome and about 12% of sporadic colorectal cancers (CRCs).

The discovery of TSGs permitted insight into familial cancer syndromes[3]. Since inactivation of both copies of a TSG is required in a neoplasm, it would be possible to inherit a mutation in just one copy of the gene, which would be associated with a normal phenotype. However, the presence of one inactivated gene in every cell would increase the likelihood of getting a cancer, and also increase the chance that the tumor would occur earlier in life than in people who inherited two wild type copies. The most important of these include the TSG that causes familial adenomatous polyposis (the APC gene), and the DNA MMR repair genes, which cause Lynch syndrome (HNPCC).

Genomic and epigenetic instability in cancer

There is a general impression in the field (but this is essentially unproven and somewhat controversial) that there are more mutations in a tumor than can be attributed to the background amount of DNA damage that occurs in normal cells. For example, it was noticed that some tumors had experienced chromosomal losses (or LOH events) in >50% of the sites examined, whereas other CRCs had relatively few losses[4]. It was not apparent initially what advantage a cell might have by losing so much of its DNA. Moreover, the tumors with the greatest number of losses were the most virulent, and associated with the worst outcomes[5]. This conundrum was raised again when microsatellite instability (MSI) was discovered and linked with ~15%

of CRCs[6, 7]. In these tumors, it was estimated that there might be as many as 100,000 simple insertion/deletion mutations at repetitive sequences. Additionally, the mutations were generated randomly, and that only a few appear to be responsible for the neoplastic phenotype.

Most gastrointestinal tumors emerge as a consequence of a process of genomic destabilization that generates a very large number of genetic (or epigenetic) alterations, only a few of which actually confer a growth or survival advantage to the cell. Rare mutational events that are "advantageous" to the cell (but not to the host) lead to clonal expansion of the cell lineage. When one analyzes the DNA from the tumor specimen, many mutations can be found – both the advantageous ones that are responsible for the growth, and the neutral ones that are passive passengers (or "hitchhikers"). Deleterious mutations also occur, but these would lead to their own extinction, and therefore be self-resolving events.

The types of genetic and epigenetic instability

There are several distinct mechanisms by which a cell could develop enough genetic alterations for a cancer to occur. The classic form of genomic instability was the first one described, and is called "chromosomal instability" (CIN), because this process generates aneuploidy, with chromosomal duplications, losses and rearrangements[8]. CIN was observed morphologically over 100 years ago, and is commonly found in most types of cancer. In these tumors, there is often an inactivating point mutation in one allele of a TSG and LOH of the other allele, reflecting biallelic loss. Aneuploidy, and CIN, are characteristic of most, but not all, cancers of the GI tract. CIN can be detected by flow cytometry, or by extracting DNA from the tumor and looking for LOH events (or allelic deletions) when compared to the DNA from non-cancerous tissues.

The loss of DNA MMR activity leads to microsatellite instability (MSI), which occurs in a minor proportion of cancers throughout the GI tract. This form of genomic instability is the only one in which the mechanistic basis is well understood. MSI creates an identifiable mutational signature in the DNA from the tumor. MSI is easily detected by performing PCR of short repetitive sequences (i.e., microsatellites), and looking for deletion mutations in the sequence[9]. Most microsatellite sequences occur between genes or in introns, and it is not clear whether mutations in most of these have functional significance for growth or potentially neoplastic behavior. However, there are a few genes (perhaps 30–40) in the human genome that *encode* a repetitive sequence, and these are the principal targets of MSI[10].

Finally, the methylation of cytosine residues at C-G pairs in gene promoters is a physiological process for silencing certain genes. This process occurs in all of the genes in one of the two X chromosomes in women, and is a process that accompanies aging. Some tumors have a marked excess of promoter methylation, and the tumors are said to have the "CpG island methylator phenotype", or CIMP[2]. Normal tissues have some degree of cytosine methylation, so the challenge has been to distinguish excessive methylation from physiological methylation. Since CpG methylation does not alter the genetic sequence per se, CIMP may be referred to as "epigenetic instability".

Tissue specific gene expression, mutation and cancer

Each tissue throughout the GI tract expresses a unique portion of the 20–25,000 genes in the human genome, and expresses each at different levels, which explains tissue-specific structure and function. A gene that is responsible for stimulating proliferation or restricting growth in one tissue may or may not have the same function in another tissue. Thus, the genes involved in esophageal carcinogenesis are different from those involved in gastric, pancreatic, hepatocellular, or colorectal cancer – although there is often overlap.

Sequential multistep carcinogenesis

Recognizing the various types of genes involved in carcinogenesis, and the processes whereby genes are altered, it becomes clear that each GI cancer must be evaluated in its own context. Moreover, each of the signaling pathways involves several proteins that work as a serial network, and there is cross-talk between parallel networks. Thus, one will not necessarily find the same combination of mutations in all tumors from a single organ. It is the variable accumulation of these genetic (and epigenetic) alterations that gives rise to the unique natural histories of the various GI cancers.

Colorectal cancer—CRCs evolve through the sequential accumulation of a variety of genetic alterations[1]. One of the earliest events in this sequence is the loss of control over WNT signaling, which usually occurs by loss of the APC gene. In the absence of additional genetic alterations, the lesion remains an adenomatous polyp. One could also disrupt WNT signaling without altering the APC gene with a specific type of mutation in the β-catenin gene that would make it impossible for β-catenin to be down-regulated. According to the initial formulation of multistep colorectal carcinogenesis, a mutation in the K-RAS gene is a later step in the sequence, but this occurs in only half of CRCs. Other cancers may achieve the same functional result by mutations upstream in this pathway (e.g., mutations in the EGF receptor) or downstream (e.g., in MAP kinase, MEK, BRAF etc). Depending upon which genes are altered, and the sequence in which these occur, the clinical and pathological appearances will vary.

After several years of slow growth as an adenomatous polyp, a critical event such as biallelic inactivation of the p53 gene can mediate the adenoma-to-carcinoma transition, leading to a significant acceleration of neoplastic progression. Alterations on chromosome 18 (perhaps involving the simultaneous losses of multiple TSGs on this chromosome) lead to the creation of a more virulent tumor capable of metastasis. This is a complex functional outcome that is not possible for adenomatous cells, and probably not possible for most CRC cells either.

Esophageal cancer—The evolution of adenocarcinoma of the esophagus is different, involving earlier losses of the p16 and p53 genes, and later losses of the APC gene[11]. These tumors evolve through a unique pathway from metaplasia, to dysplasia, and finally cancer. Aneuploidy occurs early, and can be found before cancer occurs. CIMP is more prominent in this disease, whereas the involvement of MSI is less important, and may occur through a process different from that seen in CRC.

Pancreatic cancer—Pancreatic cancers evolve through the sequential appearance of pancreatic intraepithelial neoplastic lesions (PanINs), which appear to be mediated by the sequential appearance of K-RAS mutation, inactivation of p16 (which may include LOH on 9p), followed by inactivations of p53 and genes on chromosome 18q (including the SMAD genes, which are also called DPC genes, for “deleted in pancreatic cancer”)[12].

Gastric cancer—Gastric cancers are more complicated, and many are linked at least epidemiologically to chronic infection with *H. pylori*, which is responsible for chronic inflammation, loss of acid secretory function, and altered gastric flora. Interestingly, there is evidence for involvement in gastric cancer of K-RAS mutations, loss of p53 activity, epigenetic inactivation (or relaxation) of DNA MMR activity, EGR receptor inactivation, and other features seen in the other GI cancers[13]. However, there has not been a conceptual model of sequential carcinogenesis in this disease, as has been proposed for other GI cancers. Interestingly, a unique and rare form of familial diffuse gastric cancer is caused by germline mutations in the gene for E-cadherin, an intercellular adhesion protein[14]. Thus, there are relatively unpredictable aspects to the genotype-phenotype relationships in GI cancers.

A possible unifying hypothesis

Many genes involved in GI carcinogenesis have been linked to cancers of specific organs, and three forms of genomic instability have been identified in the gut. Chronic inflammation is implicated in the pathogenesis of most GI cancers, but it is not clear whether this is quantitatively sufficient to cause cancer by itself. A transforming virus, the human polyomavirus - JC virus – is a transforming virus that has been found in nearly 90% of CRCs[15], and in the majority of esophageal[16], gastric[17] and pancreatic cancers. This virus encodes a potent oncogene (T-antigen), and a variety of animal and in vitro models demonstrate that this virus (or just the T-antigen) is capable of inducing CIN[18] and CIMP[19]. JC viral DNA can be found throughout the GI tract[20], but the T-antigen protein is only expressed in tumor tissue. It is not known what mechanism(s) maintain the virus in a latent state, or lead to the expression of the oncogene. Thus, it may be possible to account for all of the forms of genomic instability with JC virus, but this concept is not yet proven.

Clinical implications of the molecular genetics of CRC

The full story of gastrointestinal carcinogenesis is incomplete and in evolution. Each organ involves unique genes, differing mechanisms for the alterations of the genes, variable patterns for the sequential accumulation of mutations, and characteristic premalignant lesions. Understanding these processes and patterns will help us understand why some lesions have long periods of premalignant latency, why some lesions may be flat or protuberant, and why different mutations can be found in tissues, the fecal stream, or blood. This review will focus on the genetic basis of CRC, where the information has been more completely developed, and the information is summarized in broad strokes in Table 1.

Evolution of CRC from precursor lesions

CRCs evolve through one of three different pathways[21]. The commonest is the classical CIN pathway involving the loss of WNT signaling, K-RAS mutations, losses of TSGs on chromosome 18q, and biallelic losses of the p53 gene (on 17p). These changes evolve slowly over time, perhaps requiring a decade (or multiple decades) to fully develop. The familial model of this process is familial adenomatous polyposis (FAP), which begins with a germline mutation in one allele of the APC gene, and then evolves through the pathway mentioned above.

One can find evidence for CIMP in 40–50% of CRCs, which results in the methylation-induced silencing of multiple TSGs, including APC, p16, PTEN, and others. CIMP cancers have some overlap with CIN cancers, suggesting either a common pathogenesis, or the silencing of a gene that secondarily causes CIN. CpG island methylation may be a physiological process, and is associated with “normal” aging; therefore, there is not a sharp cut-off in the level of methylation between colonic tissues with or without CIMP. The temporal progression of this process is not clear at this time.

MSI is present in 15% of CRCs[22]; 20–25% of these are due to Lynch syndrome (HNPCC), but the other 75–80% are due to the acquired loss of DNA MMR activity caused by methylation of the promoter of the hMLH1 gene[23]. Therefore, MSI in sporadic CRCs is usually a consequence of CIMP. The loss of DNA MMR activity results in a very substantial increase in the mutation rate at microsatellite sequences, and these lesions appear to grow more rapidly than neoplasms from the CIN or CIMP pathways. Lynch syndrome is caused by germline mutations in DNA MMR genes[24]. When MSI is found in a CRC, if the patient is <50 years old, it is more likely to be Lynch syndrome, whereas if the patient is >65 years old, this is more likely to represent CIMP with acquired silencing of the hMLH1 gene. CRCs with MSI are more likely to occur in the proximal colon (90% of the acquired form, 65–70% of the hereditary form), and often present as bulky, cecal tumors.

Evolution of the adenomatous polyp

The typical adenomatous polyp is common in western and Japanese populations, consists of low grade dysplasia, is <10 mm in diameter, and is unpredictable in behavior. These lesions have genetic abnormalities that dysregulate the WNT signaling system, usually due to biallelic inactivation of the APC gene, occasionally due to mutational stabilization of the β-catenin gene, or less often, mutations in other genes in this signaling pathway, which regulates the proliferation program in colonic epithelium.

Some genetic aberrations distinguish adenomatous polyps from one another. For example, raised or pedunculated polyps are more likely to have mutations in the K-RAS gene[25]. Benign adenomas virtually never have biallelic inactivation of the p53 gene, as this mediates adenoma-to-carcinoma conversion[26]. Flat lesions are less likely to have K-RAS mutations, and flat cancers may have both APC and p53 inactivation[25].

The evolution of MSI CRCs is uncertain, but the adenoma-to-carcinoma conversion may occur with mutational inactivation of the TGF-β receptor II, which contains an A_{10} tract (i.e., 10 adenines in a row), and is thereby vulnerable to mutation in the absence of DNA MMR activity[27]. Relatively few lesions have been available for analysis, perhaps because of the rapid growth and evolution of MSI CRCs.

Serrated polyps of the colon and rectum (hyperplastic polyps and serrated adenomas)

Hyperplastic polyps are common lesions in the distal colon and rectum, and are not precursors of CRC. These lesions develop not because of excessive proliferation, but rather due to the failure of senescent cells to detach normally. The key is to distinguish the classic hyperplastic polyp from the serrated adenoma, but the pathological classification of serrated polyps is challenging. Classical hyperplastic polyps are the commonest serrated lesions in the colon and rectum, and these do not look dysplastic. However, serrated lesions that have dysplastic features are classified as serrated adenomas[28, 29]. Serrated adenomas (or sessile serrated adenomas) are more likely to be larger, proximally located, flat, and have BRAF mutations. It has been suggested that these may have MSI, and are putative precursors of MSI CRCs; however, this concept is controversial. Using magnifying chromoendoscopy on unselected patients undergoing screening colonoscopy, 72% had some type of polyp detected, and 9% had serrated sessile adenomas[30]. It is imperative that pathologists become familiar with these, and that approaches to the visual identification of these lesions are developed.

Aberrant crypt foci (ACF)

ACFs are small, abnormal clusters of colonic crypts that can be found in the colons of animals exposed to colorectal carcinogens, and in the colons of humans with or without CRC. These were initially postulated to be the earliest precursors of CRC. However, ACFs are heterogeneous in nature, and their fates are unclear. ACFs are monoclonal, tend to have K-RAS mutations, but tend not to have mutations in APC or β-catenin. The K-RAS mutations would tend to link them better with hyperplastic polyps than adenomas, and they rarely have BRAF mutations. These lesions are now within “reach” of the improved optics of colonoscopes, but it is not possible to interpret these lesions at this time, and they have not been proven to be predictors of risk for CRC. It is possible that very early adenomas will be called ACFs, but the current evidence suggests that most of the lesions identified as ACFs are not neoplastic, and are not the precursors of adenomas or cancer.

Molecular Markers of Gastrointestinal Cancer

The application of molecular biology to the study of GI cancers has led to a more precise understanding and classification of these diseases, and offers opportunities for molecular

diagnostics, genetic diagnosis, and novel predictive and prognostic approaches to cancer. At this time, we are able to use molecular markers for a growing number of applications. The best developed of these are genetic diagnostics of hereditary cancer syndromes. Mutational "signatures" (such as MSI, CIN or CIMP) are somewhat useful for prognosis and predicting responses to treatments in some instances. The use of molecular markers to diagnose cancer is an emerging area that is likely to expand into clinical practice soon.

Genetic diagnostics for familial cancer syndromes

There is at least one known gene responsible for nearly all of the familial GI cancer syndromes. However, for each hereditary disease, there are families for which the genetic basis cannot be found. In some instances, it is because some other (undetermined) gene is responsible for the disease in that family, and in other instances, it is because there are mutations that are difficult to identify using current technologies. Both problems will be corrected in the future.

Familial adenomatous polyposis (FAP)

FAP is caused by germline mutations in the APC gene, and is a dominantly inherited, highly penetrant disease with variable clinical presentations, due in part to the location of the mutation on the APC gene. The mutations are either premature stop codons, or deletion mutations that inactivate the gene. There are no missense mutations that cause FAP. Germline mutations can be found in 80–90% of patients. Biallelic mutations of the MYH gene cause an autosomal recessive form of FAP. Over 1% of European populations are carriers of one of the 3 commonest mutations in the MYH gene[31].

Lynch syndrome

Lynch syndrome is caused by germline mutations in any one of four different DNA MMR genes. Approximately 60% of the familial clusters of CRC will have germline mutations in one of the DNA MMR genes, but the other 40% do not, and may been called "Syndrome X"[32]. The genes responsible for Lynch syndrome are MSH2, MLH1, MSH6, and PMS2.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is caused by germline mutations in the STK11 gene. No other gene has been linked to this disease, but not all PJS patients have mutations identified. It has been reported that one can find STK11 mutations in most of patients with PJS[33].

Juvenile Polyposis Syndrome

Juvenile Polyposis Syndrome can be caused by germline mutations in several genes, including SMAD4, BMPR1A, and ENG. Mutations are found in only about half of these patients. It has been shown that careful pathological review will resolve some confusing cases, just by accurately identifying the nature of the polyps[34].

Polyposis syndromes caused by germline mutations in the PTEN gene

Cowden's Disease is caused by germline mutations in the PTEN gene. This disease can be protean in appearance, but germline mutations can be found in 80–90% of patients[33]. Bannayan-Riley-Ruvalcaba Syndrome is a pediatric disease with a complex phenotype that often includes juvenile polyps of the GI tract. Germline mutations may be found in the PTEN gene in some (but not all) of these patients.

Hereditary Diffuse Gastric Cancer

Hereditary Diffuse Gastric Cancer is a rare autosomal dominant disease caused by a germline mutation in the E-cadherin gene. No other mutation is known to lead to this disease[35].

Familial pancreatic cancer

Familial pancreatic cancer accounts for about 3% of all pancreatic cancer, but the problem is that several genes have been linked to this, and most are only weakly penetrant, so that knowing the diagnosis is of limited benefit, and may cause more problems than benefits[36]. The genes involved include STK11 (PJS), BRCA1 and BRCA2 (familial breast cancer), p16 (familial melanoma), any of the Lynch syndrome genes, APC (FAP), and the genes that cause familial pancreatitis. The imaging techniques for early pancreatic masses are not ideal for early diagnosis, and this remains a frontier in need of progress.

Li-Fraumeni Syndrome

Li-Fraumeni Syndrome is caused by germline mutations in the p53 gene, and is associated with early onset CRC[37]. Germline testing is available for this, but the disease is thought to be quite rare.

Predictive or prognostic markers in GI cancer tissues

Many attempts have been made to develop molecular markers that predict prognosis, but few have emerged into clinical practice. There has been interest in the loss of chromosome 18q as a marker of poor prognosis in colorectal cancer[38], but the actual genetic target of this has not been clearly identified, and this is not currently used clinically.

MSI has been proposed as a marker of a better prognosis in CRC. In CRC patients under the age of 50, MSI predicts a substantially better outcome, and patients with Stage I or II CRCs and MSI have 92% five year survivals[39]. MSI is principally used to identify CRC patients who may have Lynch syndrome, as >95% of such patients show MSI in the tumor DNA. MSI is also useful in predicting response to treatment using fluorouracil in CRC. Patients with Stage II or III MSI CRCs do not get a beneficial response from adjuvant chemotherapy with 5-fluorouracil, and there is a suggestion that it may be harmful in this situation[40, 41].

Fecal markers of GI cancer

There have been several trials looking for markers of tumor DNA shed from tumors into stool. There is evidence that this non-invasive approach is useful, but there are still some barriers in terms of sensitivity, specificity, and cost. At present, a panel of DNA markers can identify >50% of patients with CRC, many patients with advanced adenomas, with a false positive rate of 5–6%[42]. Technical advances promise to improve the performance of this approach, and it may be an alternative to other non-invasive diagnostic approaches such as CT colonography in the future.

Key abbreviations

CRC
: colorectal cancer

TSGs
: tumor suppressor genes

LOH
: loss of heterozygosity

BER
: base excision repair

DNA MMR
: DNA mismatch repair

HNPCC
: hereditary non-polyposis colorectal cancer

CIN
: chromosomal instability

MSI
: microsatellite instability

PCR
: polymerase chain reaction

ACF
: aberrant crypt foci

FAP
: familial adenomatous polyposis

MYH
: associated polyposis

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Table 1

Genotype-phenotype correlations in colorectal neoplasia

Pathological Lesion	Genetic alteration characteristically present
Adenomatous polyps	Biallelic inactivation of APC (or other mechanism that disrupts control of WNT signaling)
Flat adenoma	APC inactivation
Pedunculated adenoma	APC inactivation plus K-RAS mutation
Villoglandular adenoma	APC inactivation plus K-RAS mutation
Serrated polyps	
Hyperplastic polyp	K-RAS mutation (but no APC lesions)
Serrated adenoma	CIMP and BRAF mutations
Colorectal Cancer	**a.** Chromosomal instability (CIN), with mutations in APC, K-RAS, and p53 **b.** Microsatellite instability (MSI) with insertion- deletion mutations in repetitive DNA sequence (i.e., microsatellites); requires inactivation of the DNA mismatch repair system. Target gene mutations in TGFβ1RII, BAX, etc. **c.** CpG island methylator phenotype (CIMP) with epigenetic silencing of multiple genes (including p16, MGMT, MLH1, BRCA1, E-cadherin, APC, PTEN, etc.
Flat Colorectal Cancers	APC and p53 alterations, without K-RAS mutations
Aberrant Crypt Foci	K-RAS mutations, without APC alterations