LOS ANGELES

COLON AND RECTAL SURGICAL ASSOCIATES

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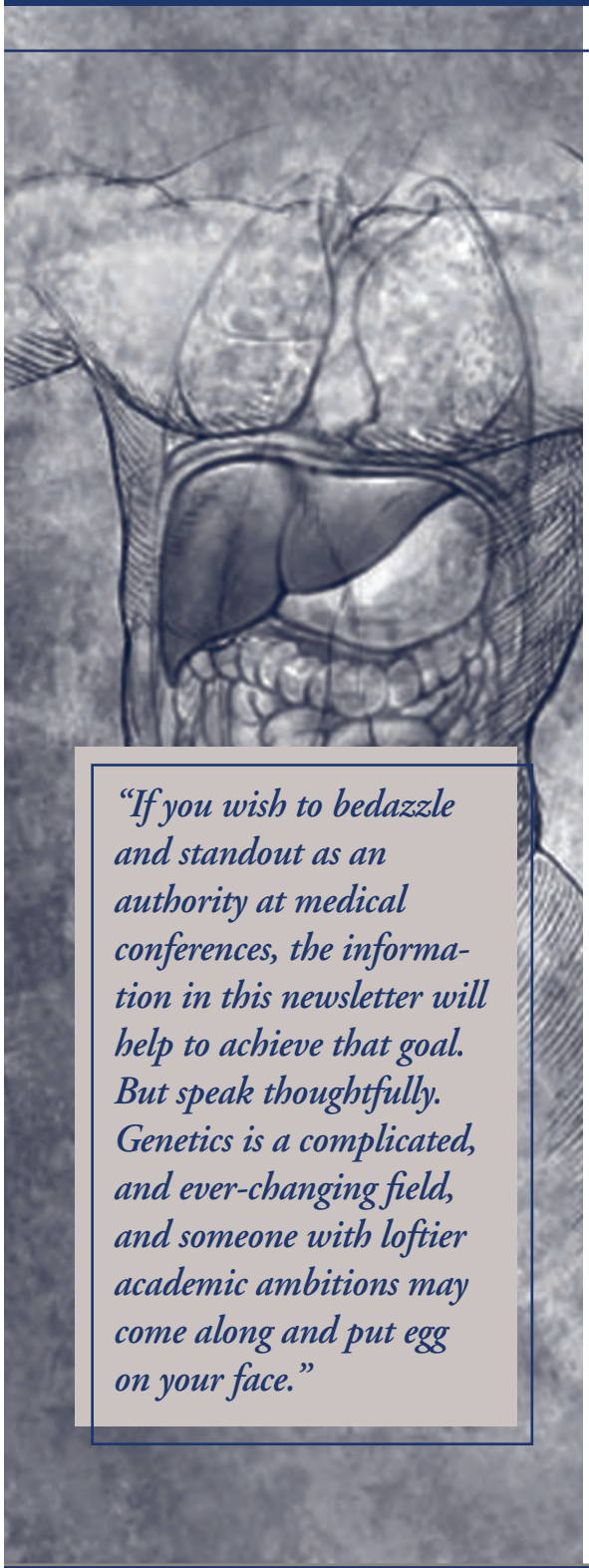

"If you wish to bedazzle and standout as an authority at medical conferences, the information in this newsletter will help to achieve that goal. But speak thoughtfully. Genetics is a complicated, and ever-changing field, and someone with loftier academic ambitions may come along and put egg on your face."

Colorectal Cancer Genetics For Dummies.

Amaze Your Friends. Dazzle Your Colleagues. (Maybe Even Save A Life)

If you wish to bedazzle and standout as an authority at medical conferences, the information in this newsletter will help to achieve that goal. But speak thoughtfully. Genetics is a complicated, and ever-changing field, and someone with loftier academic ambitions may come along and put egg on your face. However, if you wish to help patients and pursue a path to knowledge as a reward in itself, the following highly oversimplified information may serve as a good starting point. Don't groan over the biochemistry or the alphabet soup of acronyms. It is actually pretty cool stuff. Stick with it and slowly read what follows, until you arrive at the AHA! moment.

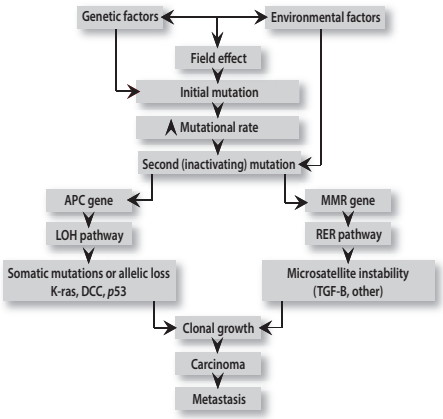

Figure 1. Genetic Pathways To Malignant Transformation.

FIRST THINGS FIRST. BUILDING PROTEINS.

Proteins, which are long strands of amino acids, participate in every process within the body. Proteins make up the structural and mechanical elements of all cells and cellular processes. They have integral roles in cellular division, cellular signaling, enzymatic activity and in cell death. The building of proteins is directed by the genome, which is a complete protein-production blueprint found in the nucleus of each cell. The genome contains all of our hereditary information.

The genome blueprint is composed of 46 inherited chromosomes, 23 from each parent. Chromosomes are composed of discrete units of information called genes. Each of our 20,000 genes contains the information necessary to produce a single protein. Each gene is composed of a long stretch of nucleotides, or DNA. A nucleotide is formed by the combination of a five carbon sugar, one or more phosphates and one of the purine nucleobases adenine or guanine, or one of the pyrimidine nucleobases cytosine or thymine. A long sequence of adjacent nucleotides (a gene) codes for the production of many amino acids which covalently bond to form proteins. The nucleotide sequence is faithfully replicated during cell division and is passed down through cellular generations during cell divisions. If there are replication errors during cellular reproduction, these errors can be repaired by a group of proteins made by mismatch repair genes. To summarize, long chains of nucleotides form genes. Genes manufacture amino acids which combine to form proteins. Proteins sustain life. Three billion nucleotides make up our genome. Simple so far.

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Half of our gene pool is inherited from the paternal side, and half from the maternal side. Therefore, each gene is represented twice within the nucleus of each cell; once on the paternal set of chromosomes, and once on the maternal set of chromosomes. Each of these two complementary, but not quite identical genes is called an allele. One allele actively produces protein and is dominant. The other allele is dormant and is recessive. An entire semester of genetics compressed into two paragraphs. Keep reading.

When a gene nucleotide mutates or is damaged, protein production may be compromised in different ways. It is thought that between four and twelve nucleotide alterations are required to begin and propagate malignant cell growth. When the mutations are incorporated into an individual's genome, they are passed down through the generations as "germline mutations" which may lead to inherited colorectal cancer development. Other spontaneous or "somatic" mutations occur on a sporadic, or non-inherited basis. External radiation or ingested dietary toxins may cause these mutations.

Ninety five percent of colorectal cancer is caused by sporadic mutations. The initial insult that begins the malignant transformation requires a "knock out" of both the dominant and recessive alleles of a critical gene.

Five percent of colorectal cancer is caused by hereditary mutations in germline cells. This is the inherited form of cancer. The inherited dominant allele of a critical mismatch repair gene is defective from birth. It is thought that a "second hit" from an environmental source knocks out the remaining normal allele and begins the process of malignant transformation. Almost done.

MORE BASICS. HOW CANCER BEGINS.

There are three categories of normal genes, which, when mutated, become dangerous cancer-facilitating genes that can silence protein production or force the production of defective proteins. These gene groups are **proto-oncogenes**, **tumor suppressor genes** and **mismatch repair genes**.

Proto-oncogenes are normal genes which make proteins that are essential for growth. When one of the alleles mutates and becomes abnormally activated, the abnormal protein products now push cellular proliferation to a *hyper*proliferative state, facilitating clonal proliferation. These mutant proto-oncogenes are now termed oncogenes. Only 20% of human cancers contain oncogenes.

Tumor suppressor genes normally manufacture proteins that can halt abnormal cellular proliferation even if cancer-facilitating oncogenes are active. Normal tumor suppressor genes such as the adenomatous polyposis coli (APC) gene located on chromosome 5, or the *p*53 gene on chromosome 17, can cause cellular replication arrest long enough for repair proteins to fix cellular damage. *p*53 is actually called "the guardian of the genome" and is a key regulator of the cellular replication cycle. If a cell is too damaged to be repaired, tumor suppressor genes such as *p*53 can drive the cell to an early death, a process termed apoptosis.

When both tumor suppressor gene alleles mutate, leading to their inactivation, cancer growth is actually promoted rather than suppressed. An APC gene mutation may occur spontaneously, or as an inherited mutation found in familial adenomatous polyposis (FAP). A mutant APC gene is found in most polyps and carcinomas.

Finally, mismatch repair (MMR) gene proteins repair DNA damaged during the cellular replication cycle. Cellular malignant transformation may result from the disruption of the anticarcinogenic functions of mismatch repair genes when both alleles have mutated. There are six known MMR genes found in humans. These may be associated with the sporadic form of colorectal cancer, or with the hereditary form of colorectal cancer called Hereditary Nonpolyposis Colorectal Cancer (HNPCC). The four most important of the six genes are MLH1, MSH2, PMS1 and PMS2. They are responsible for up to 20% of sporadic colorectal cancer.

Each of these three gene types plays a prominent role in one or both of the two genetic pathways to malignancy (Figure 1).

GENETICS, ENVIRONMENT OR BOTH? ALMOST AT THE AHA MOMENT.

Initiation is the first phase of a three step process leading to carcinoma development. The next phase, the promotion phase, follows one of two alternate pathways. The genetics of the promotion phase are complex and incompletely understood which is why this newsletter is titled "Colorectal Cancer Genetics For Dummies". Understanding the resulting cascade is what sets true superstar conference attendees apart from those simply wishing to receive free bagels and CME credit. The two promotion phase pathways then rejoin to arrive at the final common pathway, the progression phase.

AHA! TWO ROADS TO CANCER DEVELOPMENT.

Seventy to eighty percent of neoplastic colorectal lesions are found to have a mutated APC tumor suppressor gene on chromosome 5. This mutation can lead to the more common Loss of Heterozygosity (LOH) pathway which begins the adenoma to carcinoma sequence. LOH is really a multi-gene, multi-step cumulative process involving alterations in 4 to 12 genes such as MCC, TGF-ß, Rb and Myc. The LOH pathway begins with the sporadic or inherited loss of the APC gene, which causes the colonic epithelium to become *hyper*proliferative and form an early adenoma. (FAP follows the LOH pathway). The next step in the sequence involves a single nucleotide substitution leading to the activation of the K-ras oncogene on chromosome 12, which leads to the formation of an intermediate adenoma. This step is followed by the inactivation of the tumor suppressor gene DCC (Deleted in Colorectal Cancer) on chromosome 18, leading to the development of a late adenoma. Finally, there is a loss or mutation of the tumor suppressor gene *p*53 which appears to be the final step prior to the beginning of a malignant cascade. Other genes such as Nm23 are then involved in metastatic spread.

Twenty percent of tumors proceed along the replication error (RER) pathway and demonstrate a mutant mismatch repair gene on one of four chromosomes. These cancers are biologically different from the LOH cancers. Patients with HNPCC developed through the RER route usually begin life with one abnormal mismatch repair gene allele. A "second hit" inactivates the remaining normal allele, and the gene-derived protein product for mismatch repair is no longer produced. This sequence can also occur spontaneously with two somatic mutations knocking out both normal alleles. Without the normal protein involved in mismatch repair, replication errors occur and multiply as the cells begin their journey to malignancy.

When the cells have grown through one of these two abnormal pathways, they rejoin a final common path to malignant clonal growth, carcinoma formation and metastasis. Done!

BAGELS AND UNDERSTANDING.

You are now on your way to free bagels, CME credit and conference superstardom. Part two of this newsletter will examine the two genetic pathways to malignancy. Hopefully, this knowledge will help the clinician make an early diagnosis of colorectal cancer, and perhaps effect a cure.