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Gene Routes in Colorectal Cancer

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Mini Review

Colorectal cancer results from an accumulation of genetic abnormalities in the nuclei of colonic cells that allow the cells to escape the normal controls on cellular growth, death, and differentiation. The causes of these genetic abnormalities include mutations that happen during various phases of cell division, elements of life-style, personal characteristics, and inheritance. Each colorectal cancer is genetically unique, with hundreds of different mutated genes. However, the number of genes which when mutated drive carcinogenesis forward is limited [1]. Despite the genetic heterogeneity displayed in colorectal cancers there are three main routes (Figure 1) through which colorectal cancer develops [2]. These three routes produce cancers of different biology. It is important to distinguish between the routes, because the differences in biology have different clinical implications.

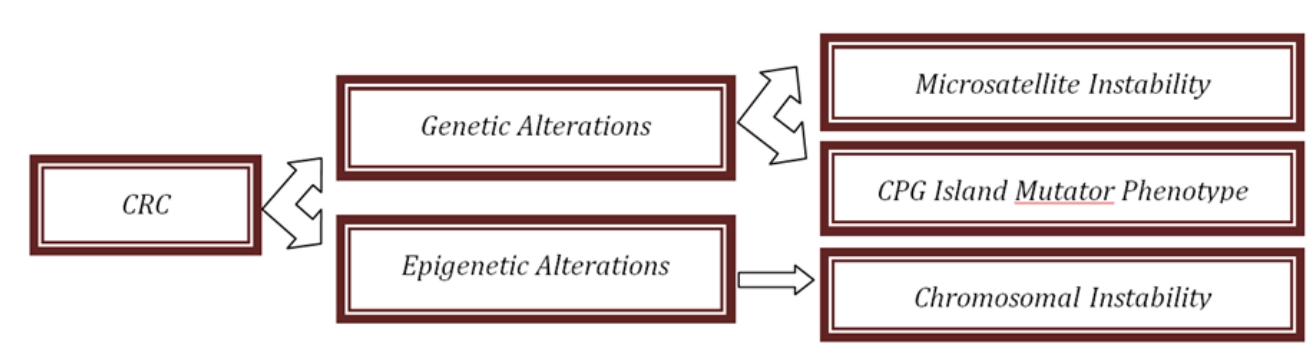

Figure 1: Genetic pathways in colorectal cancer.

Before going on to discuss the genetic pathways in colorectal cancer, let us define few basic genetic terminology. A gene is a sequence of nucleotide bases in DNA that codes for a specific protein. The genetic code is based on triplets of nucleotide bases, called codons, which encode a specific amino acid. A protein is a sequence of amino acids that performs a specific function in a cell. The nucleotide code is redundant as there are many more codons than amino acids. Thus, the actual DNA sequence can vary considerably yet still produce a consistent functioning protein. However, when changes in the DNA sequence result in a gene that encodes an abnormally functioning protein, a genetic disease may arise. This is an underlying process in cancer.

Hence, cancer is uncontrolled cell growth that results from an alteration in the normal checks and balances of cellular homeostasis. In normal cellular processes, there is a balance between the proteins produced by proto Oncogene and tumor suppressor genes. Inappropriate activation of proto-Oncogene or inactivation of tumor suppressor genes produces uncontrolled acceleration of cell growth that can ultimately lead to neoplasia. The most common way these genes are inactivated or activated is by mutation. A mutation is a permanent structural change in the DNA sequence. Some mutations are harmless due to the redundancy of the code, however, a deleterious mutation is one associated with a harmful change in the structure of the protein, which causes abnormal function. While a mutation is the most common way in which gene function is lost or disordered, other processes contribute to cancer development.

Genetic mechanisms involve the primary DNA sequence and changes or mutations to this sequence, whereas Epigenetics is the study of heritable changes in gene expression (active versus

inactive genes) that do not involve changes to the underlying DNA sequence - a change in phenotype without a change in genotype - which in turn affects how cells read the genes (Figure 2).

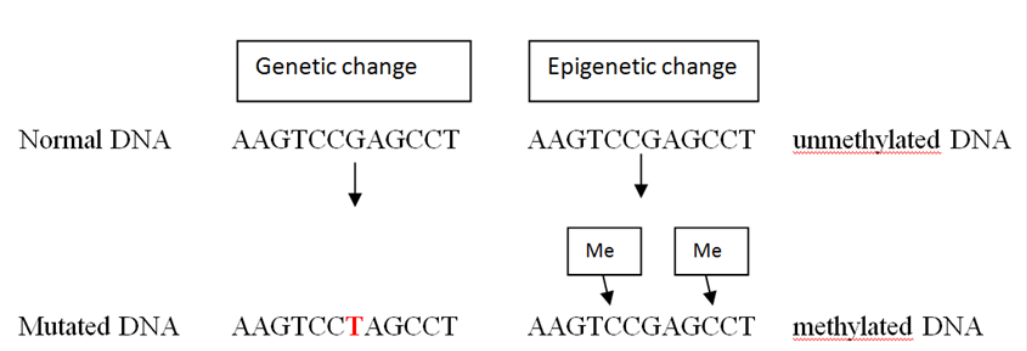

Figure 2: Difference between genetics and epigenetics.

Microsatellite Instability

Microsatellites are short repeating nucleotide base sequences that are prone to slippage during DNA replication that creates loop mismatches. Unrepaired mismatches are apparent as "unstable" microsatellites, where the length of a particular microsatellite in a tumor is different compared to that in a normal cell. The Micro Satellite Instability (MIS) pathway represents a form of genomic instability involved in the genesis of approximately 15% of sporadic colorectal cancer and >95% of Hereditary Non Polyposis Colorectal Cancer (HNPCC) syndrome. MSI is caused by the inactivity of the DNA Mismatch Repair (MMR) system. Disabled DNA MMR causes a 100-fold increase in the mutation rate in colorectal mucosa cells [3]. The MMR system is a multi-protein system, which acts like a proofing machine to increase the fidelity of DNA replications by identifications and direct repair of mismatched nucleotides [4,5]. The MMR system acts only when an error eludes the intrinsic error checking system of DNA polymerase [4].

CRC that develops through the MSI pathway presents peculiar clinical features: more often located in the proximal colon, with a poorly differentiated and a mucinous or medullary histotype, and often presents intense peritumoral and intratumoral lymphocytic infiltrations [6]. In general, the prognosis and survival of patients affected by MSI-high CRC is better and longer than that of patients with Chromosomal instability (CIN) positive CRC [6]. Multiple lines of evidence support that MSI-High tumors have worse prognosis when treated with 5-fluorouracil-based chemo-therapy alone [7]. However, such tumors do seem to respond to oxaliplatin and irinotecan [8]. Most recently, MSI-H tumors have been shown to respond very well to the use of PD-1 blocking agents [9]. This is thought to be the effect of amplifying the T-cell response to the immunogenic products of the mutator phenotype.

Chromosomal Instability

Chromosomal instability (CIN) is represented by the classic "Vogelgram," [10] (Figure 3) beginning with an inactivating mutation in the gateway driver gene APC and progressing through other driver mutations in KRAS, SMAD4, and TP53. The APC mutation predisposes the cell to chromosomal instability, which leads to Loss of heterozygosity and aneuploidy. CIN is the most common and well characterized type of colorectal pathway. The tumorigenic process involves different mitotic spindle checkpoint regulators and proteins that mutually influence mitotic chromosome stability [11,12].

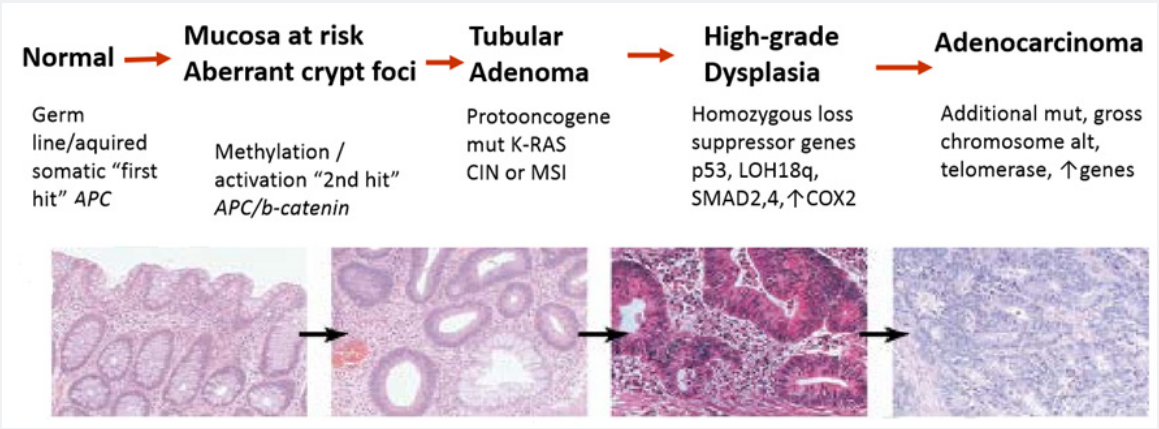

Figure 3: Adenoma carcinoma sequence.

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A "key" initial mutation is the early mutation of the adenomatous polyposis coli (APC) tumor suppressor gene, involved in both sporadic CIN and, when germline mutated, in all Familial Adenomatous Polyposis (FAP) [13,14]. This is followed by subsequent events that promote new mutations and facilitate the tumour's progression from benign to malignant stages. The adenoma to carcinoma transition is determined firstly by the K-ras gene. p53 loss of function is frequently present in the later stages of colorectal tumorigenesis [15]. The p53 gene is located on chromosome 17p and its mutation is one of the key steps in colorectal carcinogenesis and stimulates high proliferative activity through the loss of cell cycle control and apoptosis. An often co-occurring molecular alteration with the p53 loss is the LOH of chromosome 18q [16], where the genes Smad2, Smad4 and DCC genes are located. LOH of 18q has been associated with a strong negative prognosis in colon cancer, in particular with high metastatic potential [17]. Other alterations associated with CIN pathway include phosphoinositide-3 kinase (PI3KCA) signaling pathway [18], LINE-1 (long interspersed nucleotide element-1) [19], kinetochore (Centromere protein (CENP)-A and CENP-H) [20], Hypoxia Inducible Factor (HIF)-1 and HIF-2 [21] and cathepsin B (CTSB) [22].

CIMP Pathway

CIMP pathway consists of the aberrant hypermethylation of CpG dinucleotide sequences localized in the promoter regions of genes involved in cell cycle regulation, apoptosis, angiogenesis, DNA repair, invasion and adhesion. The initial event is a gene mutation in either BRAF or KRAS. Methylation of various other driver genes then advances to neoplasia that is apparent histologically as serrated mucosal lesions such as hyperplastic polyps, sessile serrated adenomas/polyps, and dysplastic serrated polyps [23]. These cancers are CIMP-positive. The promoter hypermethylations cause the loss of gene expression. CIMP is found in approximately 20%–30% of CRC and it was reported that clinical features of CIMP CRCs are similar to those associated with MSI [24]. Based on the number of methylated markers, the CIMP phenotype can be also divided into CIMP-high and CIMP-low. The BRAF oncogene mutation is often identified in CIMP-high CRC and is associated with increased cell growth, progression of carcinogenesis, and high colon cancer specific mortality [25]. However CIMP-high tumors, regardless of BRAF mutation, are associated with reduced colon cancer mortality [25]. BRAF and KRAS mutations are mutually exclusive [26]. KRAS mutation is usually found in CIMP low CRCs. This is also frequently associated with mutations in the DNA repair gene

Conclusion

The knowledge of different molecular pathway involvement in colorectal cancer development has helped us to understand how colorectal cancer initiates and progresses. The specific treatment options can target particular gene to prevent further progression of the disease. Prognostication and response to various adjuvant therapies is based on understanding of genetic pathways in colorectal cancer.

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