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Short Review

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Colorectal Cancer and Genetics

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Abstract

Colorectal cancer, a malignant tumor of the large intestine, affects both men and women. Approximately 90% of colorectal cancer cases are sporadic, which means a genetic mutation may happen in that individual person. A causative genetic event of less than 10% of this cancer has also been identified. Previously the colorectal cancer classification was based on clinical and pathological features. Today, many efforts have been made to explore the genetic and molecular properties of colorectal cancer. Colorectal cancer is a heterogeneous disease, with three common major molecular groups (Chromosomal instability, Microsatellite instability and Aberrant DNA-methylation). In this review, I would like to present a current overview of the genetics of colorectal cancer.

Introduction

Colorectal Cancer (CRC) is the third most common cancer in the world with more than 1.2 million new cases diagnosed each year. Therefore, it is considered as a major health problem. CRC cases are divided into two categories: sporadic and hereditary, and the majority of these cases are sporadic [1]. Both genetic and epigenetic changes are common in CRC, and about 5 to 10% of colorectal cancers originate from a hereditary mutation that can be passed on from parents to the child [1,2]. In 1990, Fearon and Vogelstein explained the specific pathways of CRC consisting of accumulated mutations in multiple genes that regulate cell growth and differentiation [2]. Three major mechanisms of genomic instability have been identified that give rise to colorectal cancer development and progression: Chromosome instability, Microsatellite instability and Aberrant DNA-methylation [3].

Colorectal Cancer Types

CRC is usually divided into three different groups according to the etiology and genetics of the disease: sporadic, inherited and familial [4].

Sporadic colorectal cancers

Sporadic carver that do not show any familial or hereditary predisposition constitute approximately 90% of CRC [1,4]. It is very common type of cancer in people over the age of 50, probably as a result of diet and environmental factors as well as normal aging. In addition, less than 10% of these patients have an inherited predisposition to colon cancer [4]. There are three major distinct molecular pathways leading to CRC: a) Chromosomal instability, b) Microsatellite instability and c) Aberrant DNA-methylation [1].

a) Chromosomal instability

Chromosomal Instability (CIN) is the most common genomic instability leading to many changes in the structure and number of chromosomes [3]. CIN can be caused by defects in chromosomal segregation, telomere stability and DNA damage and constitutes 65%-70% of sporadic CRC [5,6]. This pathway (CIN) is also known as an adenoma-carcinoma sequence and the genomic changes include activation of proto-oncogenes (K-Ras) [2]. CIN leads to the loss of allele of suppressor genes (APC, P 53, SMAD 4) which prevent the formation of malignant phenotypes [3]. The inactivation of the Adenomatous Polyposis Coli (APC) tumor suppressor gene results in activating mutations of KRAS [5]. The 102 human homologous sequences of the 96 known genes were determinative in the systematic identification of somatic mutations in genes with CIN potential in colorectal cancers [3]. Significant genetic mutations were found to affect WNT/APC/CTNNB1, CRAS/BRAF, FBXW7, PTEN, SMAD4, TGFBRII and TP53 genes that act as key events in CRC [6]. Molecular events due to chromosome instability are the basis of initiation, progression and tumor progression [3].

b) Microsatellite instability

Another important pathway leading to genomic instability is the microsatellite instability (MSI) pathway [1] MSI, the molecular fingerprint resulting from the loss of DNA mismatch repair activity [7]. In the colorectal cancer patients, it was observed that the genes responsible for the repair were inactive when the DNA-based pairing errors were investigated. These genes were named to as DNA mismatch repair genes (MMR) [3]. The MMR system controls and repairs defects that DNA polymerase over looked [2]. This pathway of repair is highly maintained from bacteria to humans and protects the integrity of the genome [8]. MSI was detected in approximately 15% of all colorectal cancers, 3% of which were associated with Lynch syndrome(Hereditary Non-Polyposis Colorectal Cancer[HNPCC]) and 12% were sporadic [9]. Lynch syndrome is an autosomal dominant cancer sensitivity disorder caused by germ line mutations in one of several MMR genes [2].

c) Aberrant DNA-methylation

The existence of common CpG island methylation in CRC leads us to the third pathway called the CpG Island Methyl Isolation Path (CIMP) [1]. There are multiple epigenetic regulatory mechanisms that regulate DNA expression without altering the nucleotide sequence. Abnormal epigenetic regulation is widespread in CRC and is as important as the DNA mutation in inactivating tumor suppressor genes [2]. A common alteration in mammals is the methylation of cytosine at the fifth position of the pyrimidine ring in CpG sequences [3]. In normal cells, CpG islands are usually protected in an unmethylated state (no methylation) and the gene is expressed normally. In the presence of promoter methylation, the gene is transcriptionally down-regulated and thus silenced [2]. Numerous sporadic MSI colon tumors are CIMP positive and up to 40% are located in the proximal region of the colon.CIMP positive tumors can be divided into two types: CIMP high associated with BRAF mutations and MLH1 methylation, and low CIMP associated with KRAS mutations [1].

As a result, since the definition of these three pathways mentioned above is not mutually exclusive, it is possible for tumors to show the characteristics of multiple pathways.

Inherited colorectal cancers

With kindred and twin studies, it is estimated that approximately 30% -35% of all CRC cases are hereditary [10,11]. Only 2% to 5% of CRC cases are due to hereditary mutations in well-known cancer-associated genes [10-12]. These are attributed to well-known monogenic disorders such as Lynch syndrome [HNPCC], Familial Adenomatous Polyposis (FAP), attenuated FAP, MYH-associated polyposis (MAP), rare Hamartomatous Polyposis Syndromes [11,13]. Hamartomatous polyps are primary lesions in Peutz-Jeghers Syndrome (PJS) and Juvenile Polyposis Syndrome (JPS) and Hyper Plastic Polyposis (HPP) is an unusual condition that has a significant risk of cancer and must be distinguished from other conditions [11,14]. The familial CRC was first defined by Dr. Henry Lynch and colleagues in 1966 [13,15]. Lynch syndrome is the most common hereditary CRC type and accounting for about 2-4% of all CRC cases and is caused by a germ line mutation in one of four genes (MLH1, MSH2, MSH6, or PMS2) associated with the DNA Mis Match Repair (MMR) system [11,13-15].

Familial colorectal cancers

Familial colorectal cancer is the third and least understood type of CRC whose molecular mechanism is still unknown. It was observed that 25% -30% of all CRC cases were included in this category, and the disease occurred in families with no evidence of one of the known hereditary syndromes [4,10]. Non-syndrome or familial CRC is usually identified as the clustering of CRC, which is differentiated from the hereditary syndromes. This CRC is a heterogeneous condition involving patients with unidentified hereditary syndromes and seemingly sporadic forms collected in families. Since a molecular mechanism cannot be established in these patients, it is argued that a combination of environmental and inherited genetic factors (common, low-penetration, genetic alterations) is likely to play a role in the development of the CRC in these families. Genome-wide association studies have identified a set of common genetic risk loci for CRC, and also in a recent meta-analysis, 16 variants in 13 loci are thought to have a significant association with CRC [10].

Conclusion

In conclusion, although the evidence of the studies is still lacking, our aim is to consider the molecular background of CRC and find a consensus that different types of CRC can be identified and included in classification systems such as WHO. It is important to understand the molecular genetics mechanisms of CRC's hereditary cancer subsets, to distinguish between high-and low-risk groups, to identify new loci, to develop targeted cancer control measures.

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