Chapter 11

Microsatellite Instability in Colorectal Cancer

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Abstract

Cancer is a genetic disease. Cancer cells contain various mutations, which includes SNPs to chromosomal aberrations. Together, these changes are referred to as genome instability. Genetic instability is one of the common characteristics of colorectal cancer. In colorectal cancer three major types of genetic instability have been reported. They are chromosomal translocations, microsatellite instability (MSI), and chromosome instability (CIN). Microsatellite instability occurs due to variations in DNA mismatch repair genes, while chromosomal instability is distinguished by major chromosomal alterations occurring at cell division and usually involves β-catenin and Adenomatous polyposis coli protein (APC) mutations. This chapter summarizes the major molecular mechanisms leading to genomic and microsatellite instability and tumorigenesis.

Keywords: cancer, colorectal cancer, genomic instability, microsatellite instability, mismatch repair

1. Introduction

Genomic and microsatellite instability (MSI) play critical roles in both cancer initiation and progression. This instability can manifest itself genetically on several different levels, ranging from simple deoxyribonucleic acid (DNA) sequence changes to structural and numerical abnormalities at the chromosomal level [1]. Since 1990s many researchers reported the presence of microsatellite instability as a common molecular mechanism in colorectal cancers [2]. Since then, several studies using numerous methods have characterized MSI molecular subtype [3]. Around 15% of colorectal cancer tumors with a mismatch repair (MMR) system deficiency is owing to germline, somatic, or epigenetic inactivation [4]. Large number of CRC patients is

reported to have deficient MMR system [5]. MSI has only slowly been accepted as a clinically significant aspect of tumor biology even though it is a well-established molecular marker for Lynch syndrome patients [6]. The present chapter provides an overview of genomic instability and molecular basis of the MMR system, the detection of MSI, and the molecular features of these tumors.

2. Genomic instability

Genetic instability is one of the common characteristics of colorectal cancer. Three major types of genetic instability have been reported in colorectal cancer [7–10]. Microsatellite instability occurs due to variations in DNA mismatch repair genes, while chromosomal instability (CIN) is distinguished by major chromosomal alterations occurring at cell division and usually involves β-catenin and Adenomatous polyposis coli protein (APC) mutations [11–13]. Less prevalent are mutations (germline) in DNA stability genes, including the DNA MMR genes, MSH6, MSH2, PMS2, and MLH1, which are connected with frameshift mutations and base pair substitutions in short-tandem repeat sequences causing microsatellite instability in HNPCC [14, 15].

Key changes in chromosomal instability in CRC consist of prevalent alterations in chromosome number and noticeable losses at the molecular level on 5q, 18q, and 17p chromosomes; and KRAS oncogene mutation. Major genes involved in these alterations are TP53 (17p), Adenomatous polyposis coli protein (APC) (5q), and MADH2/MADH4/DCC (18q) [16, 17]. The loss of chromosome is linked with instability at the chromosomal and molecular level. In approximately 13% of colorectal cancer tumors, MMR deficiency leads to MSI [18]. About 40% of colorectal cancer cases are distinguished by epigenetic alterations particularly DNA methylation, a phenomenon called CpG islands methylator phenotype (CIMP) [19, 20]. In the other 47% of colorectal cancers, CIN affects the tumors by insertions and deletions in chromosomes [18]. The chromosomal instability group includes cancers with polypoid or aneuploid karyotypes, and cancers which have numerous insertions or losses of chromosomal arms. Chromosomal instability results from specific molecular alterations, gene silencing, and also result from structural defects occurred during cell cycle [21]. In some of the colorectal adenomas it was observed that the tumor progression starts with chromosome 7 amplification. After this event, the other specific chromosomal alterations, such as losses on 17p, 8p, 18q, 20q, and 15q and gains on 20q, 8q, 13, and 7 will generally occur in the colorectal cancers [21–24].

Tumors with microsatellite instability are well known to possess more mutations than other tumors. Chromosomal instability and microsatellite instability tumors were primarily considered as equally special, as microsatellite instability tumors usually have constant and diploid karyotypes [25, 26]. Recent reports have illustrated that the microsatellite instability and chromosomal instability can arise in the same tumor [27, 28]. Trautmann et al. [29] found have observed that approximately 50% of hereditary microsatellite instability (MSI-H) tumors have similar level of chromosomal aberrations. Although confirmation for similar level of chromosomal instability can be observed in the majority of hereditary microsatellite instability

tumors, the specific mutations recognized differed between hereditary microsatellite instability and microsatellite stability tumors [30]. Hereditary microsatellite instability tumors harbor losses of 15q and 18q and gains of chromosomes 8, 12, and 13, whereas microsatellite stability tumors have a high level and variable range of chromosomal aberration [29, 31]. In a recent study by Lassmann et al. [32] in 22 Caucasian colorectal tumors on about 287 sequences found frequent aberrations in specific regions of chromosomes. This study suggested few candidate genes with frequent deletion and amplifications in these chromosome regions. A recent exome analysis of colorectal cancer genomes identified approximately eightfold more nonsynonymous variation in a tumor that displayed microsatellite instability [33].

Genomic instability is a basic feature of tumorigenesis. Three types of genomic instability have been reported in colon cancer: (i) chromosomal translocations, (ii) microsatellite instability, and (iii) chromosome instability [34]. The origin of chromosomal instability has been reported in few subsets of colorectal cancers. Nonetheless, microsatellite instability is renowned to result from inactivating variations or from unusual methylation of genes in the DNA MMR gene family. The MMR genes repair nucleotide mismatches arising during the replication [8]. Variations leading to inactivation of MMR system occur in 1–2% of colorectal cancers due to germline mutations in members of the mismatch repair genes, MSH2, MLH1, MSH6, and PMS2. Mutations in MMR system are one of the major causes of the familial adenomatous polyposis syndrome and hereditary nonpolyposis colon cancer syndrome [35].

In microsatellite instability or chromosomal instability the loss of genomic instability occurs after adenoma formation, but before progression to frank malignancy [36]. However, genomic instability can be a striking target for anticancer therapies as it is almost omnipresent in colorectal cancer and is a distinctive feature of cancerous cells. The possibility of targeting genomic instability for anticolorectal cancer therapy has been proved in *in vitro* systems [37]. Exploring the basis and roles of genetic and epigenetic instability in colorectal carcinogenesis has the potential to result in further development of efficient prevention methods and therapeutics for colorectal cancer [2].

According to the proposed theories, mutations in many pathways have major role in adenoma carcinoma progression series. In colon cancer, mutations in Adenomatous polyposis coli protein (APC) as well as the p53 pathways are seen in approximately 95% of the cases [38]. It has been reported that in approximately 70% of the tumors somatic mutations lead to alteration of the Ras/Raf pathway. The effect and particular roles of somatic mutations in other genes and pathways of colorectal cancer are less examined and less understood [36].

Mutational profiling and comparative studies require both tumor and normal tissue samples. Attaining tumor samples for colorectal cancer studies poses significant technical difficulty. The signal and noise are indistinguishable when the tumor samples render contamination with normal tissue. Very few studies have conducted a systematical analysis to resolve the spectrum of particular mutations in a series of genes in colon cancer tissues and their matching normal tissues, i.e., a systematic analysis of all genes in the Adenomatous polyposis coli protein (APC) pathway (Adenomatous polyposis coli protein, axin, and β-catenin), p53 pathway (BAX, p53, and MDM2), and RAS pathway (B-Raf and K-Ras) in the colorectal cancer tissues [39]. Few such studies have reported specific variations among the mutations observed in chromosomal

instability and microsatellite instability tumors. Most of the microsatellite instability tumors have 30% more mutations in β-catenin when compared to Adenomatous polyposis coli protein (APC), while β-catenin mutations are exceptionally rare in nonmicrosatellite instability cancers [40]. This is an indirect confirmation recommending that the microsatellite instability occurs prior to the inactivation of the Adenomatous polyposis coli protein Adenomatous polyposis coli protein (APC) pathway. Moreover, the spectrum of mutations is different in the Adenomatous polyposis coli protein (APC) pathway in many of the microsatellite instability tumors without β-catenin mutations when compared to nonmicrosatellite instability tumors. Specially, in simple repeat sequences of microsatellite instability there is an elevated rate of recurrence of mutations than in the nonmicrosatellite instability cancers [33].

3. Genomic instability in cancer

Genomic instability is a common symptom of most of the tumors and it includes several genomic alterations ranging from SNPs to large-scale chromosomal aberrations [41]. This can be classified into three groups based on the type of genetic changes.

3.1. Nucleotide instability (NIN)

NIN has several genetic variations which includes one or more nucleotide substitutions, deletions, and insertions. These errors may occur during DNA replication or due to faults in DNA repair mechanism, such as nucleotide excision repair (NER) and base excision repair (BER) [42]. These variations in DNA may lead to variations in gene structure and function.

3.2. Chromosomal instability

CIN is one of the common forms of genomic instability, reported in more than 90% of all cancers. CIN is detected in all stages of cancer [43]. For example, chr 10 is frequently lost in glioblastomas, which leads to the inactivation of the tumor-suppressor gene, PTEN. Generally, CIN refers to changes of chromosomal segments, or entire chromosomes, in terms of their structure or number, including translocations, additions, deletions, insertions, inversions and loss of heterozygosity (LOH) [43]. Variation in chromosome numbers is a condition known as aneuploidy. Chromosome translocation involves the merging of various chromosomes, or of two distant parts on the same chromosome, which results in the formation of a chimeric chromosome [44]. In cancer cells, CIN modifies the expression of numerous genes, leading to a poorer prognosis of patients with MIN or NIN tumors.

3.3. Microsatellite instability

Microsatellites are small tandem repetitive sequences of DNA located throughout the genome. MIN arises due to the malfunctioning of DNA mismatch repair system. This may result in the development, shrinkage, deletion, and random insertion of microsatellites [45]. The MMR system recognizes and attaches to the mismatch, and deletes the erroneous nucleotide and

maintains the genome integrity. MIN has been recognized in several cancers, including colorectal, ovarian, lung, endometrial, and gastric [46]. Till now, five MIN markers have been suggested for disease screening in patients prone to Lynch syndrome. MIN is generally observed in approximately 15% of all colorectal cancer patients, which contain both hereditary and sporadic forms. Tumors with MSI are reported to show better prognosis than nonMSI tumors [46].

4. Molecular basis of the MMR system

Microsatellites are small repetitive sequences dispersed in whole genome, which contain mono, di, trinucleotide, or tetra nucleotide repeats like $(A)_n$ or $(CA)_n$. Most of these repeats are precisely predisposed to accumulation of mutations, mainly due to the DNA polymerases, which cannot bind DNA competently at DNA synthesis period. Generally, observed errors in microsatellites are base–base mismatches, which escape the DNA polymerases proofreading activity, and insertion–deletion loops, which form DNA hairpins [47]. These unpaired nucleotides arise when the initial nucleotide and template strand separates and incorrectly reanneals in a microsatellite. Insertions or deletions in microsatellites situated in exonic regions causes frameshift mutations, which may lead to truncations of protein [47].

The MMR system is accountable for the recognition and correction of errors that occur in microsatellites. The major proteins involved in MMR system are MLH1, MSH2, MSH3, MSH6, and PMS2, and interact as heterodimers. When a mismatch is identified, MsH2 associates with either MSH6 or MSH3 (forming Mutsα and Mutsβ complexs), and MLH1 couples WITH PMS2, PMS1, or MLH3 (forms MutLα, MutLβ, or MutLγ complexes) [48]. Muts and a MutL complexes recognizes mismatches and mutations, and interacts with the replication factor C. Exonuclease 1 and proliferating cell nuclear antigen participate in the excision of mismatches [48]. As a final step, resynthesis and relegation of the nucleotide strand is done by DNA polymerase δ and DNA ligase. Variations in the genes responsible for the identification step lead to gathering of mutations in DNA, which may results in MSI. This has been recognized in various cancers, including CRC, gastric, endometrial, and few other carcinomas, such as glioblastoma and lymphomas [2].

5. Detection of MSI

Several techniques that are available to detect tumors with MSI are well established and are being used as a clinical diagnostic tool. Microsatellite repeats specific to MSI are being detected by PCR amplification. This can also be determined by comparing the length of nucleotide repeats in tumor cells and adjacent normal cells. This analysis was initially performed using polyacrylamide gels and radiolabeled primers; later on, this analysis has been made easier with fluorescent primers and capillary electrophoresis. In the 1990s, a microsatellite markers panel, known as the Bethesda panel, with appropriate sensitivity and specificity to diagnose

MSI CRC has been developed. This panel includes five microsatellite loci: two mononucleotides (BAT25 and BAT26) and three dinucleotides (D5s346, D2s123, and D17s250) [2].

Few researchers and clinicians have expanded this MSI panel to 10 markers. Three different MSI groups have been established based on the instability criteria: MSI-high (MSI-H), indicating instability at two or more loci; MSI-low (MSI-L), indicating instability at one locus; and microsatellite stable (MSS), indicating no loci with instability [49]. In most of the patients MSI-low cases only show instability for dinucleotide markers, so the analysis of dinucleotides alone may lead to the misclassification of MSS or MSI-L colorectal cancer as MSI-H. In contrast to this, mononucleotides BAT25 and BAT26 are nearly monomorphic, MSI determination could be easy using these markers in the absence of normal tissue [50]. Hence, MSI panel has an appropriate set of markers for MSI detection. These days commercial kits include a majority of mononucleotide markers with improved sensitivity [51].

MSI can also be detected by gene expression analysis methods. Immunohistochemical analysis of MMR proteins has become a standard procedure to detect MSI in the diagnosis centers and as an alternative to the genetic testing of Lynch syndrome [52]. Antibodies against MMR pathway proteins such as MLH1, MSH2, MSH6, and PMS2 will give a clear awareness about the mechanism and functioning of the MMR system [15]. Variation in functionality of one or more MMR genes is diagnostic, and concludes about the gene which is most probable to have a mutation or which gene got inactivated. Elucidation of the Immunohistochemistry (IHC) pattern may give more benefit for the dependent expression of heterodimers in the diagnosis of CRC as described by Vilar and Gruber [2]. They reported that CRCs that are deficient of expression of MLH1 and PMS2, but gain expression of MSH2 and MSH6, show scarcity in the expression of MLH1. In this state, deficiency of expression of PMS2 is simply a result of the inactive MLH1. Whether the absence of MLH1 is initiated by promoter hypermethylation that leads to inactivation of the gene or a germline mutation that causes Lynch syndrome need more exploration, but Immunohistochemistry (IHC) results direct the evaluation to concentrate on *MLH1* than the other MMR genes.

6. Conclusions

Genetic instability and microsatellite instability are the most common characteristics of colorectal cancer. Microsatellite instability is a subclass of CRC, which is reported to show a clear histopathological and therapeutic profile compared to other molecular subtypes. Various advanced methods have been developed in the past two decades for the detection of MSI. The molecular basis of MSI in cancer is still being explored. Recent findings revealed that MSI is caused due to mutations in genes coding for kinases. Further studies are required to identify the molecular basis of MSI and also to develop more cost-effective diagnosis and prognosis methods.

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