ACTA SCIENTIFIC CANCER BIOLOGY (ISSN: 2582-4473)

Volume 4 Issue 7 July 2020

Review Article

Role of DNA Mismatch Repair in Cancer

Ganguli D*

Department of Biochemistry, Indian Institute of Science, India

***Corresponding Author:** Ganguli D, Department of Biochemistry, Indian Institute of Science, India.

Received: April 08, 2020

Published: June 03, 2020

Abstract

DNA mismatch repair (MMR) specifically recognizes and removes mismatched base pairs and small insertion-deletion loops (IDLs) from the genome thereby maintaining the genomic integrity. Deficiency or complete loss of MMR in human leads to different kinds of cancer. The most common cancer associated with MMR deficiency is Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Lynch syndrome. In addition to this, MMR deficiency has been found to be correlated with other types of cancer, as well. Loss of MMR functions increases the frameshift mutations in different tumor suppressor genes leading to cancer in a tissue dependent manner. In this review, the role of MMR in the development and prognosis of different types of cancer has been discussed.

Keywords: DNA Mismatch Repair (MMR); Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

DNA mismatch repair (MMR)

There are several sources of mismatched base pairs in the genome. For example, during DNA replication DNA polymerase can insert a wrong base resulting in the insertion of mismatch in the genome. Homologous chromosomes have the same but not identical sequences. Recombination between such two chromosomes can incorporate mismatches in the genome. Moreover, spontaneous deamination of 5-methylcytosine can also result in a mismatch in the genome. These mismatches, if not corrected can be deleterious to the cell. So, cells have evolved a mechanism by which it can specifically recognize and correct the mismatches in the genome. Thus, DNA Mismatch Repair (MMR) is essential to maintain the genomic integrity of the cell and is highly conserved in all three domains of life. In Escherichia coli MMR decreases the spontaneous mutation rate by 50- 1000-fold [1]. Inactivation of the MMR pathway in humans leads to hereditary nonpolyposis colon cancer [2].

DNA mismatch repair in human

In human, MMR begins with the recognition of mismatch by bacterial MutS homologue (MSH); MutSα (MSH2- MSH6) or small insertion-deletion loops (IDLs) by MutSβ (MSH2-MSH3) [3]. This is followed by the recruitment of bacterial MutL homolog (MLH). Humans have three MutL homologs. MutLα (MLH1- PMS2), MutLβ (MLH1- MLH2) and MutLγ (MLH1- MLH3). MutLα and MutLβ have a latent endonuclease activity residing in their C-terminal domain. The N- terminal domain of MLH is responsible for the dimerization and regulation of the endonuclease activity [3]. The most important step in MMR is to discriminate between parental and daughter strands. In humans, a pre-existing nick serves as the discrimination signal [4]. The communication between MSH bound to the mismatch (or IDLs) and the discrimination signal may involve DNA looping or active transportation of MSH complex from the site of mismatch to the discrimination signal site [5]. Once the MSH complex encounters the pre-existing nick, the excision step of MMR is initiated. Proteins involved in the excision step depend on the location of the nick relative to the mismatch [6]. In 5' nick directed excision MutS, ExoI, PCNA, Polδ and Pol€ are involved. ExoI, a 5' to 3' exonuclease cleaves the daughter strand followed by the resynthesis of the strand by Polδ and Pol€ and the ligation by DNA ligase. In 3' nick directed excision in addition to the proteins mentioned above, MutLα is also required. MutLα is believed to nick the daughter strand at the 5' end of the mismatch which allows ExoI to cleave the daughter strand. The geometrical orientation of PCNA is also believed to help in strand discrimination [7]. Once, the daughter strand is cleaved, high fidelity replicative polymerases resynthesize the strand. The resulting nick is then ligated by DNA ligase. Unlike prokaryotes, the role of helicases in human MMR is debatable. Human lacks bacterial UvrD homolog. However, several RecQ family of helicases such as WRN, BLM, are speculated to be involved in MMR [6].

DNA mismatch repair and cancer

MMR in hereditary nonpolyposis colorectal cancer

Hereditary nonpolyposis colon cancer or Lynch syndrome is the most common form of colon cancer affecting people across the globe. 3 to 10% of colorectal cancer is caused by Lynch syndrome [8]. This disease is inherited in an autosomal dominant pattern with 85% penetrance [9]. Patients with Lynch syndrome often are pre-disposed to multiple types of cancers such as gastric cancer, intestinal cancer, gall bladder cancer, upper urinary tract cancer, lung cancer and skin cancer. In women, it increases the frequency of ovarian and uterine endometrium cancer [10].

Lynch syndrome is characterized by microsatellite instability (MSI) resulting from strand slippage during DNA replication [11].

MSI leads to either expansion or contraction of the length of repetitive DNA sequences causing genomic instability. Most of the mutations responsible for the syndrome mapped into six MMR genes; hMSH2, hMLH1, hPMS1, hPMS2, hMSH6 and hMLH3. Among them, mutations in hMSH2, hMLH1 and hMSH6 account for 38%, 60% and 7% respectively [12]. hMLH1- C680G, hMLH1-R659X and hMSH2-R171K have been found in patients with early onset of cancer indicating the important roles of these amino acid residues in MMR [13,14]. In many other cases, deleterious mutations in the coding region, splice junction mutations and the overall gross deletion of the genes are also observed [15]. Patients with hMSH6 mutations are often characterized by the late onset of the disease and less MSI in the tumors. The exonic distribution of mutations in hMLH1, hMSH2, and hMSH6 associated with Lynch syndrome are shown in figure 1 [12]. As it is evident, the distribution is mostly random with some hotspots around exon 12 and 3 in hMSH2, exon 16 and 1 in hMLH1 and exon 4 in hMSH6. In addition, some mutations are also identified in the promoter region of MSH2 and MLH1 responsible for the syndrome. Frameshift mutations, resulting in the formation of truncated proteins in hMSH2 and hMLH1 also account for Lynch syndrome. Most of these mutations result in the loss of interaction with other MMR proteins or change the overall structure of the proteins leading to an impaired MMR [12].

Figure 1: Distribution of germline mutation in MSH2, MLH1 and MSH6 gene. Adapted from Reference [12].

Crosstalk between MMR and other cellular pathways may determine the phenotypic outcome and the treatment of the disease. Patients carrying a stabilizing mutation in Cyclin D, in addition to a mutation in MMR proteins, may result in a very early onset of cancer [15]. Similarly, mutations in the enzymes responsible for metabolizing amino compounds also show a cumulative effect in HNPCC patients [16]. MMR is also responsible for repairing DNA damages resulting from oxidative and alkylating stress. Cyclooxygenase 2 activity is mainly responsible for the oxidative stress on DNA. Recently, inhibitors of COX2 has been found to be effective to reduce polyp formation in HNPCC patients [17]. Many alkylating agents are used as anti-cancer drugs. Loss of MMR makes cells tolerant to alkylating agents in a p53 dependent manner thereby diminishing their effect [18]. 5-fluorouracil used as an anti-cancer drug for the treatment of advanced colorectal cancers. Studies have shown MMR deficient cells become resistant to this drug easily as compared to MMR proficient cells [19]. A detailed study of the interplay between MMR and other cellular activities is thereby required to have a full understanding of Lynch syndrome.

MMR and head, neck and lung cancer

MMR deficiency has also been linked to the development of lung cancer. hMSH2 level was found to be comparatively less expressed in different types of lung cancer [20]. Inactivation of hMLH1 due to the hypermethylation of its promoter has also been found in lung cancer patients [21]. It has been shown that MMR deficiency can accelerate the tumor formation in mice having the k-Ras mutation [22]. Specific nucleotide polymorphism has been found in different MMR genes such as hMLH1, hMSH2, hMSH3 and EXOI associated with head and neck cancer [23] indicating an important role of MMR in these types of cancers.

MMR and sporadic tumors with high MSI

Numerous sporadic colon cancers are characterized by a high degree of MSI, as well. In the majority of this type of cancers epigenetic inactivation of hMLH1 gene has been observed. Hypermethylation of the promoter region of hMLH1 plays the most significant role in hMLH1 silencing [24]. This epigenetic change has been found to be biallelic affecting both the paternal and maternal alleles [25]. The pathway responsible for the hypermethylation is not clearly understood. The involvement of other MMR genes is MSI abundant sporadic tumors are less significant.

Deficiency in MMR leads to mutations in tumor suppressor genes

Loss of MMR functions lead to high degree of frameshift mutations of many tumors suppressor genes containing repetitive DNA sequences either in their coding region or in their promoter region due to increased rate of replication slippage. These important genes affected by the loss of MMR are summarized in table 1 [26]. Most of the gene products play a significant role in regulating cell growth in actively proliferating cells. Mutations in these genes often lead to different kinds of cancers in a tissue-dependent manner.

Gene or locus	Chromosomal location
Genes identified and germline mutations demonstrated	
TGFβRII	3p22
CHD1 (E-cadherin)	16q22
I1307K variant of APC	5q21
E1317Q variant of APC	5q21
Genes mapped but not yet identified	
HMPS	6q
CRAC1	15q14-q22

Table 1: The name and location of tumour suppressor genes affected by MMR deficiency. Adapted from Reference 26.

Conclusion

MMR in humans play a significant role in maintaining genome stability. It reduces the frequency of MSI that leads to an increase in genomic integrity. A complete understanding of the human MMR mechanism will provide us a better understanding of its role in different types of cancer and will help us to design new effective anti-cancer drugs.

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