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SHORT REVIEW

DNA mismatch repair deficiency in lung and oral cavity carcinomas: the role of histogenetic origin

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Summary

DNA mismatch repair system (DNA MMR) is a crucial genetic mechanism for DNA homeostasis in prokaryotic and eukaryotic cells. During DNA replication and also recombination, point intra-nucleotide errors including base deletion, insertion, and mis-incorporation happen. These raised abnormalities in the newly synthesized DNA strand could affect negatively the stability of the molecule and the function of the corresponding genes. DNA MMR proteins prevent these errors by recognizing and repairing them, securing directly the normal anatomy of the DNA double strand and indirectly the expression of the genes. Specific genomic alterations - mutations, loss of heterozygosity (LOH), or promoter hypermethylation - regarding the MMR genes (human homologues) hMLH1, hMSH2, hMSH3, hMSH6, hPMS1 and hPMS2 modify negatively their expression leading to loss of their function in repairing the corresponding base to base errors. The result known as microsatellite instability (MSI) was initially recognized in colonic carcinoma, especially in its inherited aspect - the Lynch syndrome -, the most common form of hereditary colon carcinoma. Since then, acquired deficiencies in specific DNA MMR genes have been detected in a broad spectrum of malignancies including different anatomic regions and histologies such as stomach, prostate, esophageal, endometrial, lung and head & neck. In the current special review we explored the role of DNA MMR deficiency in lung and oral cavity carcinomas in order to identify similarities and differences regarding the corresponding genes alterations.

Key words: *carcinoma, gene, microsatellites, lung, oral, repair*

Introduction

Structural stability of the DNA molecule secures and enhances its multiple normal functional aspects. Among the genetic mechanisms that provide a stable microenvironment inside the molecule, DNA MMR plays a leading role. DNA MMR is a very primitive, highly conserved but totally efficient mechanism in a series of premature and mature organisms including bacteria, prokaryotic and eukaryotic cells [1]. The common characteristic in all of them is the ability of the corresponding genes to detect and repair intranucleotide base to base errors mainly in the complementary DNA strand. MMR mechanism is capable to distinguish the newly synthesized strand from the template (parental). During DNA replication and also recombination, a variety of intranucleotide

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errors including base deletion, insertion, and misincorporation happen. Mismatches are involved in base tautomerization process during G2 phase. The base abnormalities such as G/T or A/C pairing are repaired by firstly recognition of the deformity, excision of the invalid incorporated base and replacement it with the suitable, complementary nucleotide. Sometimes, a significant number of bases (hundreds even thousands pairs) must be removed in the newly synthesized DNA strand compared to its template in order to prevent abnormal base to base conjunction [2].

Humanized homologues of DNA MMR main genes are located on chromosomes 2, 3, 5 and 7 including MLH1, MSH2, MSH3, GTBP/MSH6, PMS1 and PMS2 (Figure 1). Additionally, other molecules that involve in DNA structural genomic stability are DNA polymerase delta, PCNA, RPA, HMGB1, RFC and DNA ligase I, combined with histone and chromatin domains. Specific genomic alterations – germline mutations, accompanied by usually allelic loss (LOH), or epigenetic changes such as promoter hypermethylation - in the MMR genes lead to loss of their expression, affecting their function in repairing the corresponding base to base errors [3]. Thus, inherited as well as acquired deficiencies in DNA MMR genes are associated with the development of MSI, a genetic phenomenon frequently observed mainly in hereditary (familial) and sporadic colorectal carcinoma (CRC).

Microsatellites are referred to repetitive nucleotide sequences including usually 1 to 5 base pairs repeated for 15-30 times which are normally relatively stable. Thousands of microsatellites are detectable throughout the human genome. In fact, during DNA replication, accumulation of them forms a small loop in any of two strands. Insertion or deletion of these repeated nucleotide chains are identified also inside the introns of the genes. For all these molecular reasons, MSI is a biomarker for detecting DNA MMR deficiency in CRCs and also in a variety of malignancies of different histogenetic origin [4].

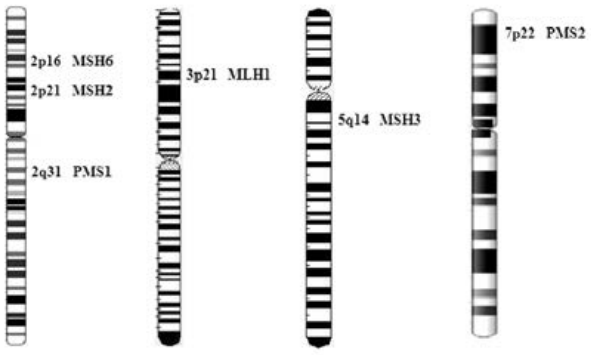

Figure 1. Human homologues of DNA MMR genes and their corresponding chromosomal locations.

The aim of this special review was to present DNA MMR deficiency in lung and oral cavity carcinomas in order to identify similarities and differences regarding the corresponding genes.

DNA MMR-depended MSI: the analytical model of inherited CRC

Hereditary non-polyposis colorectal cancers (HNPCC) - an autosomal dominantly inherited disorder of cancer susceptibility - demonstrate the highest levels of DNA MMR-depended MSI (~90% cases), whereas sporadic CRCs only 15%. About 70% of HNPCC patients have a germline mutation in either hMSH2 or hMLH1, reflecting a risk of about 80% for CRC development. HNPCC includes two different syndromes: Lynch I and II [5]. Lynch syndrome I is associated with carcinoma of the right colon (70%), whereas Lynch syndrome II is associated with CRC combined with extracolonic carcinomas, such as stomach, pancreas, small bowel, hepatobiliary tract and also endometrium, ovary, kidney or ureter. HNPCC was the model for molecular analysis by specific sequencing based polymerase chain reaction (PCR) techniques for detecting MSI or replication errors (RER+: positive carcinomas). Mainly, a set of five microsatellite markers: three dinucleotide (D2S123, D5S346, D17S250) and two mononucleotide (BAT25 and BAT26) are suggested for PCR analysis. Generally, mononucleotide repeat markers have been shown to be highly sensitive in detecting MSI-H tumors. According to the levels of abnormality in the examined microsatellite markers, MSI is divided in high level MSI (MSI-H) with more than 30% of the standard markers, low level MSI (MSI-L), when alterations are detected in less than 30% but greater than 0 % of the markers and microsatellite stable (MSS) in the situation of complete absence of any microsatellite alterations.

Interestingly, HNPCC and also sporadic RER+ cancers are diploid or near diploid in chromosomal constitution in contrast to the majority of CRCs which demonstrate an aneuploid chromosomal pattern. This chromosomally stable molecular profile explains partially the better prognosis that MSI positive (RER+) CRCs demonstrate. Based on some studies, these CRCs are characterized by a mucinous pathological pattern combined with significant lymphocyte penetration of the tumor, reflecting an increased immune response activi-

ty [6]. Additionally, at the genetic level , loss of hMLH1 or hMSH2 expression is considered to modify the mutational status of other genes including KRAS, BRAF, APC, P53, and TGF-β [7].

DNA MMR deficiency in lung carcinomas

Lung cancer is the leading cause of death related to cancer and its incidence is still on the increase worldwide according to the recently published 2015 WHO data and classification [8]. Epidermal growth factor receptor (EGFR) mutational landscape regarding lung adenocarcinoma (LAC) predominantly and also lung squamous cell carcinoma (LSCC) is detected in a subset of patients (10-30%) affecting their response rates to targeted therapeutic agents (tyrosine kinase inhibitors-TKIs) and also the survival status. EGFR-activating somatic mutations in exons 18/19/20/21 modify patients' sensitivity (i.e. exon 21 L858R, exon 19 LREA deletion) or resistance (i.e. exon 20 T790M and/or insertion) to them [9]. In these patients, the role of DNA MMR-depended MSI is not clear. According to published data, it seems that MMR affects gene mutations in LAC. A study group analyzing both EGFR and k-ras genes for point mutations showed that high hMLH1 expression was correlated to a higher frequency of EGFR mutations in exon 19 and 21. Furthermore, the expression of another MMR gene, the hMSH2, was also increased in these cases. Interestingly, according to extensive statistical analyses, overall overexpression of hMLH1 and the LAC histological subtype were both independent factors that related to EGFR mutations [10]. Concerning k-ras instability, there was no statistical significance with both hMLH1 and hMSH2 expression levels. Another similar study based on an analysis of clinicopathological parameters showed that lower hMLH1 expression was more frequent in heavy smokers. The same study group concluded also that HMSH2 and hMLH1 expression were different in LACs compared to SCCs [11]. Concerning tobacco consumption, two independent studies found that exposure to tobacco smoke inactivates MMR function by inducing chromosomal instability and polymorphisms of the hMLH1 gene [12,13]. In order to explore the pivotal role of hMLH1 alterations in lung carcinomas showed that specific polymorphisms of the gene are related more often in LSCC than in LAC. Furthermore, another study group showed that MMR mRNA phenotypes may be added to the known biological differences between LSCC and LAC and also correlated with smoking status [14]. Concerning hMLH1 and hMSH2 phenotypes, they were distributed differently according to the NSCLC stage modifying also patient response to adjuvant chemotherapy. Despite some controversial results regarding the involvement of DNA MMR deficiency in lung carcinomas genesis and progression and the relationship between them and EGFR/K-ras mutations, a recently published study reported that DNA mismatch repair deficiency accelerates lung neoplasm development in K-ras (LA1/+) transgenic line mice [15].

DNA MMR deficiency in oral cavity carcinomas

In contrast to CRC and lung carcinomas, there is limited data regarding DNA MMR and MSI in oral cavity carcinomas. Two independent study groups reported that hypermethylation of the hMLH1 gene may be the principal inactivating mechanism in oral cancer with MSI in HPV-related lesions and also that the hMLH1 -93 A>G polymorphism is associated with higher risk of tobacco-related oral squamous cell carcinoma (OSCC) and could be useful in screening population at a higher risk [16,17]. These studies were based on patients with different ethnicity (Korean vs Asian Indians) exploring specific genetic polymorphism of the hMLH1gene. Similarly, another study investigated the role of complex hMSH2 and hMSH6 protein expression in OSCCs. They found that high levels of expression was an independent prognostic factor for poor overall survival suggesting that the complex may constitute a molecular marker for the poor prognosis in these patients [18]. Additionally, hypermethylation of hMLH1 and hMSH2 might play a role in oral carcinogenesis and may be correlated with a tendency to develop multiple oral malignancies. Furthermore, expression of hMLH1, hPMS2 and hMSH2 genes seem to be related progressively with oral epithelial dysplasia and squamous cell carcinoma. Immunohistochemical analyses showed that reduced expression of these markers was correlated with dysplasia to carcinoma progression and also with the grade of the carcinomas (poorly differentiated from well-differentiated) [19]. Exploring the role of another MMR DNA gene, the hPMS1, another study group reported that this is most likely deregulated by post-transcriptional modification in oral carcinomas, whereas its mRNA expression was not deregulated in either MSI positive or MSI negative tumor cell lines. Interestingly, DNA analysis of hPMS1 did not show any mutational

changes in exonic or promoter regions [20].

In conclusion, identification of specific gene deregulation mechanisms regarding DNA MMR genes is a significant issue for understanding their altered protein expression. Reduced expression levels of these markers are correlated with MSI both in lung and oral cavity carcinomas. hMLH1 is a crucial gene for both of them and its abnormal expression and function influences the progression and the biological behavior of the corresponding malignancies. Concerning the other genes, there are controversial data regarding their clear role depended on their anatomic and histogenetic characteristics.

Conflict of interests

The authors declare no confict of interests.

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