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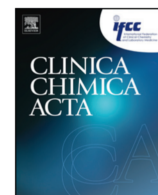

1 Invited critical review

Q5 DNA mismatch repair enzymes: Genetic defects and autoimmunity ☆

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ABSTRACT

DNA mismatch repair (MMR) is one of the several DNA repair pathways conserved from bacteria to humans. The 18 primary function of MMR is to eliminate the mismatch of base–base insertions and deletions that appear as a 19 consequence of DNA polymerase errors at DNA synthesis. The genes encoding the DNA MMR enzymes 20 (MMREs) are highly conserved throughout evolution. In humans, there are two sets of MMREs, corresponding 21 to homologues of the bacterial MutLS systems. The human MutS enzymes consist of MSH2, MSH3 and MSH6, 22 and the human MutL enzymes include MLH1, MLH3, PMS1 and PMS2. Since the beginning of this century, a 23 few reports on autoantibodies to some MMREs have been reported in autoimmune inflammatory myopathy, 24 cancer and hematological disorders. This review charts the functional structures of MMREs, their genetic defects 25 and associated disorders, and autoimmunity to MMREs, including our recent data that was the first to analyze 26 autoantibodies against all seven kinds of MMREs in systemic autoimmune diseases, including idiopathic 27 inflammatory myopathies. 28

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1. Introduction 45

The production of autoantibodies to various cellular constituents is a 46 hallmark of systemic autoimmune rheumatic diseases such as systemic 47 lupus erythematosus (SLE), systemic scleroderma (SSc) and polymyositis 48 (PM)/dermatomyositis (DM) [1,2]. Recent studies on myositis-specific 49 autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) 50 have clarified that they are useful tools for identifying clinical subsets of 51 patients with idiopathic inflammatory myopathies (IIMs) [3,4]. Although 52 there have been sporadic reports on autoantibodies to some DNA 53 mismatch repair (MMR) enzymes (MMREs) in patients with IMM [5,6], 54 their clinical significance remains unclear. We conducted a systematic 55 investigation of autoantibodies against all seven kinds of MMREs in 56 patients with IIMs and other systemic autoimmune diseases [7], and the 57 results prompted the present review of the literature on autoimmunity 58 to MMREs. In addition, as several common genes are involved in genetic 59

Abbreviations: AA, aplastic anemia; ARS, aminoacyl tRNA synthetase; CMMR-D, constitutional mismatch repair-deficiency syndrome; DM, dermatomyositis; DM1, myotonic dystrophy type I; DNA-PK$_{cs}$, DNA-dependent protein kinase; ELISA, enzyme-linked immunosorbent assay; HD, Huntington's disease; HNPCC, hereditary nonpolyposis colorectal cancer; HSPC, hematopoietic stem/progenitor cell; IIM, idiopathic inflammatory myopathy; IPP, immunoprecipitation; LS, Lynch syndrome; MAA, myositis-associated autoantibody; MDA5, melanoma-differentiation associated gene 5; MMR, mismatch repair; MMRE, mismatch repair enzyme; MOS, myositis overlap syndrome; MSA, myositis-specific autoantibodies; MSI, microsatellite instability; MTS, Muir–Torre syndrome; PARP, poly(ADP-ribose) polymerase; PC, pancreatic cancer; PM, polymyositis; RA, rheumatoid arthritis; SEREX, serological identification of tumor antigens by cDNA expression cloning; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic scleroderma; TIF1, transcription intermediary factor 1; TNR, trinucleotide repeats; TnT, in vitro transcription and translation product.

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neuromuscular disorder and autoimmunity in IIM [8], we also summarize diseases associated with defects in MMRE genes.

2. The human DNA mismatch-repair system

MMR is a highly conserved pathway that removes base–base mismatches and insertion/deletion mispairs that arise during DNA replication and recombination, thus contributing a 50-fold to 1000-fold increase in fidelity [9,10]. The genes of the MMREs are highly conserved throughout the evolution. In eukaryotes, there are two sets of MMREs, corresponding to homologs of the bacterial MutLS system. The human MutS proteins consist of MSH2, MSH3 and MSH6, and the human MutL proteins include MLH1, MLH3, PMS1 and PMS2 (Fig. 1) [11].

The MMR process begins with the binding of the MutS heterodimer to DNA mismatches (Fig. 2). The heterodimer is formed by either MSH2–MSH6 (MutSα) or MSH2–MSH3 (MutSβ). The MSH2–MSH6 complex preferentially recognizes single base mismatches and 1- or 2-nucleotide insertion/deletion mispairs, whereas the MSH2–MSH3 complex preferentially recognizes insertion/deletion mispairs containing two or more extra bases. Upon binding, the MutS complex undergoes an ADP–ATP exchange-driven conformational change and recruits the MutL heterodimer. The human homologues of MutL are MLH1–PMS2 (MutLα), MLH1–PMS1 (MutLβ) and MLH1–MLH3 (MutLγ). MLH1–PMS2 (MutLα) is the most active of these complexes and supports repairs initiated by the MutS complex. It possesses endonuclease activity that cleaves the defective strand near the mismatch site. MLH1–PMS1 (MutLβ) has not been shown to have significant activity in MMR in vitro studies [12]. MLH1–MLH3 (MutLγ) can participate in MMR to some extent but is primarily involved in meiotic recombination by its endonuclease activity [13,14]. The formation of MutS–MutL protein complexes, which can translocate in either direction along the DNA contour, is thought to be involved in the recruitment of an exonuclease (ExoI) and subsequent strand-specific excision. For synthesis of the leading strand, bound PCNA determines the orientation of incision by MLH1–PMS2. For the lagging strand, the 5′ ends of Okazaki fragments are thought to be important for discrimination. After the appropriate selection of the strand and the incision, PCNA coordinates with ExoI, harboring intrinsic 5′-3′ exonuclease activity, to excise the mismatch-containing region. The removed DNA segment is resynthesized by DNA polymerase δ and the repair process is completed by DNA ligase. These processes have been described in several reviews [9,10,15–17].

3. Mismatch repair genes and cancer

Approximately 2% to 5% of all colorectal cancers arise from an inherited cancer syndrome [18]. Lynch syndrome (LS), formerly known as hereditary nonpolyposis colorectal cancer (HNPCC), is caused by heterozygous germ line mutations in the DNA MMR genes MSH2, MSH6, MLH1 or PMS2 [19]. Approximately 70% to 90% of LS is estimated to be attributable to deleterious mutations in MLH1 and MSH2 (MSH2 is slightly more involved than MLH1 [20,21]), with the remaining 10% to 30% distributed equally between MSH6 and PMS2 [22]. Up to 3% of LS cases are due to mutations in the *EPCAM* gene, which encodes the epithelial cell adhesion molecule [23]. Deletions of the 3′ end of *EPCAM* mediate epigenetic alteration of MSH2 to result in mosaic epigenetic silencing of MSH2 [24].

Cancers associated with LS include colorectal, endometrial, ovarian, stomach, small bowel, hepatobiliary tract, urinary tract and skin (see below). Although LS diagnostic criteria have been published, they relied mainly on age and family history, thereby missing many LS families [25,26]. In 2009, the Jerusalem workshop recommended routine microsatellite instability (MSI) testing or immunohistochemistry for all colorectal cancers diagnosed in patients below the age of 70 years [27]. This recommendation was included in the *Evaluation of Genomic Application in Practice and Prevention* evidence report [28]. Germline mutations in the MMR genes result in the accumulation of mutations during DNA replication, particularly in repetitive sequences known as microsatellites. Defective MMR causes variations within the microsatellites, manifesting as a gain or loss in repeat length, which is called MSI.

Sebaceous neoplasms and/or keratoacanthomas in individuals and families with other internal malignancy are referred to as Muir–Torre syndrome (MTS) [29]. Germline mutations in patients with MTS most commonly affect MSH2 (>90%), followed by MLH1 (<10%) [29]. Lack of expression of MSH6 in sebaceous tumors of patients with MTS was also

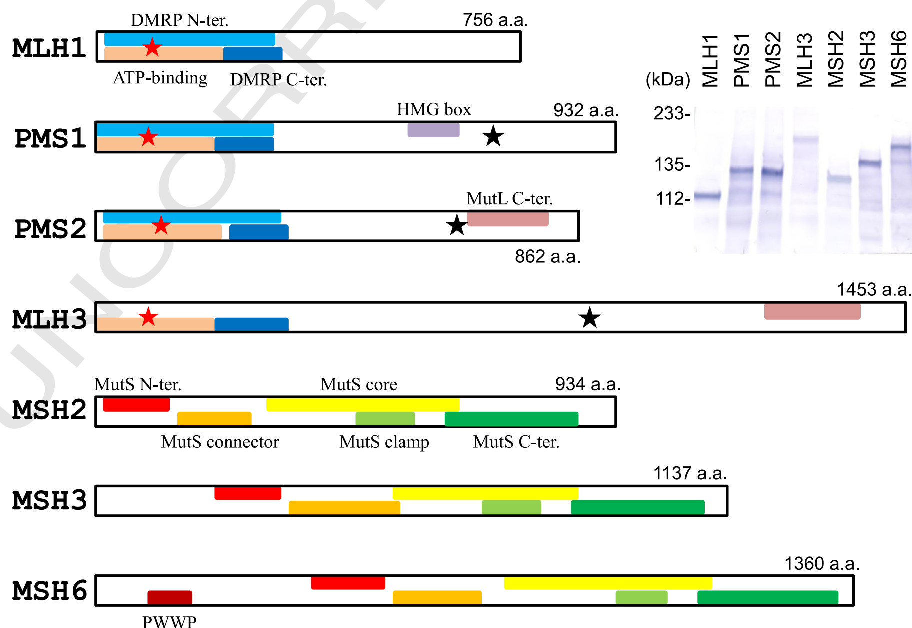

Fig. 1. The domain structures of the seven DNA mismatch-repair enzymes. The domains of the seven proteins were searched for on the InterPro website (http://www.ebi.ac.uk/interpro/), which provides functional analysis of proteins by classifying them into families and predicting domains and important sites. Each domain is shown by colored bars. The DNA mismatch-repair protein conserved sites containing heptapeptide (GFRGEAL) are shown by red stars. PMS1, PMS2 and MLH3 contain a region of 36 homologous amino acid residues depicted by black stars, which can interact with the N-terminal region of MLH1 [61]. MLH1, PMS1, PMS2 and MSH2 are reported to be autoantigens. The inset shows biotinylated recombinant protein of the seven proteins in SDS-PAGE. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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