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Review

Structural, molecular and cellular functions of MSH2 and MSH6 during DNA mismatch repair, damage signaling and other noncanonical activities

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ABSTRACT

The field of DNA mismatch repair (MMR) has rapidly expanded after the discovery of the MutHLS repair system in bacteria. By the mid 1990s yeast and human homologues to bacterial MutL and MutS had been identified and their contribution to hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome) was under intense investigation. The human MutS homologue 6 protein (hMSH6), was first reported in 1995 as a G:T binding partner (GTBP) of hMSH2, forming the hMutSα mismatch-binding complex. Signal transduction from each DNA-bound hMutSα complex is accomplished by the hMutLα heterodimer (hMLH1 and hPMS2). Molecular mechanisms and cellular regulation of individual MMR proteins are now areas of intensive research. This review will focus on molecular mechanisms associated with mismatch binding, as well as emerging evidence that MutSα, and in particular, MSH6, is a key protein in MMR-dependent DNA damage response and communication with other DNA repair pathways within the cell. MSH6 is unstable in the absence of MSH2, however it is the DNA lesion-binding partner of this heterodimer. MSH6, but not MSH2, has a conserved Phe-X-Glu motif that recognizes and binds several different DNA structural distortions, initiating different cellular responses. hMSH6 also contains the nuclear localization sequences required to shuttle hMutSα into the nucleus. For example, upon binding to O^6meG:T, MSH6 triggers a DNA damage response that involves altered phosphorylation within the N-terminal disordered domain of this unique protein. While many investigations have focused on MMR as a post-replication DNA repair mechanism, MMR proteins are expressed and active in all phases of the cell cycle. There is much more to be discovered about regulatory cellular roles that require the presence of MutSα and, in particular, MSH6.

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Abbreviations: MMR, DNA mismatch repair; HMGB1, high mobility group DNA binding protein; IRC, initial recognition complex; URC, ultimate recognition complex; CAF-1, chromatin assembly factor-1; PIP, PCNA interacting protein; NLS, nuclear localization signal; MNNG, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; TMZ, temozolomide; ATR, ataxia-telangiectasia mutated and Rad3-related; MRN, Mre11/Rad50/Nbs1 complex; HR, homologous recombination; DSB, double-strand break; BLM, Bloom syndrome helicase; ICL, interstrand crosslink.

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1. Introduction

The DNA mismatch repair system is conserved from bacteria to humans, indicative of the vital role of this pathway in all living cells. To date, the best understood DNA mismatch repair (MMR) pathway is the methyl-directed MutHLS system in *Escherichia coli*, essentially a post-replication genomic maintenance mechanism. This model has provided the basic framework for understanding eukaryotic MMR. The essential proteins required for MMR in *E. coli* have been purified to homogeneity, cloned, and the entire repair reaction has been reconstituted *in vitro*, for review [1–6]. Several eukaryotic homologues of bacterial MutS and MutL proteins have now been identified [7–13]. The MutS homologous genes identified in yeast include; *msh*1 through *msh*6, MutL homologues are *mlh1*, *pms1*, *mlh2* and *mlh3* (Wang 1998). Homologous human genes that play instrumental roles in MMR include *MSH2*, *MSH6*, *MSH3*, *MLH1* and *PMS2* [7,13–15]. Notable differences exist between bacterial and eukaryotic MMR [16]. Whereas bacterial MutS and MutL function as homodimeric proteins, eukaryotic homologues have evolved as heterodimers composed of three related, yet distinct protein subunits, MutSα (MSH2 + MSH6), MutSβ (MSH2 + MSH3) and MutLα (MLH1 + PMS2). Bacterial MMR requires a unique MMR protein – MutH – for strand discrimination by hemi-methyladenine d(GATC) sequence recognition. MutH initiates strand-directed gap repair by endonuclease activity 5′ of the unmethylated daughter strand sequence. Eukaryotes do not have hemimethylated adenines, nor an equivalent sequence-specific MutH endonuclease. Excellent reviews of the origin, evolution and diversification of the MMR gene families have been published [17,18].

The eukaryotic MutSα complex is the evolutionary product of gene duplication and divergence of homodimeric MutS. This process has resulted in two distinct proteins required for initiation of MMR, as well as for additional functions that are not required of the bacterial MMR system. MSH2 and MSH6 share five similar domains, but with sufficient differences to give MSH6 several distinct functions. MSH6 also has a unique N-terminal disordered domain that is absent in its MSH2 partner. The human MSH6 protein was first reported in 1995 as G/T mismatch binding protein (GTBP), binding partner of hMSH2 to form the MutSα complex [7,11,19]. The human *MSH6* gene includes 10 exons that encompass a total genomic sequence of 24 kb, and is located on the petite arm of chromosome 2 (2p16.3), within 1 Mb of *hMSH2*. The hMSH6 gene product is a 160 kDa protein that is unstable without heterodimerization with hMSH2, and consequently utilizes 80–90% of available hMSH2 [20].

The hMutSα heterodimer binds to DNA mispairs and short insertion deletion loops (IDLs) [7,15,21] and hMutSβ binds larger IDLs. hMutLα is a mismatch-specific endonuclease, and is the intermediary for activation of the downstream mismatch gap repair process. MMR has been reconstituted *in vitro* using extracts from mammalian cells [22–26] as well as purified proteins [16,27,28]. The least complex *in vitro* system to initiate 5′ directed mismatch excision requires MutSα, RPA, and EXO1 together with ATP. 3′ directed mismatch excision also requires MutLα, PCNA and RFC, indicating that MutLα is required to nick 5′ of the mismatch to allow efficient repair when a pre-existing nick is not present [20,27]. Therefore, to achieve bidirectional mismatch repair from a strand break located either 3′ or 5′ of a mismatch, PCNA, RFC and DNA polymerase δ are required in addition to MutSα, MutLα, RPA, and EXO1 [16]. A metal binding site on the C-terminal of PMS2 invokes a latent endonuclease property of MutLα that is essential for 3′ nick-directed repair [29]. Genetic and cellular evidence bolstering the requirement of MutLα in 3′ repair is that cells deficient in MutLα expression are able to initiate 5′ but not 3′ nick-directed MMR [30]. Additional studies using purified protein extracts have also identified the participation of a high mobility group DNA binding protein (HMGB1) in MutSα-activated EXO1 excision. HMGB1 increases the processivity of MMR-dependent excision [31]. These *in vitro* studies have contributed much to our understanding of this complex DNA repair system. Nonetheless, there are still unanswered questions, as purified proteins used for *in vitro* MMR biochemical assays do not yet perfectly mimic the complexity of MMR within the human cell.

This review will be focused primarily on MutSα, with particular emphasis on MSH6 and its functional and biochemical contributions as part of the MutSα complex. The literature in the DNA MMR field is large and illuminates a myriad of cellular pathways in which MutSα activity has been implicated. Clearly, there are still many unanswered questions left to investigate.

2. Structural insight into MSH2 + MSH6 mismatch binding

Crystallography studies reveal that eukaryotic MutSα contain several structural regions similar to the bacterial MutS complex, with the exception of the N-terminal region of MSH6 [32,33].

MSH2 and MSH6 are divided into five conserved domains (1–5) comparable to *E. coli* MutS, excluding the N-terminal disordered domain of MSH6 (Fig. 1). MutSα dimerizes from Domains 1–5 as an asymmetric mirror image with each domain juxtaposed. Domain 1 is the DNA mismatch binding domain. Domain 2 represents the connector between mismatch binding and the levers comprising Domain 3. Domain 3 folds in 2 distinct areas that, together, form a lever to Domain 5. Domain 4, the clamp region, allows for non-specific DNA contact, while Domain 5 confers adenosine binding and hydrolysis (ATPase) (Fig. 1) [32–34]. The preponderance of biochemical discovery of specific MSH6 functions has been driven based upon sequence differences from MSH2 within these five domains.

Crystal structures of human MutSα bound to a 15 basepair oligomer containing either a G:T, single base T insert, O^6-meG:T, or G:U mismatch have recently been determined [32]. Full length MSH2 and a major fragment of MSH6, containing all five domains except the first 340 amino acids comprising the N-terminal unstructured fragment, were used to obtain these protein–DNA crystal structures. The DNA binding structure of MutSα was not altered appreciably when bound to each DNA substrate, regardless that each DNA lesion is known to elicit different biological pathways. This may indicate that the hMutSα–DNA binding structure is not directly signaling different downstream pathways. Alternatively, the missing N-terminal unstructured domain of hMSH6 may play a significant role in pathway signaling [35]. In all cases, the DNA structure bound by hMutSα undergoes a bent conformation. Atomic force microscopy studies further demonstrate that DNA confers an initial bent conformation when interacting with MutS. In the presence of a mispair the DNA becomes kinked by

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