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Regulation of mismatch repair by histone code and posttranslational modifications in eukaryotic cells☆

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ABSTRACT

DNA mismatch repair (MMR) protects genome integrity by correcting DNA replication-associated mispairs, modulating DNA damage-induced cell cycle checkpoints and regulating homeologous recombination. Loss of MMR function leads to cancer development. This review describes progress in understanding how MMR is carried out in the context of chromatin and how chromatin organization/compaction, epigenetic mechanisms and posttranslational modifications of MMR proteins influence and regulate MMR in eukaryotic cells.

1. Introduction

DNA mismatch repair (MMR) ensures genome stability by correcting DNA replication-associated mispairs (see Ref. [88]), modulating DNA damage response (see Ref. [89]) and regulating homeologous recombination (see Ref. [90]). By coupling with DNA replication [1–3], MMR preserves replication fidelity by removing misincorporated bases and insertion–deletion mispairs from newly synthesized daughter DNA strands. Loss-of-function mutations or hypermethylation of MMR genes can increase the mutation frequency, and in mammalian cells, this can increase susceptibility to certain cancers, including hereditary non-polyposis colorectal cancer (HNPCC; also called Lynch syndrome) [4–7] (also see Refs. [88,91]). The eukaryotic protein components that are sufficient to reconstitute MMR in vitro on naked heteroduplex DNA include MutSα (MSH2-MSH6) and MutSβ (MSH2-hMSH3), MutLα (MLH1-PMS2 in humans and Mlh1-Pms1 in yeast), proliferating cell nuclear antigen (PCNA), exonuclease 1 (EXO1), replication protein A (RPA), replication factor C (RFC), DNA polymerase δ, and DNA ligase I [8–11].

In the past two decades, the biochemical characteristics of the MMR pathway has been extensively studied, primarily using a well-established in vitro assay and a model nucleosome-free heteroduplex DNA substrate. Those studies demonstrate that MMR is targeted specifically to the nicked (newly synthesized) DNA strand [12,13], also see Ref. [92]. It is generally accepted that MMR is initiated by the binding of MutSα or MutSβ to a mispair (either a base–base mismatch or a small insertion–deletion mispair), which triggers concerted interactions between MutSα, MutLα, PCNA and RPA, and facilitates communication between the mismatch and a strand break. Subsequently, EXO1 is recruited to a pre-existing nick or a nick generated by MutLα [14], typically lying 5′ to the mismatch on the daughter DNA strand. EXO1 then excises nascent DNA from the nick toward and beyond the mismatch to generate a single-strand gap, which is filled by polymerase δ using the parental DNA strand as template. Finally, the nick in the daughter DNA strand is ligated by DNA ligase I [15–17].

Abbreviations: MMR, mismatch repair; MSI, microsatellite instability; PCNA, proliferating cellular nuclear antigen; RPA, replication protein A; RFC, replication factor C; EXO1, exonuclease 1; H3K36me3, histone H3 lysine 36 trimethylation.

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It came as a surprise that neither purified MMR proteins nor nuclear extracts of human cells could repair DNA mismatches in the context of chromatin in vitro [18,19]. One possible explanation for this result is that chromatin structure itself inhibits communication between the mismatch and nick site. Alternatively, MutS may not efficiently recognize a DNA mispair when it is bound by a histone octamer and/or condensed in compact chromatin bound to other non-histone chromosomal proteins [20]. These observations suggest that additional factors are required for efficient MMR in human cells. Consistent with this, emerging evidence suggests that chromatin remodeling/modification factors interact with both MMR proteins and the DNA replication machinery, and that epigenetic marks on histones play a role during initiation of MMR in vivo [1,18,21–24]. Recent studies also strongly implicate post-translational modifications of MMR proteins and crosstalk between epigenetic and non-epigenetic mechanisms in regulating MMR in human cells. This review describes progress in understanding how MMR is carried out in the context of chromatin and how post-translational modifications of MMR proteins influence and regulate MMR in eukaryotic cells.

2. Role of chromatin remodeling and assembly factors in MMR

The idea that chromatin structure modulates MMR [20] and the local or regional mutation rate is not new [25]. For example, a heterotrimeric remodeling complex called RFX that regulates transcription by facilitating histone acetylation [26] also stimulates MMR in vitro [27], although a similar role in vivo has not been verified. In addition, it has been reported that human MutSα (hMutSα) can disassemble nucleosomes on heteroduplex DNA [28]. Nevertheless, fully-modified nucleosomes from HeLa cells, which presumably carry an intact HeLa cell histone code, including H3 acetylation, inhibit MMR in vitro [18,24]. Therefore, the hMutSα nucleosome disassembly activity, if present, is insufficient to support MMR on chromatin, and additional factors that allow MMR to proceed in the context of chromatin have yet to be identified.

Kadyrova et al. [21] recently showed that chromatin assembly factor 1 (CAF-I), also thought to be a histone chaperone, is required during cell-free MMR to facilitate nick-dependent nucleosome assembly. Furthermore, hMutSα suppresses CAF-1-catalyzed nucleosome assembly in a mismatch-dependent manner, and nucleosome deposition by CAF-1 following mismatch removal protects the nascent DNA strand from excessive degradation by the MMR machinery. Schopf et al. [24] also demonstrated that CAF-1-catalyzed chromatin assembly occurs more slowly on heteroduplex than on homoduplex DNA. Although the detailed mechanism is not known, PCNA is thought to coordinate MMR with nucleosome loading [24] by interacting with both the hMSH6 subunit of hMutSα [29–31] and CAF-1 [24]. Interestingly, hMutSα and CAF-1 also interact with each other [24]. It is possible that in the presence of a mispair, PCNA recruits hMutSα to the mismatch to promote MMR [32]; and after mismatches are removed, PCNA interacts with CAF-1, triggering nucleosome assembly in nascent DNA, limiting the extent of DNA excision by the MMR machinery [21,24]. Although evidence is lacking to support the idea, ubiquitylation, phosphorylation, or acetylation of PCNA might control the balance between its two roles, as reported for DNA polymerases during translesion DNA synthesis [33].

3. Role of histone modifications in MMR in vivo

Many chromatin modifying/remodeling factors contain a Pro–Trp–Trp–Pro (PWWP) domain, a member of the 'Royal Family' that also consists of Tudor, chromodomain and MBT [34]. PWWP domain-containing proteins are often involved in chromatin-associated DNA metabolisms [35]. The common feature of the "Royal Family" members is their ability to interact with methylated lysine/arginine residues in histones or other proteins through an aromatic cage [35–38]. The hMSH6 subunit of hMutSα possesses a PWWP domain [36,39], suggesting that it interacts with histone(s). Recent studies provide evidence to support this idea, showing that hMSH6 is a 'reader' for trimethylated Lys36 of histone H3 (H3K36me3) [40,41]. Surprisingly, hMutSα without the hMSH6 PWWP domain is active in MMR in vitro and forms a "normal" DNA–protein co-crystal [42] as observed for other MutS family proteins lacking a PWWP motif [43–45]. The physiological function of the hMSH6 PWWP domain and its interaction with H3K36me3 were only recently discovered [18].

Using a biochemical and cellular approach, Li et al. provided evidence that the H3K36me3-hMSH6 PWWP interaction, although dispensable in vitro, is required for MMR in vivo [18]. Both H3K36me3 and the hMSH6 PWWP domain are essential for localization of hMutSα to chromatin, a process that varies through the cell cycle according to the abundance of H3K36me3. This is because H3K36me3 peaks in late G1/early S and dips in late S/G2, effectively increasing the efficiency of MMR when MMR is needed during the cell cycle to repair replication-associated misincorporation. Cells defective in H3K36 trimethyltransferase SETD2, despite being MMR-proficient in vitro, display a mutator phenotype, as if they were functionally MMR-deficient. Recent studies have confirmed the importance of H3K36me3 in MMR and genome stability. Down-regulation of SETD2 by long non-coding RNA (LncRNA) HOTAIR leads to MSI and MMR deficiency [46]. Similarly, depletion of H3K36me3 by overexpressing H3K36me2/3 demethylases, KDM4A-C, disrupts MSH6 chromatin localization and induces a mutator phenotype [47]. Taken together, these observations strongly suggest that the H3K36me3 histone mark plays a critical role in MMR in vivo. We now understand that H3K36me3 effectively recruits hMutSα to chromatin through its interaction with the hMSH6 PWWP domain, immediately before DNA replication initiates.

A working model for the role of H3K36me3 in MMR is presented in Fig. 1. First, before cells enter S phase, SETD2 converts H3K36me2 to H3K36me3. Then, trimethylated H3K36 recruits hMutSα onto chromatin through its interaction with the hMSH6 PWWP domain. DNA replication initiates and nucleosomes are disassembled ahead of the replication fork, which also disrupts the H3K36me3-hMSH6 PWWP interaction, leading to release of hMutSα from histone octamers. hMutSα then readily binds to temporarily histone-free nascent DNA through its strong DNA binding activity and/or by interacting with PCNA via the hMSH6 PCNA-interaction protein (PIP) box. hMutSα, which possesses an ATP-dependent sliding activity [48–51], then slides along the nucleosome-free DNA [50] to locate mispairs generated during DNA replication. When hMutSα binds a mismatch, downstream MMR events ensue, such that mispaired bases are removed before mismatch-containing nascent DNA is wrapped into a nucleosome. The precise timing and sequence of events are critical, as nucleosomes inhibit MMR [19,21,24]. The discovery of the relationship between H3K36me3 histone and the precise kinetics of MMR has been an important step in understanding how the histone code contributes to high replication fidelity in eukaryotic cells, by enhancing MMR efficiency when cells need it the most.

However, there are many unanswered questions. For example, is SETD2/H3K36me3 a useful biomarker for cancer susceptibility, and might its absence correlate with microsatellite instability (MSI) in MMR-proficient cells (i.e., cells that lack mutations in MMR genes)? Could errors in the histone code explain the MSI-positive tumors, including some in HNPCC families, that do not have detectable