NIH Public Access
Author Manuscript
Cancer Res. Author manuscript; available in PMC 2014 November 01.

Published in final edited form as:
Cancer Res. 2013 November 1; 73(21): . doi:10.1158/0008-5472.CAN-13-1870.

Decoding the Histone Code: Role of H3K36me3 in Mismatch Repair and Implications for Cancer Susceptibility and Therapy

Guo-Min Li
Graduate Center for Toxicology, Markey Cancer Center, University of Kentucky College of Medicine, Lexington, Kentucky, 40536, USA; Tsinghua University School of Medicine, Beijing, 10084, China

Guo-Min Li: gmli@uky.edu

Abstract

DNA mismatch repair (MMR) maintains genome stability primarily by correcting replication-associated mismatches. Defects in MMR lead to several human cancers characterized by frequent alterations in simple repetitive DNA sequences, a phenomenon called microsatellite instability (MSI). In most MSI-positive cancers, genetic or epigenetic changes that alter the function or expression of an essential MMR protein have been identified. However, in a subset of MSI-positive cancers, epigenetic or genetic changes have not been found in known MMR genes, such that the molecular basis of the MMR defect in these cells remains unknown. A possible answer to this puzzle emerged recently when it was discovered that H3K36me3, a well-studied post-translational histone modification or histone mark, plays a role in regulating human MMR *in vivo*. In this review, we discuss potential roles for this histone mark to modulate genome stability and cancer susceptibility in human cells.

Introduction

DNA mismatch repair (MMR) is a replication-coupled reaction (1, 2), in which the repair event is targeted only to the newly synthesized DNA strand (Figure 1A), thereby ensuring exquisitely high fidelity of DNA replication. Human MMR is a multistep process summarized as follows: 1) mismatch recognition protein hMutSα (hMSH2–hMSH6) or hMutSβ (hMSH2–hMSH3) binds to a mismatch in nascent heteroduplex DNA, in a reaction that is facilitated by proliferating cell nuclear antigen (PCNA); 2) hMutS bound to nascent heteroduplex recruits hMutLα (hMLH1-hPMS2) to the complex; 3) MMR protein-DNA and protein-protein interactions facilitate recruitment of exonuclease 1 (EXO1) to a proximal DNA strand break; 4) EXO1 carries out DNA excision from the nick up to and beyond the mismatch (with DNA excision strongly dependent on the presence of hMutSα (or hMutSβ), hMutLα, and replication protein A (RPA)); and 5) DNA polymerase δ, PCNA, RPA and replication factor C (RFC) carry out gap-filling DNA synthesis, and the nick is sealed by DNA ligase I.

The importance of human MMR for genome stability was first recognized when it was discovered that genetic or epigenetic changes that impair MMR gene function or expression dramatically increase the susceptibility to certain types of cancer, including hereditary non-polyposis colorectal cancer (HNPCC) or Lynch Syndrome (3–7). Interestingly, most tumors from patients with HNPCC exhibit frequent alterations in simple repetitive DNA sequences (8), a phenomenon referred to as microsatellite instability (MSI). However, a subset of MSI-positive tumors from HNPCC patients (9) or other types of cancer (10, 11) do not carry detectable mutations or epigenetic changes (i.e., promoter hypermethylation) in known MMR genes. Recent studies have provided partial answers for this long-standing mystery. First, germline mutations affecting the proofreading nuclease activity of DNA polymerase δ

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

or ε cause hypermutation and predispose to colorectal and/or endometrial cancers (12, 13). Second, defects in histone H3 Lys36 (H3K36) trimethyltransferase SETD2 result in MSI and loss of MMR function *in vivo* (14). This review will only discuss potential roles of H3K36 methylations in MMR and implications for cancer susceptibility and therapy.

H3K36me3 is involved in MMR *in vivo*

We recently reported that trimethylated H3K36 (H3K36me3) plays a critical role during initiation of MMR *in vivo* (14), an observation that, at least in part, explains the previously-noted puzzle that some MSI-positive human cancer cells carry wild-type MMR genes and no promoter hypermethylation. Interestingly, this observation came to light in the context of our studies of *in vitro* reconstituted human MMR. In particular, while investigating the fact that MMR is relatively efficient on nucleosome-free "naked" heteroduplex DNA (15, 16) (Figure 1A), but relatively inefficient on heteroduplex DNA wrapped around histone octamers (i.e., in the context of chromatin) (17, 18), we observed that histone octamers inhibit the sliding of hMutSα along the DNA helix (17) which is thought to be essential for MMR (19). Another related observation is that H3K36me3 interacts with many proteins containing a Pro-Trp-Trp-Pro (PWWP) domain (20–22) which is present in the N-terminus of the hMSH6 subunit of hMutSα (23). After linking these three important observations, we began to investigate in detail the roles of H3K36me3 and the hMSH6 PWWP domain in human MMR. Ultimately, we provided partial explanation, as described below, for the MMR and cancer susceptibility puzzle that had remained unsolved for many years.

In this study, we observed that H3K36me3 specifically interacts with and recruits hMutSα to chromatin through the hMSH6 PWWP domain. This occurs early in S phase, prior to the initiation of DNA replication. The abundance of H3K36me3 increases and reaches a plateau in late G1/early S (14), which correlates with the most critical need for hMutSα on chromatin: namely, immediately before replication-associated mismatches form during DNA replication. Because of this, most H3K36me3 marks are bound by hMutSα (14). In contrast, the abundance of H3K36me3 decreases rapidly in late S and G2, when MMR is no longer relevant or helpful. Because H3K36me3 is responsible for recruiting hMutSα to chromatin, the H3K36-specific trimethyltransferase SETD2 is critical for MMR, and depletion of SETD2 by shRNA results in a classic MMR-deficient phenotype, characterized by MSI and an elevated mutation rate (14). Similarly, tumor cells that possess an active MMR activity but are defective in *SETD2* exhibit MSI and elevated mutation frequencies at the *HPRT* locus (14). These observations strongly indicate that the H3K36me3 histone mark plays an important role in regulating human MMR *in vivo*.

However, additional questions remain to be answered concerning this conclusion. For example, can microsatellites be stabilized in *SETD2*-deficient and MMR-proficient tumor cells when a functional SETD2 is expressed in these cells? Despite that substitutions of the H3K36me3-interacting amino acid residues of the hMSH6 PWWP domain abolish chromatin localization of ectopically-expressed hMSH6 in host cells (14), whether or not such a native hMSH6 PWWP domain mutation eliminates hMSH6 foci formation and causes an MMR-deficient phenotype is unknown. Answering these questions will provide definitive evidence for the involvement of H3K36me3 in MMR in human cells.

H3K36me3 as a potential biomarker for cancer

If H3K36me3 is proved to be essential for MMR *in vivo*, lack or depletion of H3K36me3 can cause or lead to cancer. Therefore, future studies should investigate the correlation between: 1) MSI-positive cancers, MMR status and abundance of H3K36me3; and 2) defects in H3K36me3 metabolism, MMR status and genome instability.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Our studies show that tumor cell lines defective in H3K36me3-specific trimethylatransferase SETD2 exhibit a classic MMR-deficient phenotype (14). Consistent with this observation, a subset of gastric tumors displaying MSI contain no mutations in the known MMR genes, but are defective in *SETD2* (11). Interestingly, recent exome sequencing studies have identified *SETD2* mutations, although with a low percentage, in renal cell (24–27), lung (28, 29), and hematological (30) cancers. Whether or not these *SETD2*-deficient cancers are defective in MMR remains to be determined. Similarly, future studies are also erquired to determine if *SETD2* mutations are genetic basis of some MSI-positive colorectal cancers, including HNPCC cases that lack germline mutations in MMR genes (9).

SETD2 converts H3K36me2 to H3K36me3 in mammalian cells, but it is only one of many enzymes involved in H3K36me3 metabolism. As for other epigenetic marks in the histone code, many cellular/chromatin functions are modulated by the dynamic balance between H3K36me1, H3K36me2 and H3K36me3, and defects in H3K36me3 metabolism are linked to human diseases (31, 32), including cancer. Appropriately, the abundance of H3K36me3 is tightly regulated by multiple histone methyltransferases and demethylases (Figure 1B). The SET-domain-containing proteins and the DOT1-like proteins, e.g., SETD2, SETD3, SETMAR, NSD1, NSD2, NSD3, ASH1L, and SMYD2, catalyze various forms of H3K36 methylation (Figure 1B, left side). Conversely, methylated H3K36 can be demethylated by two families of demethylases, i.e., the amine oxidases and jumonji C-domain-containing, iron-dependent dioxygenases (32) such as KDM2A, KDM2B, KDM4A, KDM4B, KDM4C and NO66 (Figure 1B, right side). Together, these enzymes ensure appropriate levels of all H3K36 variants. Our recent study demonstrates that loss of SETD2 function, which affects H3K36 trimethylation, can inactivate MMR. How defects in other histone methyltransferases or histone demethylases imbalance the H3K36 metabolism that leads to reduced H3K36me3 level is not yet known. This will be an exciting area for future study, because it has implications, as discussed below, for cancer risk prediction and cancer therapy.

H3K36me3 distribution and specific gene mutations

It is well recognized that some genes are more susceptible to mutations than others in all tissues/organs or in a specific tissue/organ. For example, *p53* is a mutation-prone genetic region for all tissues/organs, because >50% of human cancers carry base substitution or deletion mutations in *p53* (33). However, the exact mechanism leading to 'hot' genes or gene segments is not fully known.

Our recent studies show that H3K36me3 is required to recruit hMutSα to nucleosomes (14). If hMutSα chromatin localization is essential for removing mispairs generated during DNA replication as proposed (14), lack of the H3K36me3 mark in a nucleosome, and subsequent failure to localize hMutSα to the nucleosome, could potentially lead to mutations in the nucleosome-residing gene (Figure 1C). It is possible to test this prediction using chromatin immunoprecipitation and next-generation sequencing analysis (ChIP-Seq) to determine the whole genome distribution of H3K36me3, followed by comparing mutational frequencies between DNA fragments co-immunoprecipitated with nucleosomes carrying an H3K36me3 mark and those associated with nucleosomes containing no H3K36me3 mark. If H3K36me3 is indeed involved in MMR *in vivo*, the latter DNA fragments will have a mutation frequency higher than the former fragment. Both the distribution of H3K36me3 and the typical mutation spectrum are expected to vary significantly in different types of cells and tissues. By analyzing how these factors correlate with each other, we may gain significant insight into specific gene mutations in specific cancers. These studies will promote progress towards the holy grail of "personalized" medicine.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Implications for cancer therapy

It is well established that MMR plays an important role in programmed cell death (34) in cells exposed to chemotherapeutic drugs, such as temozolomide and cisplatin, which induce massive levels of DNA damage. This is because hMutSα binds to chemically-modified DNA and activates downstream events in MMR to remove the damaged DNA. Unfortunately, since MMR is a strand-specific system that targets only the newly-synthesized strand for heteroduplex repair, a "futile repair cycle" can result as the DNA lesion that activates the MMR reaction is located in the template DNA strand. Such a futile repair cycle triggers an "SOS"-like response, leading to programmed cell death (34). As a result, MMR-defective cancer cells, which fail to induce apoptosis in response to chemotherapy, fail to benefit from chemotherapy. Therefore, chemotherapy is ill-advised and may have serious deleterious consequences when given to patients with MSI-positive cancers.

With the identification of H3K36me3 as a recruiter for hMutSα, new chemotherapy options may evolve for patients with MSI-positive cancers. This is especially important for leukemia patients, for whom chemotherapy is the only option. As demonstrated in our recent study (14), cells depleted of SETD2/H3K36me3, despite possessing an active MMR system, display MSI; and restoration of H3K36me3 by transfecting yeast *Set2* in these cells restores hMutSα chromatin localization (14), thereby restoring MMR *in vivo*. Therefore, it is possible that transfection of cancer cells with SETD2 methyltransferase could reestablish normal MMR function in cells lacking H3K36me3 and facilitate effective chemotherapy. However, future preclinical studies must first confirm that H3K36me3 is expressed properly in transfected human cancer cells before chemotherapy can be tested in the clinic.

Formally, it may also be possible to restore drug sensitivity to MMR gene-defective cancer cells by direct MMR gene therapy. However, this is a very challenging task, likely to fail, unless the ectopically-expressed MMR protein is expressed at the correct stoichiometry to endogenous MMR proteins. This is because expression of the MMR gene at a high or low level kills patients' normal cells (35) or fails to achieve drug-sensitivity, respectively. However, high-level expression of H3K36me3 appears to have little influence on cell killing (36). Nevertheless, additional studies are needed to develop and fine-tune a method to deliver effective chemotherapy to all patients with MSI-positive cancers.

Reevaluating hMSH6 PWWP germline mutations in HNPCC

Several germline mutations have been identified in the hMSH6 PWWP domain in HNPCC kindreds, including R128L, W142X (X stands for a unspecified residue), S144I, and S156X (37–40). These mutations do not affect MMR function when assessed using a functional *in vitro* MMR assay (37, 38). In addition, the N-terminal 340 amino acid residues of hMSH6, which include the entire PWWP domain, are not required for *in vitro* MMR (41). Therefore, these germline mutations were previously thought to be unrelated to the HNPCC phenotype, even though other disease-causing mutations were not identified. Our recent studies confirm that the hMSH6 PWWP domain is not required for MMR *in vitro*; however, we now show that the H3K36me3-interacting residues Y_{103}, W_{106} and F_{133}, are critical for recruiting hMutSα to chromatin *in vivo* (14). This interesting observation clearly deserves additional study, with a careful examination of the role of the hMSH6 PWWP domain in MMR.

We hypothesize that some residues in the PWWP domain that do not interact with H3K36me3 are nevertheless critical, because they are needed to maintain the aromatic cage structure formed by residues Y_{103}, W_{106}, and F_{133}. As such, defects in these residues could also impair MMR *in vivo*, leading to genome instability and cancer susceptibility.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Additional structural and functional studies are needed to explore these possibilities and to clarify the genetic basis of all cases of HNPCC.

Perspectives

Previous studies have established that the histone code, including histone acetylation, ubiquitylation, phosphorylation and methylation, plays an important role in regulating gene expression through its ability to modulate chromatin compaction/organization and interactions between chromatin and protein and/or nucleic acid complexes. Our recent finding that H3K36me3 functions as a regulator of a genome maintenance system in MMR expands our concept of the realm of influence of the histone code. Additional studies are needed to fully 'decode' the histone code, including detailed investigation of how H3K36me3 and other histone modifications modulate genome maintenance pathways and other cellular pathways and events. If one considers the histone code as a library, H3K36me3 is just the most highly cited chapter of one book in a large library with many volumes. In other words, this is the proverbial 'tip of the iceberg'. The language of the H3K36me3 chapter is not fully readable at this time because its interaction with hMutSα is one of many similar interactions with PWWP-containing proteins (20–22). How H3K36me3-dependent processes, including MMR, chromatin remodeling and transcription, are coordinated throughout the cell cycle remains to be investigated.

Human cells possess at least two mismatch recognition proteins, hMutSα (hMSH2–hMSH6) and hMutSβ (hMSH2–hMSH3). Unlike hMSH6, hMSH3 does not contain a PWWP domain, suggesting that H3K36me3 may not regulate hMutSβ-dependent MMR. Does hMutSβ recruitment requires a different histone modification? Like hMutSβ, yeast MutS proteins do not contain a PWWP domain. However, yeast MutSα is localized to chromatin/the replication machinery in a mismatch-independent manner (1), possibly before replication initiates, similar to hMutSα. Therefore, hMutSβ may also be recruited to chromatin through a histone mark, even though it lacks a PWWP domain. Histone modifications could also regulate other DNA pathways such as base excision repair, nucleotide excision repair and double strand break repair. As these fascinating research areas are explored, and the histone code is 'decoded,' new opportunities for cancer detection and therapy are likely to emerge.

Acknowledgments

The author acknowledges research support from the National Institutes of Health (CA167181 and GM089684) and the Kentucky Lung Cancer Research Program. Due to the restriction of the number of citations permitted, the author regrets the lack of citations for many important observations mentioned in the article. The author holds the James-Gardner Chair in Cancer Research.

References

1. Hombauer H, Campbell CS, Smith CE, Desai A, Kolodner RD. Visualization of eukaryotic DNA mismatch repair reveals distinct recognition and repair intermediates. Cell. 2011; 147:1040–1053. [PubMed: 22118461]
2. Simmons LA, Davies BW, Grossman AD, Walker GC. Beta clamp directs localization of mismatch repair in Bacillus subtilis. Mol Cell. 2008; 29:291–301. [PubMed: 18280235]
3. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell. 1993; 75:1027–1038. [PubMed: 8252616]
4. Parsons R, Li GM, Longley MJ, Fang WH, Papadopoulos N, Jen J, et al. Hypermutability and mismatch repair deficiency in RER+ tumor cells. Cell. 1993; 75:1227–1236. [PubMed: 8261516]

NIH-PA Author Manuscript

5. Leach FS, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, et al. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell. 1993; 75:1215–1225. [PubMed: 8261515]

6. Umar A, Boyer JC, Thomas DC, Nguyen DC, Risinger JI, Boyd J, et al. Defective mismatch repair in extracts of colorectal and endometrial cancer cell lines exhibiting microsatellite instability. J Biol Chem. 1994; 269:14367–14370. [PubMed: 8182040]

7. Kane MF, Loda M, Gaida GM, Lipman J, Mishra R, Goldman H, et al. Methylation of the hMLH1 promoter correlates with lack of expression of hMLH1 in sporadic colon tumors and mismatch repair-defective human tumor cell lines. Cancer Res. 1997; 57:808–811. [PubMed: 9041175]

8. Aaltonen LA, Peltomäki P, Leach FS, Sistonen P, Pylkkänen L, Mecklin J-P, et al. Clues to the pathogenesis of familial colorectal cancer. Science. 1993; 260:812–816. [PubMed: 8484121]

9. Peltomaki P. Role of DNA mismatch repair defects in the pathogenesis of human cancer. Journal of clinical oncology. 2003; 21:1174–1179. [PubMed: 12637487]

10. Gu L, Cline-Brown B, Zhang F, Qiu L, Li GM. Mismatch repair deficiency in hematological malignancies with microsatellite instability. Oncogene. 2002; 21:5758–5764. [PubMed: 12173046]

11. Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. Nat Genet. 2011; 43:1219–1223. [PubMed: 22037554]

12. Church DN, Briggs SE, Palles C, Domingo E, Kearsey SJ, Grimes JM, et al. DNA polymerase {varepsilon} and delta exonuclease domain mutations in endometrial cancer. Hum Mol Genet. 2013; 22:2820–2828. [PubMed: 23528559]

13. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013; 45:136–144. [PubMed: 23263490]

14. Li F, Mao G, Tong D, Huang J, Gu L, Yang W, et al. The Histone Mark H3K36me3 Regulates Human DNA Mismatch Repair through Its Interaction with MutSalpha. Cell. 2013; 153:590–600. [PubMed: 23622243]

15. Constantin N, Dzantiev L, Kadyrov FA, Modrich P. Human mismatch repair: Reconstitution of a nick-directed bidirectional reaction. J Biol Chem. 2005; 280:39752–39761. [PubMed: 16188885]

16. Zhang Y, Yuan F, Presnell SR, Tian K, Gao Y, Tomkinson AE, et al. Reconstitution of 5'-directed human mismatch repair in a purified system. Cell. 2005; 122:693–705. [PubMed: 16143102]

17. Li F, Tian L, Gu L, Li GM. Evidence that nucleosomes inhibit mismatch repair in eukaryotic cells. J Biol Chem. 2009; 284:33056–33061. [PubMed: 19808662]

18. Schopf B, Bregenhorn S, Quivy JP, Kadyrov FA, Almouzni G, Jiricny J. Interplay between mismatch repair and chromatin assembly. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109:1895–1900. [PubMed: 22232658]

19. Gradia S, Acharya S, Fishel R. The human mismatch recognition complex hMSH2–hMSH6 functions as a novel molecular switch. Cell. 1997; 91:995–1005. [PubMed: 9428522]

20. Musselman CA, Avvakumov N, Watanabe R, Abraham CG, Lalonde ME, Hong Z, et al. Molecular basis for H3K36me3 recognition by the Tudor domain of PHF1. Nature structural & molecular biology. 2012; 19:1266–1272.

21. Vezzoli A, Bonadies N, Allen MD, Freund SM, Santiveri CM, Kvinlaug BT, et al. Molecular basis of histone H3K36me3 recognition by the PWWP domain of Brpf1. Nat Struct Mol Biol. 2010; 17:617–619. [PubMed: 20400950]

22. Wagner EJ, Carpenter PB. Understanding the language of Lys36 methylation at histone H3. Nature reviews Molecular cell biology. 2012; 13:115–126.

23. Laguri C, Duband-Goulet I, Friedrich N, Axt M, Belin P, Callebaut I, et al. Human mismatch repair protein MSH6 contains a PWWP domain that targets double stranded DNA. Biochemistry. 2008; 47:6199–6207. [PubMed: 18484749]

24. Dalgliesh GL, Furge K, Greenman C, Chen L, Bignell G, Butler A, et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature. 2010; 463:360–363. [PubMed: 20054297]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

25. Duns G, van den Berg E, van Duivenbode I, Osinga J, Hollema H, Hofstra RM, et al. Histone methyltransferase gene SETD2 is a novel tumor suppressor gene in clear cell renal cell carcinoma. Cancer Res. 2010; 70:4287–4291. [PubMed: 20501857]
26. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. The New England journal of medicine. 2012; 366:883–892. [PubMed: 22397650]
27. Varela I, Tarpey P, Raine K, Huang D, Ong CK, Stephens P, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. Nature. 2011; 469:539–542. [PubMed: 21248752]
28. Govindan R, Ding L, Griffith M, Subramanian J, Dees N, Walker KL, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012; 150:1121–1134. [PubMed: 22980976]
29. Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell. 2012; 150:1107–1120. [PubMed: 22980975]
30. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012; 481:157–163. [PubMed: 22237106]
31. Albert M, Helin K. Histone methyltransferases in cancer. Semin Cell Dev Biol. 2010; 21:209–220. [PubMed: 19892027]
32. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet. 2012; 13:343–357. [PubMed: 22473383]
33. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science. 1991; 253:49–53. [PubMed: 1905840]
34. Li GM. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008; 18:85–98. [PubMed: 18157157]
35. Zhang H, Richards B, Wilson T, Lloyd M, Cranston A, Thorburn A, et al. Apoptosis induced by overexpression of hMSH2 or hMLH1. Cancer Res. 1999; 59:3021–3027. [PubMed: 10397236]
36. Luco RF, Pan Q, Tominaga K, Blencowe BJ, Pereira-Smith OM, Misteli T. Regulation of alternative splicing by histone modifications. Science. 2010; 327:996–1000. [PubMed: 20133523]
37. Kariola R, Hampel H, Frankel WL, Raevaara TE, de la Chapelle A, Nystrom-Lahti M. MSH6 missense mutations are often associated with no or low cancer susceptibility. Br J Cancer. 2004; 91:1287–1292. [PubMed: 15354210]
38. Kariola R, Raevaara TE, Lonnqvist KE, Nystrom-Lahti M. Functional analysis of MSH6 mutations linked to kindreds with putative hereditary non-polyposis colorectal cancer syndrome. Hum Mol Genet. 2002; 11:1303–1310. [PubMed: 12019211]
39. Kolodner RD, Tytell JD, Schmeits JL, Kane MF, Gupta RD, Weger J, et al. Germ-line msh6 mutations in colorectal cancer families. Cancer Res. 1999; 59:5068–5074. [PubMed: 10537275]
40. Wu Y, Berends MJ, Mensink RG, Kempinga C, Sijmons RH, van Der Zee AG, et al. Association of hereditary nonpolyposis colorectal cancer-related tumors displaying low microsatellite instability with MSH6 germline mutations. Am J Hum Genet. 1999; 65:1291–1298. [PubMed: 10521294]
41. Warren JJ, Pohlhaus TJ, Changela A, Iyer RR, Modrich PL, Beese LS. Structure of the human MutSalpha DNA lesion recognition complex. Mol Cell. 2007; 26:579–592. [PubMed: 17531815]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

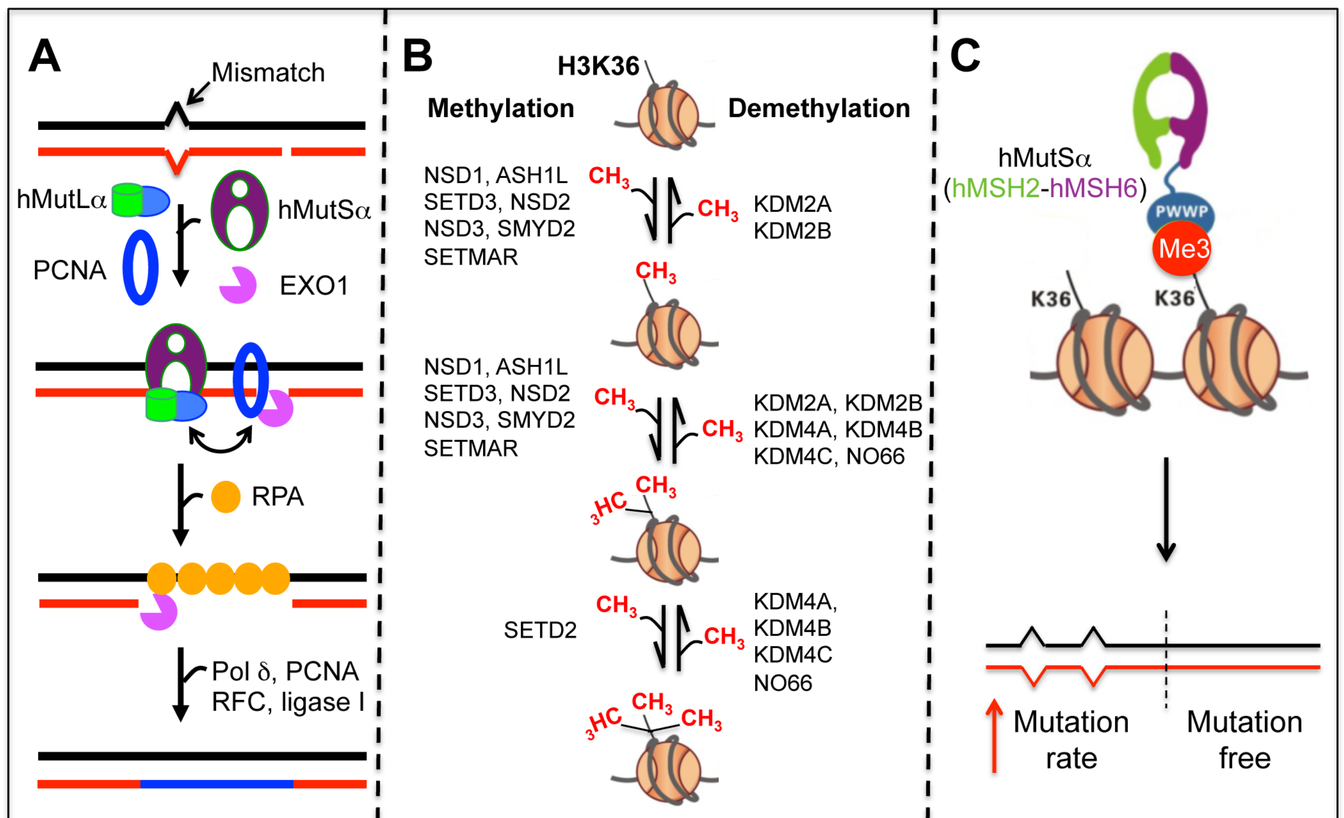

Figure 1. Influence of H3K36me3 on MMR and genome stability

A. DNA mismatch repair (MMR) reaction. MMR in human cells is nick-directed and targeted to the newly-synthesized strand. MMR begins with mismatch recognition by hMutSα or hMutSβ (not shown), which triggers concerted interactions/communications among hMutSα, hMutLα and PCNA, leading to the recruitment of EXO1 at a nick. EXO1 then excises the mismatch to generate a single-stranded DNA gap, which is filled by DNA polymerase (pol) δ in the presence of PCNA, RFC and RPA, followed by ligase I-catalyzed nick ligation. B. Regulation of H3K36me3 level by histone methyltransferases (left) and histone demethylases (right). C. Proposed model for modulation of specific gene mutation by H3K36me3.