Control of replication associated DNA damage responses by Mismatch Repair

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Chapter 2:

DNA mismatch repair-dependent DNA damage responses and cancer

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Abstract

Canonical DNA mismatch repair (MMR) excises base-base mismatches to increase the fidelity of DNA replication. Thus, loss of MMR leads to increased spontaneous mutagenesis. MMR genes also are involved in the suppression of mutagenic, and the induction of protective, responses to various types of DNA damage. In this review we describe these non-canonical roles of MMR at different lesion types. Loss of non-canonical MMR gene functions may have important ramifications for the prevention, development and treatment of colorectal cancer associated with inherited MMR gene defects in Lynch syndrome. This graphical review pays tribute to Samuel H. Wilson. Sam not only made seminal contributions to understanding base excision repair, particularly with respect to structure-function relationships in DNA polymerase β but also, as Editor of DNA Repair, has maintained a high standard of the journal.

Main text

High-fidelity DNA replication is crucial to preserve the genomic integrity of eukaryotic cells and, consequently, is beneficial for organismal health. Although DNA replication by the processive DNA polymerases δ and ε is highly accurate, inadvertent nucleotide misincorporations occasionally do occur. Polymerase selectivity and proofreading are the first lines of defense against such misincorporations (1). When a misincorporation escapes proofreading, DNA mismatch repair (MMR) provides a last line of defense. Consequently, inactivation of any of the MMR genes causes a spontaneous mutator phenotype (2).

In addition to correcting base-base mismatches, MMR plays multiple roles in responses to a wide spectrum of DNA damage-induced mutagenic insults (Fig. 1), including methylated nucleotides, oxidative DNA lesions, interstrand crosslinks (ICLs) and helix-distorting nucleotide lesions. Helix-distorting DNA lesions include a variety of nucleotide lesion types, including intrastrand crosslinks induced by ultraviolet (UV) light and bulky nucleotide adducts induced by dietary compounds such as the heterocyclic amines 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and the polycyclic aromatic hydrocarbon (PAH) benzo(a)pyrene (BaP) (3, 4).

The role of MMR in DNA damage responses has been described most comprehensively for monofunctional methylating agents that, amongst others, methylate the O^6 position of guanine. When unrepaired by O^6-Methylguanine-DNA methyltransferase (MGMT) (Fig. 2A), O^6-methylguanine can be replicated by either the replicative polymerases δ and ε or by the translesion synthesis (TLS) polymerase η (5) (Fig. 2B). The methylation of guanine alters its tautomeric state, allowing it to base-pair with both cytosine and thymine during replication (6). The MMR machinery excises the thymidine in the daughter strand of O^6-methylguanine:thymine mismatches, together with a tract of adjacent nucleotides. However, during gap filling, O^6-methylguanine again may direct misincorporation of thymine, which results in recurrent cycling between excision and error-prone gap filling (Fig. 2C). During the next cell cycle the excision tracts lead to double stranded DNA breaks by replicative run-off (7). These double stranded DNA breaks induce apoptosis or genomic deletions and rearrangements when mis-repaired (Fig. 2D). Thus, MMR-induced damage responses ultimately prevent the accumulation of G>A transitions and, when the damage load exceeds a threshold, protects the cell from genomic instability by inducing delayed apoptosis.

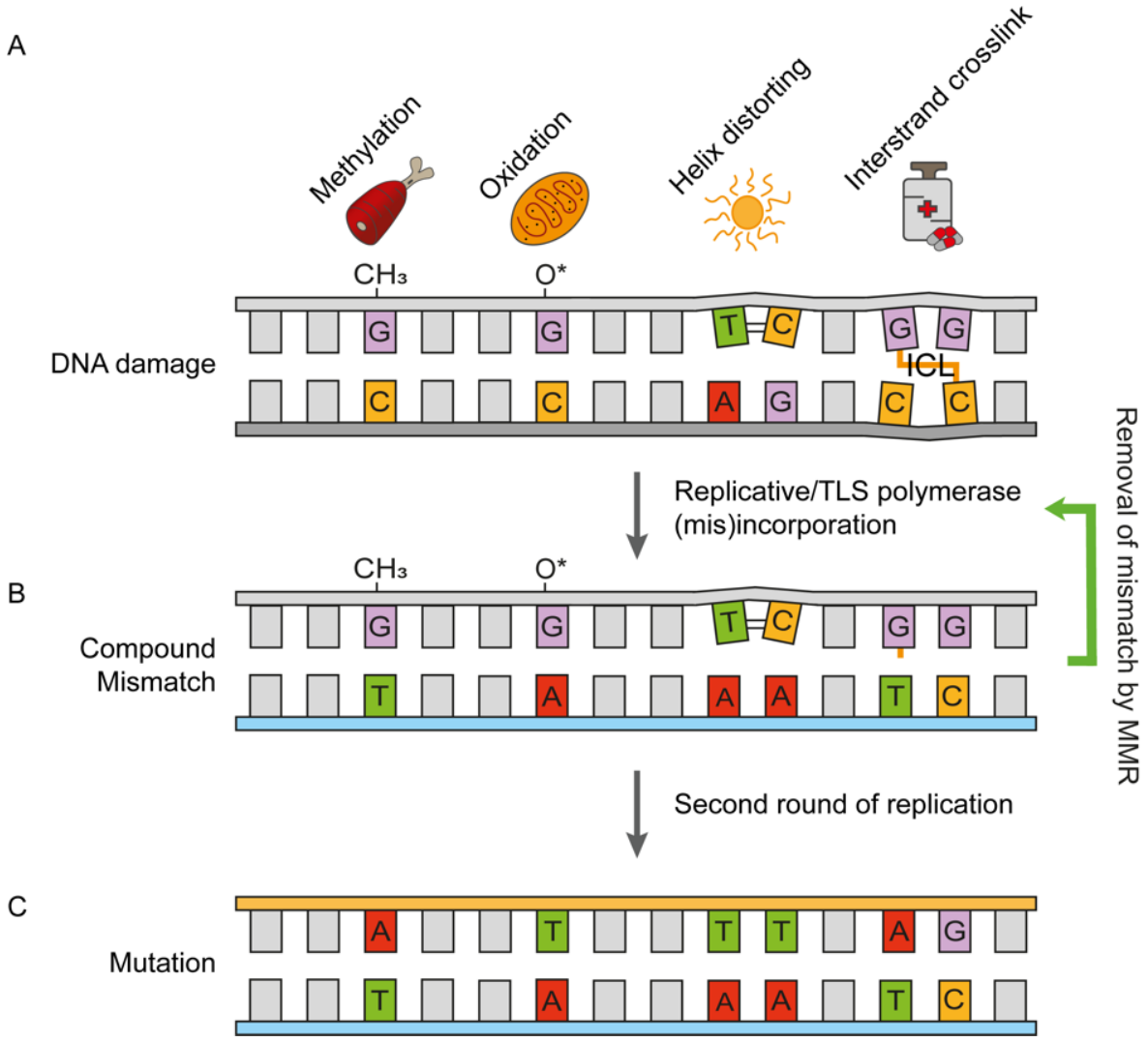

Figure 1| Replication of damaged DNA
A: DNA is continuously threatened by multiple sources of DNA damage, including diet (e.g. red meat), radical oxygen species (dysfunctional mitochondria), UV radiation (sunlight) and various (cytostatic) drugs leading to methylation (CH_3), oxidation (O*) or helix distorting DNA damage (=), as well as interstrand crosslinks (ICL). B: DNA damages are replicated by either replicative polymerases or TLS polymerases, leading to different types of compound mismatches. C: When mismatches remain in the DNA, mutation fixation occurs during successive rounds of replication. Mismatch repair/post-TLS repair may remove misincorporations, preventing DNA damage-induced mutagenesis.

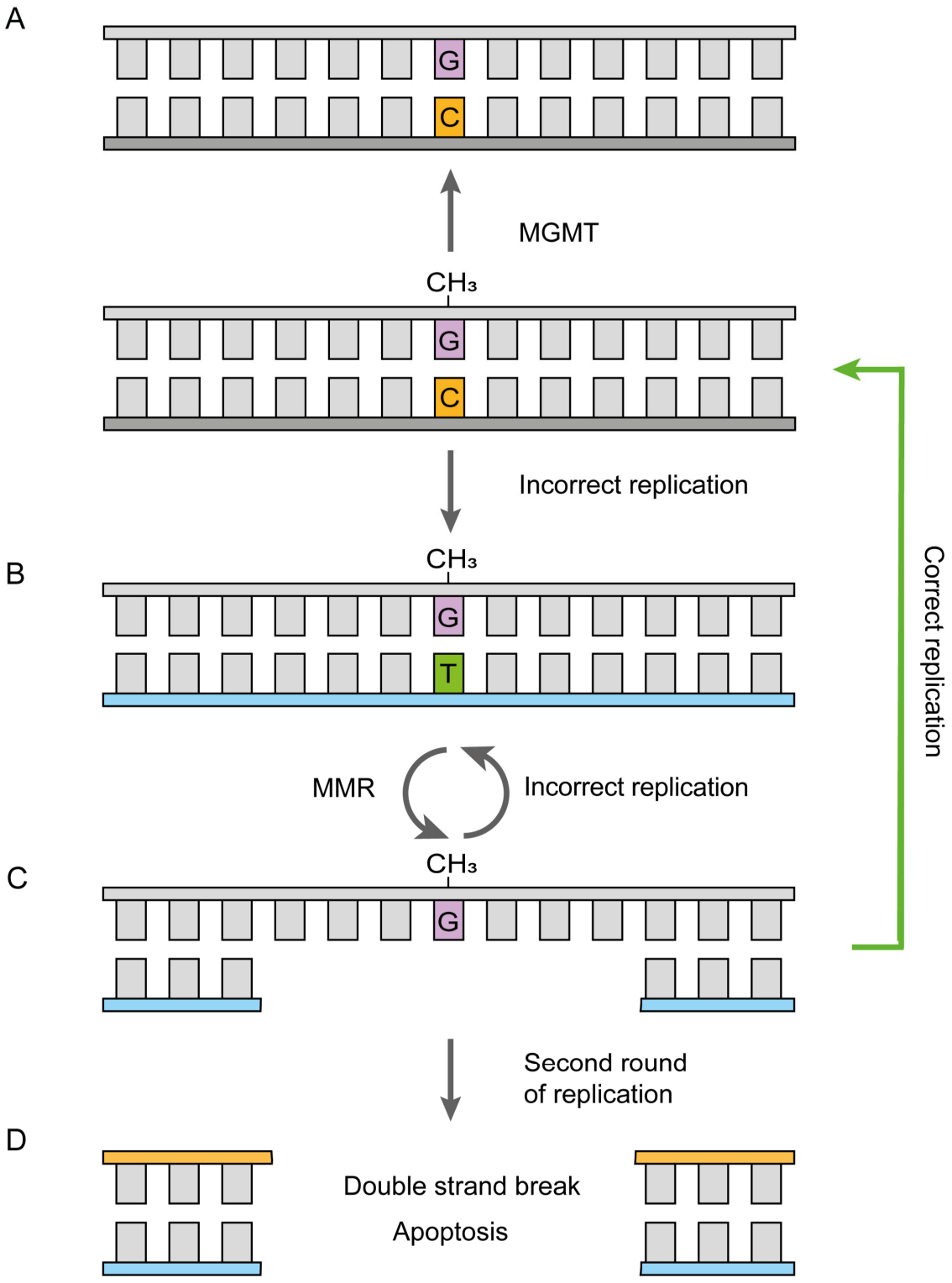

Figure 2| Roles of MMR in responses to O^6-methylguanine
A: O^6-methylguanine (CH_3) can be repaired by O^6-Methylguanine-DNA methyltransferase (MGMT) leading to damage reversal. B: Replication of O^6-methylguanine can lead to a O^6-methylguanine.T mismatch, which can be removed by MMR resulting in a transient single stranded DNA tract. C: Gap filling can either lead to incorporation of a cytosine or to another misincorporation, that again is a substrate for MMR. D: Futile cycles of excision and misincorporation can lead to recurrent ssDNA tracts. In a subsequent round of replication these can lead to double stranded DNA breaks and consequent rearrangements or apoptosis.

Cells are under constant assault from oxidative DNA damage, induced by reactive oxygen species (ROS) (8). Again, guanines seem to be a preferred target, with 8-oxoguanine being a predominant oxidative DNA lesion (9). Similar to O^6-methylguanine, replication of this damaged base can lead to a misincorporation, most frequently adenine (10) that can be excised by MMR and MUTYH (11) to reduce the mutagenicity of 8-oxoguanine (Fig. 3A). In addition, MMR-deficient cells retain a higher amount of oxidative lesions in the DNA than MMR-proficient cells (12). Overexpression of *MTH1,* which removes 8-oxoguanines from the nucleotide pool, reduces both spontaneous and oxidatively induced mutagenesis in MMR-deficient cells. These data indicate that MMR also excises 8-oxoguanine, incorporated from the nucleotide pool opposite adenine during replication. In contrast, removal of the template adenine by MUTYH results in mutagenesis (Fig. 3B) (13). Moreover, they suggest that oxidative DNA damage derived from the pool may significantly contribute to the spontaneous mutator phenotype of MMR-deficient cells.

In contrast to methylation and oxidative base damage, helix-distorting nucleotide lesions are poorly instructive and therefore arrest the processive DNA replication machinery. To counteract the toxicity of such lesions the cell employs specialized TLS DNA polymerases that can replicate across the damaged nucleotides, albeit in an error-prone fashion, resulting in DNA damage-directed mutagenesis (14). Interestingly, MMR can suppress this mutagenesis and increases checkpoint activation and apoptosis induced by UV, PhIP and BaP [(4, 15), Ijsselsteijn *et al.* manuscript in preparation]. In support, the MMR heterodimer MSH2-MSH6 is recruited to sites of localized UV damage (16) and selectively binds “mismatched” but not “matched” nucleotides opposite photolesions (17). The mechanistic basis for the involvement of MMR proteins in responses to such DNA lesions is not yet fully elucidated, but it has been suggested that a non-canonical MMR pathway, dubbed “post-TLS repair”, excises the nucleotide that was mis-incorporated by TLS opposite the damaged nucleotide. Thereby, post-TLS repair decreases DNA damage-induced mutagenesis while the resulting lesion-containing single-stranded DNA tracts activate DNA damage signaling (Fig. 4) (15). Another model to explain the increased mutagenesis by photolesions suggests that MMR plays a role in the recruitment of the relatively error-free TLS polymerase η, via Proliferating Cell Nuclear Antigen (PCNA) mono-ubiquitination (18, 19). However, knocking out both Polymerase η and *Msh6* in mouse embryonic stem cells shows a synergistic, rather than an epistatic, response to UV radiation in terms of mutagenesis (Ijsselsteijn *et al.* manuscript in preparation), supporting the post-TLS repair model.

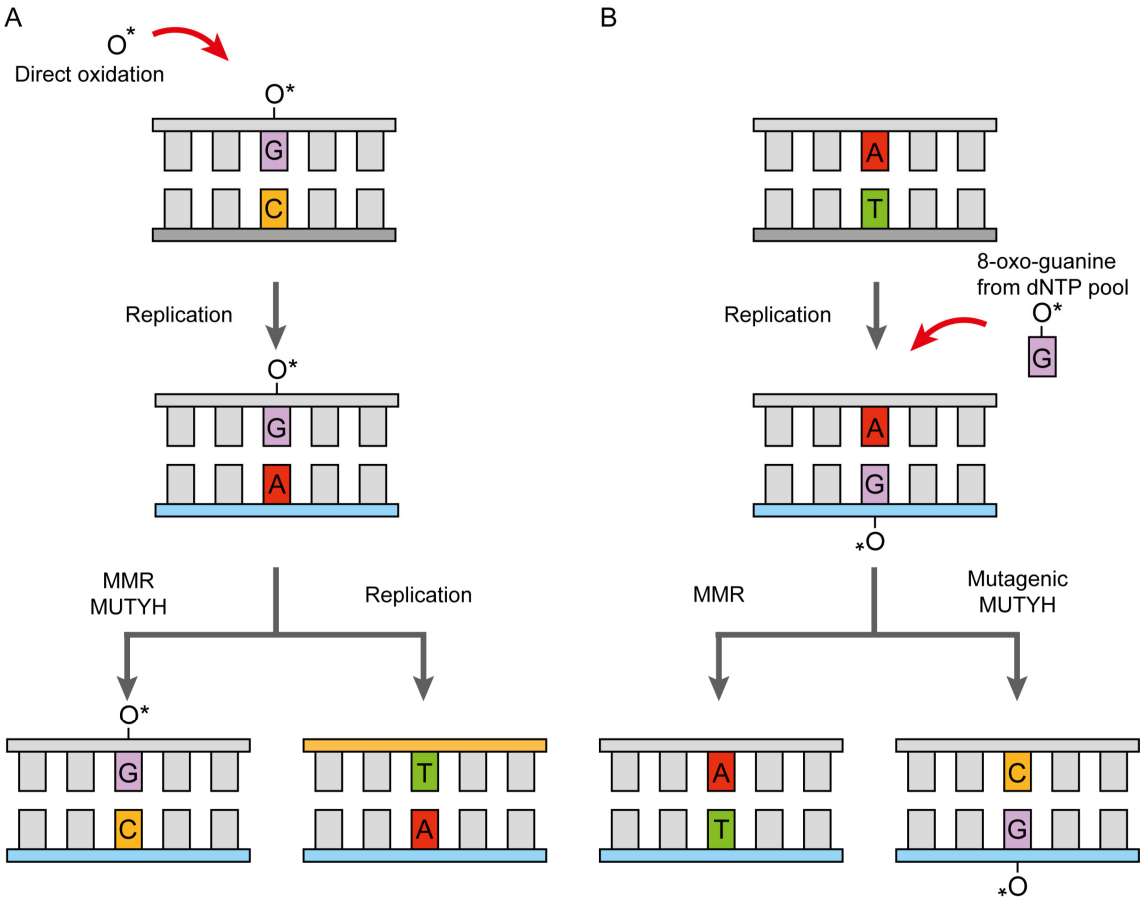

Figure 3|Processing of 8-oxoguanine.Adenine 'mispairs' by MMR and MUTYH
A: Guanines in the DNA can be oxidized by reactive oxygen species (ROS) to 8-oxoguanines (O*). Replication can lead to misincorporations of mostly adenines opposite 8-oxoguanines. When not removed by MMR and MUTYH, these misincorporations result in G>T transversions. B: Guanines that are oxidized (O*) in the free dNTP pool can be incorporated in the DNA opposite adenines. MMR recognizes these mismatches and removes the 8-oxoguanines from the DNA. In contrast, inadvertent repair of the nucleotide opposite the 8-oxoguanine by MUTYH leads to a mutation.

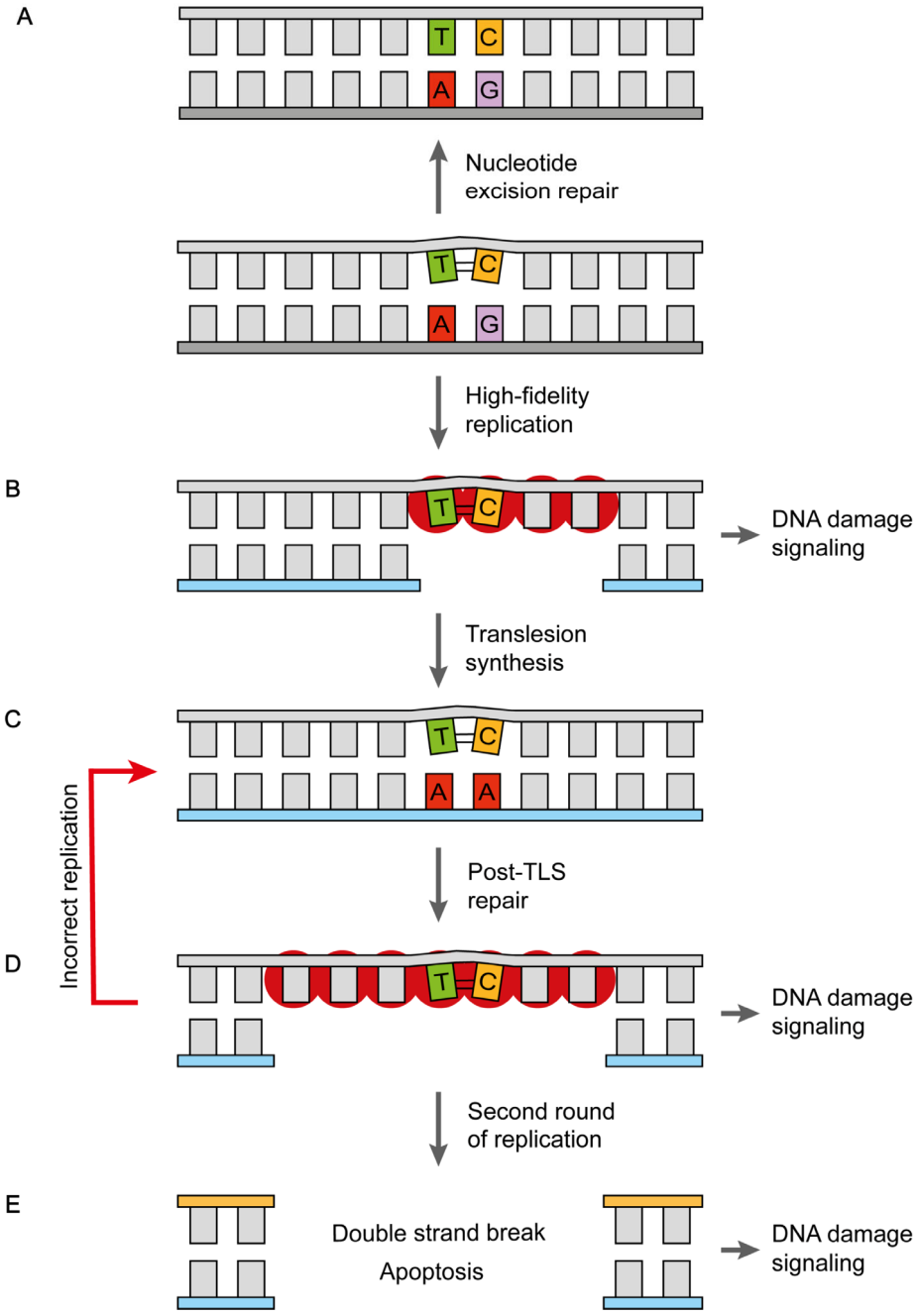

Figure 4| The role of MMR/post-TLS repair in responses to helix-distorting DNA damage
A: Exposure of DNA to sunlight (UV-light) results in helix-distorting nucleotide lesions (=) that can be repaired by nucleotide excision repair. B: Unrepaired helix-distorting nucleotide lesions arrest replicative polymerases resulting in single-stranded DNA tracts. When sufficiently long, these are coated by Replication Protein A (RPA ●) multimers, activating DNA damage signaling. TLS can replicate across the damaged nucleotides to mitigate their toxicity. C: TLS often leads to a 'misincorporation' opposite the lesion. Such a compound lesion can be recognized by post-TLS repair, likely resulting in long excision tracts. D: The resulting single-stranded DNA gap is coated by RPA multimers. Filling of these extended gaps by, successively, replicative and TLS polymerases may be a lengthy process and, therefore, underlie the strong post-TLS repair-associated DNA damage response. E: Persistent ssDNA can lead to a double stranded DNA break in the subsequent cell cycle, resulting in apoptotic signaling (3, 15).

One of the most difficult to repair DNA damages are ICLs that require a multi-step process where multiple repair pathways converge to repair the covalent linking of two opposite DNA strands. ICLs can result from aldehydes, derived from ethanol or from lipid peroxidation, from some vegetables and they are also induced by several chemotherapeutics, such as Cisplatin, used in the treatment of (amongst others) breast cancer. The repair of ICLs involves Fanconi Anemia (FA)-associated proteins, but also requires homologous recombination, TLS and in some cases nucleotide excision repair (20). It has been suggested that MMR-deficient cells display reduced sensitivity to ICL-inducing agents, indicating a role for MMR in responses to ICLs (21). 'Misincorporations', generated during gap-filling by TLS opposite the unhooked ICL might be a substrate for MMR, comparable to post-TLS repair of UV-induced intra-strand crosslinks (15). For specific ICLs, base excision repair polymerase β (Polβ) and MMR play an epistatic role. Both the toxicity and repair of ICLs are diminished in cells, knocked down for MSH2, MLH1 or Polβ, but is not further reduced in a double knock-down of Polβ and MSH2 or MLH1 (21), suggesting that the role of MMR is post-replicative and linked to Polβ.

Absence of MMR/post-TLS repair causes both a spontaneous mutator phenotype and increased DNA damage-induced mutagenesis, as well as aberrant DNA damage responses. It therefore is not surprising that loss of MMR/post-TLS repair is strongly associated with carcinogenesis (22). As mentioned before, MMR/post-TLS repair deficiency results in tolerance of various types of DNA damage and thus MMR/post-TLS repair-deficient cancers might benefit from a targeted treatment. For instance, the tolerance of MMR/post-TLS repair-deficient cells to chemotherapeutic drugs that induce O^6-methylguanines, such as Dacarbazine and Temozolomide, indicates that these agents may be ineffective for the treatment of MMR/post-TLS repair-deficient tumors. Furthermore, exposure of MMR-proficient cells to DNA-damaging drugs might lead to selection for MMR/post-TLS repair-deficiency. For instance, glioblastomas have been shown to acquire tolerance to Temozolomide by inactivating MMR/post-TLS repair (23). Another example is provided by acute myeloid leukemia (AML), which can be a late consequence of immunosuppression by Azathioprine after organ transplantation (24). Its S^6-(thio)guanine metabolite is methylated endogenously and induces MMR-dependent cytotoxicity, which leads to selection of MMR/post-TLS repair-deficient cells. Also, recurring AML in non-transplant patients is often MMR/post-TLS repair deficient, which might be associated with acquired tolerance to treatment of the primary AML with 6-thioguanine (25, 26). Melanomas frequently display hallmarks of MMR/post-TLS repair deficiency too (27). Sunlight, which is the major etiological agent of these tumors, induces not only intrastrand DNA crosslinks but also oxidative DNA damage (28). As described above, MMR/Post-TLS repair is associated with protective responses to both types of DNA lesions, which might provide a rationale for its loss in melanoma. Finally, MMR is lost in 15% of the sporadic colorectal cancers (CRC) (29). The mechanism of action of most chemotherapeutic treatments of CRC is based on the induction of DNA damage, leading to senescence or death of the rapidly cycling tumor cells. For instance, 5-fluoruracil (5-FU) is incorporated in RNA but also

causes nucleotide pool imbalances, while its metabolite 5-FdU can be incorporated in DNA instead of thymidine. MMR-deficient cells display a mild tolerance to 5-FU, suggesting a role for MMR in processing misincorporations due to nucleotide pool imbalances as well as misincorporations opposite 5-FdU residues (30). In support, treatment with 5-FU provides no benefit to MMR-deficient CRC (31).

Apart from the causal involvement of MMR deficiency in sporadic cancer, inheritance of a germline mutation in one allele of any of the four MMR genes is responsible for the common cancer predisposition Lynch syndrome, historically called Hereditary Non-Polyposis Colorectal Cancer (HNPCC). Carriers have an approximate 40-60% risk of developing gastrointestinal tumors and, for females, approximately 40% risk of endometrial tumors, depending on which MMR gene is mutated (32). Inheritance of a bi-allelic germline mutation in one of the MMR genes leads to constitutional MMR deficiency (cMMRd), a childhood cancer syndrome. In contrast to Lynch syndrome, cMMRd involves a wide spectrum of tumors, which is dominated by brain, hematological and intestinal cancers (33). The prevalence of sporadic MMR deficiency in CRC and the restricted cancer tropism in Lynch syndrome, as compared with cMMRd, suggest that roles of MMR/post-TLS repair in the intestine, beyond the correction of simple base-base mismatches are involved in the development of these cancers.

Cancer development requires an array of mutagenic (tumor initiation and progression) and non-mutagenic (tumor promotion and progression) events. The exposure of intestinal epithelial cells to endogenous and food-derived mutagenic compounds is pertinent to all stages of oncogenesis (34), but might be even more so in the development of MMR/post-TLS repair-deficient cancer. For instance, in gastrointestinal stem cells from individuals with Lynch syndrome, these compounds can promote the mutational inactivation of the remaining wild-type allele of the germ-line mutated MMR gene (Fig. 5). The resulting MMR/post-TLS repair-deficient cells may be prone to oncogenic derailment in different ways. For example, exposure to butyrate produced by the intestinal microbiome from carbohydrates, may provide a specific growth advantage to MMR-deficient crypts (35). Furthermore, exposure of these crypts to DNA methylating agents from the diet or bile (36, 37) may promote their expansion to adjacent crypts (38). Also, the signatures of spontaneous mutations caused by the MMR deficiency and those induced by helix-distorting nucleotide lesions are different (39). This increases the number of “hittable” oncogenic targets and therefore both mutagenic processes may synergize in cancer development. Furthermore, as described above, MMR/post-TLS repair-deficient cells may be intrinsically hypermutable by agents that induce helix-distorting nucleotide lesions while cell cycle arrests and apoptosis may be impaired (3, 15). These factors might further contribute to CRC development in Lynch syndrome. Moreover, intestinal mutagens such as PhIP might damage mitochondria, leading to the generation of ROS, which is another source of DNA damage (40). Finally, neoepitopes resulting from the mutator phenotypes MMR and from the exposure to intestinal mutagens in the absence of MMR/post-TLS repair may elicit an immune response (41). This immune response

may not only be tumor suppressive, but can also contribute to tumor progression, since neutrophils produce ROS that further damage the DNA (42). Given the role of MMR in responses to oxidative DNA injury, the increase of oxidatively injured DNA might provide another selective advantage to MMR-deficient cells.

In conclusion, diverse phenotypic characteristics of MMR/post-TLS repair-deficient cells can contribute to cancer development and treatment resistance. We anticipate that further understanding the involvement of MMR/post-TLS repair in responses to DNA damaging compounds may improve the prevention and management of cancers associated with inherited or somatic MMR gene defects.

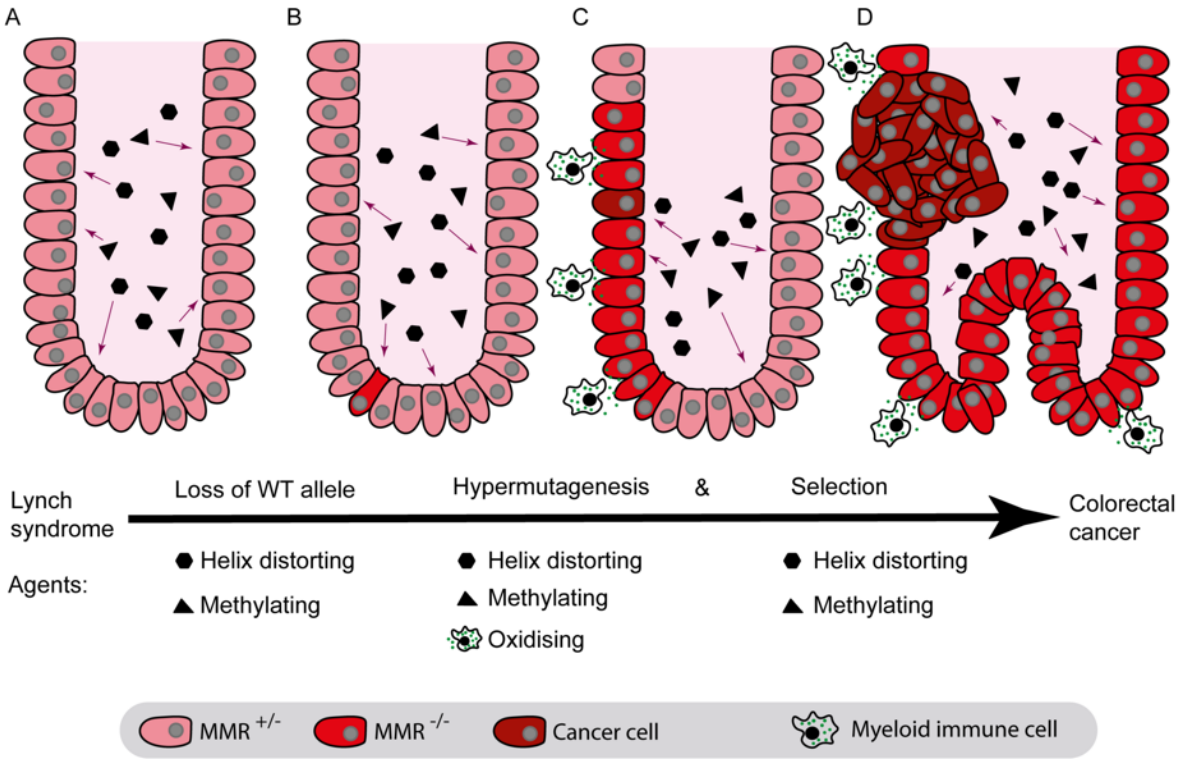

Figure 5| Etiology of cancer of the gastro-intestinal tract in Lynch syndrome
A: All gastro-intestinal crypt cells of Lynch syndrome carriers are heterozygous for an MMR gene (light red) and are continuously exposed to agents that induce methylating and helix-distorting DNA lesions. B: Methylating and helix-distorting DNA lesions can induce inadvertent loss of the wild type allele of the germ-line mutated MMR gene (bright red). C: Loss of MMR/post-TLS repair leads to hypermutagenesis, which results in the accumulation of oncogenic mutations (dark red). In addition, neoepitopes in these cells trigger the recruitment of myeloid immune cells that excrete reactive oxygen species, which may further increase mutagenesis in MMR/post TLS repair-deficient cells. D: MMR/post TLS repair-deficient cells also are more tolerant to methylated and to helix distorting DNA damage, which leads to their expansion. Ultimately, these selective ‘advantages’ can result in rapid carcinogenesis.

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