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Review

Hypermutated tumours in the era of immunotherapy: The paradigm of personalised medicine

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Abstract Immune checkpoint inhibitors have demonstrated unprecedented clinical activity in a wide range of cancers. Significant therapeutic responses have recently been observed in patients presenting mismatch repair-deficient (MMRD) tumours. MMRD cancers exhibit a remarkably high rate of mutations, which can result in the formation of neoantigens, hypothesised to enhance the antitumour immune response. In addition to MMRD tumours, cancers mutated in the exonuclease domain of the catalytic subunit of the DNA polymerase epsilon (*POLE*) also exhibit an ultramutated genome and are thus likely to benefit from immunotherapy. In this review, we provide an overview of recent data on hypermutated tumours, including MMRD and *POLE*-mutated cancers, with a focus on their distinctive clinicopathological and molecular characteristics as well as their immune environment. We also discuss

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the emergence of immune therapy to treat these hypermutated cancers, and we comment on the recent Food and Drug Administration approval of an immune checkpoint inhibitor, the programmed cell death 1 antibody (pembrolizumab, Keytruda), for the treatment of patients with metastatic MMRD cancers regardless of the tumour type. This breakthrough represents a turning point in the management of these hypermutated tumours and paves the way for broader strategies in immunoprecision medicine.

1. Deficiency in replication error repair pathways leads to a hypermutator phenotype

Faithful DNA replication is necessary to maintain genome stability and prevent mutations, and thus carcinogenesis [1]. In eukaryotes, normal cells replicate their DNA with remarkable fidelity, accumulating less than one mutation per genome per cell division [2]. It is estimated that the replicative DNA polymerases epsilon and delta make errors approximately once for every 10^4–10^5 nucleotides that they polymerise [3,4]. Thus, each time a mammalian cell divides, approximately 100,000 polymerase errors occur, which must be corrected at near 100% efficiency to avoid deleterious mutations. Correction is accomplished through the combined actions of the 3′–5′ exonuclease activity (proofreading) of polymerase epsilon and delta and the mismatch repair (MMR) system [3,4]. Indeed, owing to their proofreading activities, these replicative polymerases can recognise and remove misincorporated nucleotides during genome replication, and *in vitro* studies have shown that proofreading improves replication fidelity by approximately 100-fold [5,6]. However, some errors always escape proofreading and are then corrected by the MMR system, which is a post-replication repair process that is activated when incorrect nucleotides have been incorporated into newly synthesised strands [7]. Essential MMR system components include the heterodimer of MSH2 and MSH6 (MutSα) that detects base–base mismatches or 1–2 base pair insertion/deletion loops (IDLs) and the heterodimer of MSH2 and MSH3 (MutSβ) that identifies larger IDLs [8]. IDLs are mainly caused by replicative polymerase slippage during the replication of DNA regions containing short tandem repeats (mono-to tetra-nucleotide repeats), also known as microsatellites. Then, the MutLα heterodimer, consisting of MLH1 and PMS2, forms a ternary complex with one of the MutS complexes bound to the mismatch site, and together with exonuclease 1, proliferating cell nuclear antigen and the DNA polymerase delta, execute error removal and DNA resynthesis. In this way, the MMR system improves the fidelity of replication by several orders of magnitude [9]. Recent large-scale genomic studies have revealed that hundreds to thousands of somatic mutations can exist in a single cancer genome and the highest mutated cancer genomes exhibit alteration of the MMR system and/or mutations in the exonuclease domain of the catalytic subunit of the polymerase epsilon (*POLE*) and to a lesser extent, polymerase delta (*POLD1*). The clinicopathological and molecular characteristics as well as the immune environment of these hypermutated tumours will be described, with a focus on the emerging immune therapy to treat them.

2. Lynch syndrome and sporadic MMR deficient tumours

2.1. Mutations in MMR genes

Lynch syndrome (LS), previously known as hereditary non-polyposis colorectal cancer, is a cancer-predisposing syndrome characterised by the autosomal dominant inheritance of a heterozygous germline mutation in one of the MMR genes (mutations in *MLH1, MSH2, MSH6* or *PMS2*) [10]. The proportion of mutations in LS is *MLH1* (40%), *MSH2* (34%), *MSH6* (18%) and *PMS2* (8%), although the *PMS2* mutation frequency may be underdiagnosed due to technical issues. Deletion of the last exons of *EPCAM*, located immediately upstream of the *MSH2* gene, is also involved in LS [11]. However, the cancer risks appear to be variable according to the gene involved, with a lesser penetrance being observed for the *MSH6* or *PMS2* mutation [12]. In addition to familial form, sporadic MMR deficient (MMRD) tumours also exist and result mainly from hypermethylation of the *MLH1* promoter, thus provoking *MLH1* expression silencing, leading to a complete loss of MLH1 protein expression [13,14]. This methylation can be sporadic or associated with a CpG island methylation phenotype [15,16].

2.2. Mutational burden and signatures in MMRD cancer genomes

LS and sporadic MMRD tumour genomes harbour a high frequency of insertion/deletion due to unrepaired DNA polymerase slippage in microsatellites sequences (microsatellite instability [MSI] events). Thus, the MSI phenotype is the hallmark of MMRD [14]. Microsatellites are distributed throughout the genome, both in