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Mini-review

Immunotherapy holds the key to cancer treatment and prevention in constitutional mismatch repair deficiency (CMMRD) syndrome

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ABSTRACT

Monoallelic germline mutations in one of the DNA mismatch repair (MMR) genes cause Lynch syndrome, with a high lifetime risks of colorectal and endometrial cancer at adult age. Less well known, is the constitutional mismatch repair deficiency (CMMRD) syndrome caused by biallelic germline mutations in MMR genes. This syndrome is characterized by the development of childhood cancer. Patients with CMMRD are at extremely high risk of developing multiple cancers including hematological, brain and intestinal tumors. Mutations in MMR genes impair DNA repair and therefore most tumors of patients with CMMRD are hypermutated. These mutations lead to changes in the translational reading frame, which consequently result in neoantigen formation. Neoantigens are recognized as foreign by the immune system and can induce specific immune responses. The growing evidence on the clinical efficacy of immunotherapies, such as immune checkpoint inhibitors, offers the prospect for treatment of patients with CMMRD. Combining neoantigen-based vaccination strategies and immune checkpoint inhibitors could be an effective way to conquer CMMRD-related tumors. Neoantigen-based vaccines might also be a preventive treatment option in healthy biallelic MMR mutation carriers. Future studies need to reveal the safety and efficacy of immunotherapies for patients with CMMRD.

Introduction

Lynch syndrome (LS) is an autosomal dominant tumor syndrome predisposing to predominantly colorectal cancer (CRC) and endometrial carcinoma at an early age of onset, with a mean age of 45 years [1]. Monoallelic germline mutations in one of the DNA mismatch repair (MMR) genes cause malignancies in patients with LS when a second hit inactivates the wildtype allele (Fig. 1) [2–5]. The MMR genes involved in LS are *MLH1, MSH2, MSH6,* and *PMS2*. Biallelic mutations in one of these MMR genes cause constitutional mismatch repair-deficiency (CMMRD). CMMRD is a rare recessively inherited syndrome mainly characterized by café-au-lait spots and a broad spectrum of childhood malignancies, primarily hematological, brain and intestinal tract tumors [6–9]. The prognosis for patients with CMMRD is much worse than for patients with LS due to the types of cancer and the high risk of multiple primary malignancies [10]. In children with CMMRD, no somatic mutations have to arise in the MMR genes to start tumorigenesis, since affected individuals inherit a germline MMR mutation from each parent. These biallelic MMR mutations, either homozygous or compound heterozygous, cause loss of genomic integrity by the inability of cells to repair DNA damage. This results in high numbers of mutations, mainly consisting of insertion and deletion mutations at repetitive DNA sequences known as microsatellites. Repeated DNA structures are prone to DNA polymerase slippage during DNA replication [11]. Due to these insertions and deletions, the length of the repeating sequences increases or decreases leading to

Abbreviations: CMMRD, constitutional mismatch repair deficiency; COX, cyclooxygenase; CRC, colorectal cancer; CTLs, cytotoxic T lymphocytes; GBM, glioblastoma multiforme; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; Tregs, regulatory T cells.

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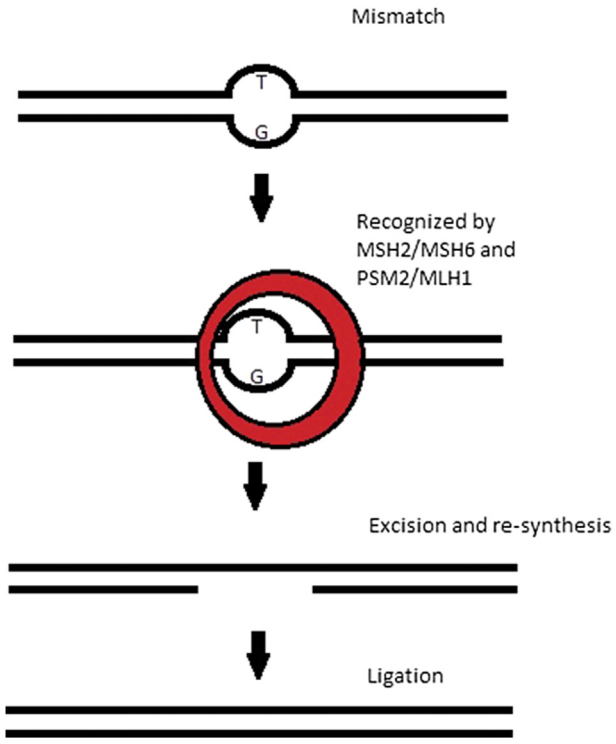

Fig. 1. Schematic figure of the mismatch repair pathway. A base mismatch is recognized by mismatch repair proteins (MSH2/MSH6 and PMS2/MLH1). The mismatch on the newly synthesized strand is excised and the correct nucleotides are synthesized. Finally, the DNA strands are ligated.

microsatellite instability (MSI). When microsatellites in gene-encoding regions are affected it can cause inactivation of the gene products through shifting of the translational reading frame leading to truncated or nonfunctional proteins (Fig. 2) [12–14]. Truncated proteins can be processed into peptides and presented on the surface of mutated cells. Eventually, so-called ultra-hypermutated tumor cells arise. All ultra-hypermutated tumors harbor mutations in polymerase genes *POLE* or *POLD1* and have an upper limit of exonic mutations which is tolerable [15,16]. Fortunately, endogenous ultra-hypermutated tumor cells can be recognized by the immune system as foreign as they can be identified by their private mutanome-derived epitopes called neoantigens. Most of the tumors that present in patients with CMMRD are ultra-hypermutated and thus express neoantigens, which can result in an immune response against these tumor-specific neoantigens [17]. Generally speaking, tumors that are recognized by the patients' own immune system have an improved prognosis [18,19]. Studies have shown that microsatellite instable CRCs of LS patients with a high density of tumor-infiltrating lymphocytes are associated with a better prognosis than microsatellite stable (MSS) CRCs [20,21]. Until now, very little is known about immune responses against neoantigens in CMMRD patients. In this review we discuss the potential of neoantigens to elicit immune responses in patients with CMMRD and probable immunotherapeutic treatment options.

Biallelic mutations in MMR genes and their risk of cancer

Individuals with CMMRD are at increased risk for developing malignant gliomas, hematologic malignancies, and gastrointestinal tract cancers at young age. It is a highly penetrating cancer predisposition syndrome, with most biallelic mutation carriers developing cancer in the first two decades of life [8,9]. Hematological malignancies usually arise in infancy or early childhood and are more frequent in patients with *MLH1* or *MSH2* mutations than in patients with mutations in *MSH6* or *PSM2* [6]. The latter group appears to have a higher prevalence of brain tumors which develop later during childhood. CRC in patients with CMMRD is most frequently found as a second or third primary malignancy and arises in adolescence or young adulthood. The prevalence of CRC is higher in patients with biallelic *PMS2* and *MSH6* [6,22–24].

Prophylactic cancer surveillance and preventive treatments

When a patient is diagnosed with CMMRD syndrome, family members can be screened for heterozygous and homozygous mutations by performing a mutation analysis of peripheral blood DNA. Especially, siblings need to be screened since the chance for a homozygous mutation is 25% resulting in CMMRD, and an additional

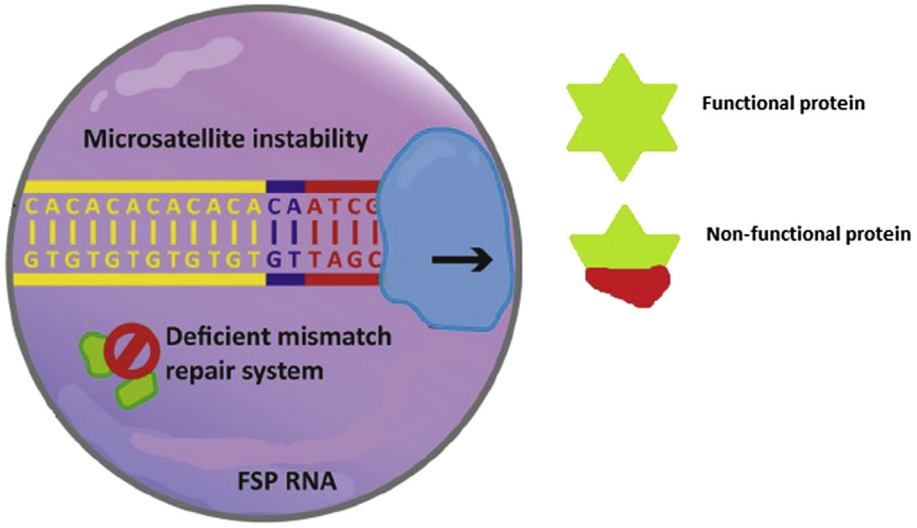

Fig. 2. Normally an insertion or deletion in a microsatellite sequence is repaired by the mismatch repair pathway to prevent that mutations become permanent and affect the protein. Mismatch repair deficient cells are unable to repair insertions or deletion, here indicated with an inserted CA sequence (purple), leading to a frameshift mutation. The coding sequence is altered due to shifting of the translational reading frame, which can result in a truncated or non-functional protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)