

Colorectal cancer: Disorders of DNA repair mechanisms and their medical implication.

Walter Hernán Pavicic^{1,2}, Julieta Natalia Soarez^{1,2}

¹ Instituto de Medicina Traslacional e Ingeniería Biomédica (IMTIB) Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas (HIBA-IUHI-CONICET), Ciudad Autónoma de Buenos Aires (CABA), Argentina.

² Programa de Cáncer Hereditario (Pro.Can.He.), Hospital Italiano de Buenos Aires (HIBA), Ciudad Autónoma de Buenos Aires (CABA), Argentina.

ABSTRACT

All tumors, whether hereditary or sporadic, are characterized by genetic instability (chromosomal or microsatellites instability) which is a key mechanism that gives the cancer cell all its harmful characteristics (growth advantage, migration, etc.). Although a DNA repair-deficiency disorder that causes microsatellite instability has historically been associated with Lynch Syndrome, this molecular characteristic is also observed in sporadic tumors and determines not only the prognosis but also just as relevant, the response to new immunological therapies.

Keywords: colon cancer, Lynch Syndrome, MMR.

INTRODUCTION

DNA repair mechanisms maintain genome stability by preventing the multiplication of genetic errors, which are caused by intracellular processes and environmental factors. Unrepaired damage can permanently alter the genome and cellular functions, leading to, for example, malignant transformation of the cell. Several DNA repair mechanisms are necessary to ensure genomic stability and can be divided according to the DNA damage they repair or the associated genetic syndromes. Elucidating these mechanisms has been important, and researchers who carried out pioneering work were awarded the 2015 Nobel Prize in Chemistry.

When DNA damage occurs, both DNA strands can break, causing a double-strand break, or it can be more restricted and occur only on one DNA strand, affecting one or more bases -nucleotides-. Due to their relevance in tumor development, the two mechanisms studied in more detail are: (i) homologous recombination (HR), and (ii) the mismatch repair system (MMR). Mainly, they are associated with hereditary syndromes that predispose to the development of breast and ovarian cancer (HBOC) or colorectal cancer (Lynch), respectively.

Repair of DNA replication errors

Although this type of error is common during DNA replication, the stability of the genetic code is ensured by the specialized mismatch repair mechanism, called the “MMR system.” Briefly, the process is detailed to denote the key MMR genes involved: the repair is initiated by the MutSa protein complex (*MSH2* + *MSH6* genes) that recognizes the error. Then, MutLa (*MLH1* + *PMS2* genes), together with the enzyme that synthesizes DNA (DNA polymerase) correct the error. Germline genetic alterations affecting MMR gene’s function, a single allele, is associated with Lynch syndrome (LS), an autosomal dominant genetic disorder, and the most common inherited cause of colorectal cancer (CRC). Carriers of pathogenic or causal alterations in these genes also have a higher risk of developing LS-associated cancer. This includes cancers such as endometri-

um, small intestine, stomach, pancreas and bile ducts, ovary, brain, upper urinary tract, and skin. The incidence rate in the general population can be as high as 1:370 and it is estimated to cause around 3% of all colon and rectal cancers. On the other hand, congenital alterations of both alleles cause a rare cancer syndrome known by the acronym CMMRD (constitutional mismatch repair deficiency). Furthermore, the MMR mechanism is altered in approximately 15% of CRC and other non-hereditary cancers, the most common

mechanism being deficiency in the *MLH1* gene function, caused by promoter region hypermethylation and, consequently, silencing of gene expression. Tumors with a deficiency MMR system are called “unstable tumors.”

Lynch Syndrome Diagnosis

The suspicion of LS can be based on clinical criteria (Amsterdam or Bethesda) or molecular criteria (immunohistochemistry or microsatellite analysis by a PCR assay). Further details of these complementary studies exceed the editorial focus. However, it is important to note that currently a definitive LS diagnosis requires identification of a germline genetic alteration in the MMR or in the EPCAM genes. The analysis should cover small sequence changes and large rearrangements (which can be achieved by DNA sequencing plus copy number variant analysis by, for example, MLPA study). Currently, multigene panel sequencing test (along with MLPA) has become the most widespread assay, compared to traditional syndrome-specific gene testing. Ultimately, this information allows alteration carriers to be referred for follow-up or surveillance in pursuit of cancer prevention or treatment.

Implications of molecular advances in Surveillance, Prevention and Treatment of CRC Surveillance recommendations.

Recent advances have allowed us to understand in more detail the differences linked to each MMR gene and tumor development risk. Therefore, clinical surveillance and treatment guidelines have incorporated new specific rules for each of these genes. For example, heterozygous *PMS2* variant carriers show a low cumulative CRC incidence, suggesting that colonoscopy surveillance might be less stringent for this group. In both Europe and the US, new colonoscopy surveillance recommendations for *MSH6* and *PMS2* variant carriers suggest an onset at an older age. Similarly, association of urothelial cancer with *MSH2* variants is making urologic screening recommendations more gene specific.

The authors declare no conflict of interest. **Walter Pavicic:** walter.pavicic@hospitalitaliano.org.ar

Pavicic W. [ORCID:0000-0001-7840-4943](https://orcid.org/0000-0001-7840-4943)

Importance of DNA repair mechanisms defects and cancer treatment. Immune system.

A functional or dysfunctional DNA repair mechanism can predict both the course of the disease and the effectiveness of drugs in cancer treatment, that is, it can act as a prognostic and predictive marker. Patients with colon cancer whose MMR system is altered, either congenitally (Lynch syndrome) or because of somatic *MLH1* gene methylation (sporadic cancer), have a better prognosis compared to patients whose cancers have a normal MMR mechanism. There are several possible explanatory factors. One of the most accepted is that inadequate DNA errors repairs leads to a higher number of genetic alterations and consequently to an increased quantity of abnormal peptides (neoantigens) in the cell. The strong immune defense reaction derived from this could be a possible explanation for the better prognosis.

Repair mechanism deficiency: Prognostic and predictive value.

For several decades, it has been observed that tumors with deficiencies in DNA repair mechanisms (unstable tumors)

are associated with a more favorable long-term prognosis. Furthermore, these tumors tend to be relatively resistant to 5-fluorouracil. Recent results from adjuvant or neoadjuvant immunotherapy are especially encouraging for these tumors. In fact, checkpoint inhibitors have displayed promising responses compared to traditional regimens in metastatic unstable tumors. In locally advanced rectal cancer with PD-1 blockers such as dostarlimab showed significant levels of complete clinical response without including irradiation.

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