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Tumour Review

The evolving role of microsatellite instability in colorectal cancer: A review

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ABSTRACT

Microsatellite instability (MSI) is a molecular marker of a deficient mismatch repair (MMR) system and occurs in approximately 15% of colorectal cancers (CRCs), more frequently in early than late-stage of disease. While in sporadic cases (about two-thirds of MSI-H CRCs) MMR deficiency is caused by an epigenetic inactivation of MLH1 gene, the remainder are associated with Lynch syndrome, that is linked to a germ-line mutation of one of the MMR genes (MLH1, MSH2, MSH6, PMS2). MSI-H colorectal cancers have distinct clinical and pathological features such as proximal location, early-stage (predominantly stage II), poor differentiation, mucinous histology and association with BRAF mutations. In early-stage CRC, MSI can select a group of tumors with a better prognosis, while in metastatic disease it seems to confer a negative prognosis. Although with conflicting results, a large amount of preclinical and clinical evidence suggests a possible resistance to 5-FU in these tumors. The higher mutational load in MSI-H CRC can elicit an endogenous immune anti-tumor response, counterbalanced by the expression of immune inhibitory signals, such as PD-1 or PD-L1, that resist tumor elimination. Based on these considerations, MSI-H CRCs seem to be particularly responsive to immunotherapy, such as anti-PD-1, opening a new era in the treatment landscape for patients with metastatic CRC.

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Introduction

Colorectal cancer is still a major public health problem in Western countries, representing the third most common cancer in both women and men. Actually the 5 year-overall survival rate approaches 65%, depending on stage of disease (90% in stage I, 15% in stage IV). Thanks to screening programs, in 2015 more than 70% of new cases underwent potentially curative resection [1].

Although traditional clinical-pathological staging remains useful in predicting the outcome, CRC shows a significant heterogeneity in both prognosis and response to therapy, even within the same pathological stage.

This clinical heterogeneity may be at least in part linked to genetic alterations that occur during the pathogenesis of CRC: in 85% of CRCs the process is driven by chromosomal alterations, either qualitative or quantitative (chromosomal-instability pathway), while in 15% is driven by a defective function of DNA MMR system (microsatellite-instability pathway) [2].

MSI represents a molecular hallmark of hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome (LS), usually linked to a germ-line mutation in one of MMR genes. Nevertheless, the majority of cases with MSI are sporadic, more often due to an epigenetic inactivation of hMLH1 [3,4].

The prevalence of CRCs with microsatellite instability (MSI) is different among disease stages: 15% in stage II–III (more common in stage II) [5,6], 4–5% in stage IV [7].

The current review summarizes the clinical-pathological features of MSI CRCs, the prognostic and predictive significance of MSI status in early-stage and metastatic disease and the implications on new drugs development.

Microsatellite instability: definition

MMR system is of pivotal importance for the rectification of DNA sequence mismatches during DNA replication. This repair system is mainly composed of four proteins (MLH1, MSH2, MSH6 and PMS2) interacting together to detect mismatches and cut out them, so that DNA polymerase and DNA ligase can resynthesize and rebind correct DNA strand [8].

Microsatellites are short DNA motifs of 1–6 bases repeated and distributed throughout the genome both in coding and non-coding

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regions. Owing to their repeated structure, microsatellites are particularly prone to replication errors that are normally repaired by the MMR system. Loss of function of one of the MMR proteins causes a deficient MMR system leading to the accumulation of mistakes in microsatellites, such as insertions or deletions, which result in a genetic instability. MSI may have an oncogenic potential when it occurs in coding regions of genes involved in several crucial cellular functions and pathways [9]. MSI is detected by PCR amplification of specific microsatellite markers or by immunohistochemical loss of expression of one of the above mentioned proteins. While in LS MSI is related to germ-line mutation in one of MMR genes (usually MLH1 or MSH2), in sporadic MSI CRCs there is usually an epigenetic inactivation of the hMLH1 gene via methylation of the gene promoter [10,11].

Lynch syndrome

LS, the most frequent form of hereditary CRC, is an autosomal dominant condition with incomplete but high penetrance, caused by an inactivating germ-line mutation of one of the four genes involved in the DNA MMR system (MLH1, MSH2, MSH6, PMS2). LS is characterized by early-onset colorectal and endometrial tumors and an increased risk of certain extra-colonic cancers, including tumors elsewhere in the gastrointestinal tract (e.g., stomach, small bowel, biliary tract), in the urinary collecting system (renal pelvis, ureter) and in the female reproductive system (ovaries). Recent population-based studies showed a lifetime CRC risk of about 52.2% in women and 68.7% in men and a median age at diagnosis of 61.2 years [10–12].

Amsterdam and Bethesda criteria were developed to identify potential LS patients candidates for genetic testing [13,14], as shown in Tables 1 and 2 [15,16]. Nowadays, many guidelines suggest two possible approaches to screen out LS: a universal one, that is to test every patient with CRC, and a selective one, that is to test every patient with CRC diagnosed prior than 70 plus patients diagnosed at older age who meet the Bethesda criteria, with the latest approach missing more than a quarter of patients with LS (Fig. 1) [17].

The results of immunohistochemistry and genetic testing show excellent concordance. Nevertheless, few cases of MSI cannot be detected by immunohistochemistry because missense mutations can lead to a dysfunctional protein, which is dismantled with loss of antigenicity [18,19].

The first proposed panel of MSI markers consisted of two mononucleotides (BAT-25, BAT-26) and three di-nucleotides (D2S123, D5S346, and D17S250) [20]. A new expert consensus recommend the use of a panel of 5 quasi-monomorphic mononucleotide repeats (BAT-25, BAT-26, NR21, NR24 and NR27), characterized by a constant number of nucleotide repeats and an identical size between individuals, unlike most microsatellites are polymorphic [15]. CRCs can be classified into microsatellite instability-high (MSI-H), and microsatellite instability-low (MSI-L), depending on the percentage of loci with MSI. In particular, a MSI-H phenotype is defined by the presence of at least two unstable markers among the 5 analyzed (or $\geqslant$30% of unstable markers if a larger panel is used). Conversely, most of the sporadic CRCs are designated as microstallite-stable (MSS), because they show chromosomal instability and a lack of MSI features [21].

With immunohistochemistry it should be considered that MMR proteins PMS2 and MSH6 cooperate with MLH1 and MSH2 respectively and their expression closely depends on the binding to the major partner (i.e. MLH1 and MSH2). Therefore, loss of expression of MSH2 is frequently associated with loss of expression of MSH6 and this pattern is highly suggestive of MSH2 germ-line mutation. Similarly, loss of expression of MLH1 is frequently associated with loss of expression of PMS2 and this pattern may results either from MLH1 germ-line mutation or from acquired somatic hypermethylation of the MLH1 gene promoter. Germ-line mutations of MSH6 and PMS2 are generally associated with isolated loss of expression of MSH6 and PMS2 protein respectively [22].

Clinical-pathological features

From a clinical point of view, MSI-H CRCs are diagnosed at a younger age, with a predominance in the right colon, frequently raised from sessile serrated adenoma and are diagnosed at an earlier stage as compared to MSS CRCs, most commonly in stage II [23,24]. Moreover, as opposed to LS cases, sporadic CRCs are characterized by older age at diagnosis and are more often associated with female sex and cigarette smoking [25–27].

Histologically, there are some peculiarities that may suggest the MSI status, beyond IHC or genetic testing. A great production of

Table 1
Bethesda revised guidelines for Lynch syndrome related CRC.

Tumors from individuals should be tested for MSI in the following situations:
1. CRC diagnosed in a patient who is less than 50 y.o
2. Presence of synchronous, metachronous CRC or other Lynch Syndrome related tumours, regardless of age (*endometrial, stomach, ovarian, pancreas ureter and renal pelvis, biliary tract and brain tumors, small bowel cancers, sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome*)
3. CRC with the MSI-H histology diagnosed in a patient who is less than 60 y.o (*presence of tumor-infiltrating lymphocytes, Chron's-like reaction, mucinous/signet-cell differentiation or medullary growth pattern*)
4. CRC diagnosed in a patient with one or more first-degree relatives with Lynch Syndrome-related cancers, with one of *the cancers* diagnosed before 50 y.o
5. CRC diagnosed in a patient with two or more 1st or 2nd degree relatives with Lynch Syndrome related cancers regardless of age

Adapted Ref. [15]

Table 2
Amsterdam II criteria.

At least three relatives must have cancer associated with Lynch Syndrome (colorectal, endometrium, small bowel, ureter or renal-pelvis); all of the following criteria should be present:
– One must be a first-degree relative of the other two
– At least two successive generations must be affected
– At least one relative with cancer associated with Lynch Syndrome should be diagnosed before age 50
– FAP should be excluded in the CRC cases
– Tumors should be verified by pathological examination

Adapted Ref. [16].

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