DNA mismatch repair deficiency and melanoma immunotherapy at immunohistochemical glance

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DNA mismatch repair (MMR) is a safeguard system for the detection and repair of DNA errors, which can randomly occur in the phase of DNA replication inside the cell, often due to tautomerization of single nucleotide bases. In humans, seven DNA MMR proteins, namely Mlh1 (mutL homolog 1), Mlh3 (mutL homolog 3), Msh2 (mutS homolog 2), Msh3 (mutS homolog 3), Msh6 (mutS homolog 6), Pms1 (PMS1 homolog 1) and Pms2 (PMS1 homolog 2), work in a coordinated and sequential manner to repair DNA mismatches. When this system is defective, the cell are exposed to a series of replication errors in terms of new microsatellites; therefore, a condition of genetic hypermutability and microsatellite instability (MSI) takes place inside the cell itself. For this reason, MSI may result in the occurrence of many tumor histotypes; being more specific, the hereditary non-polyposis colorectal cancers (Lynch syndrome) are attributed to damaged germline variants in the tumor suppressor genes encoding for one or more DNA MMR proteins. Similarly, the hereditary syndromes Muir-Torre and Turcot are associated with deficient MMR (dMMR) tumors at different location of onset (gut, brain, skin). Sporadic dMMR cancers are instead characterized by epigenetic alterations that reduce DNA MMR gene expression in most cases. MSI is a frequent condition in malignant melanoma, too. Therefore, dMMR melanoma is a particular subset of disease, which can be identified with high sensitivity and specificity by immunohistochemistry (IHC), as an entity with complete loss of one or more DNA MMR proteins. IHC is in fact an excellent technique for labeling detection of selected cell proteins, which exploits the principle of antigen-antibody specific binding in biological tissues. Firstly, implemented by Albert Coons in 1941, over time it has achieved great success for diagnostic purposes (diagnostic IHC), often allowing avoidance of diagnostic disputes, then for prognostic ones (prognostic IHC), at the basis of wise choices for a proper patient management. Several molecular pathways are altered in skin melanoma and some of these can be targeted in oncotherapy. Therefore, a growing field of IHC application has evolved to predict those melanomas which are likely to respond to precision therapy (predictive IHC), by detecting the presence or high expression levels of altered gene products. Today, great attention has been paid to melanoma immunotherapy; it is a type of passive immunotherapy aimed to enhance pre-existing anti-tumor responses of the organism. In this regard, the Pd1 (Programmed cell death protein 1) has attracted the interest of many researchers. More in detail, Pd1 is a surface receptor of activated T lymphocytes which plays an important role in down-regulating the immune system and promoting self-tolerance. Its ligand, known by the acronym Pd-L1 (Programmed death-Ligand 1), is highly expressed in 40-50% cases of melanoma and, hence, the role of Pd1 in melanoma immune evasion is now well established. Pembrolizumab is an anti-Pd1 human monoclonal immunoglobulin G4 capable to block the interaction between Pd1 and Pd-L1 (immune check-
point blockade), favoring the melanoma cell attack by T cells\textsuperscript{17}. In 2017 the Food and Drug Administration has approved the use of pembrolizumab also for unresectable or metastatic solid dMMR tumors\textsuperscript{18}. In line with what has been recently hypothesized by other authors\textsuperscript{19,20}, my working group has noticed, in daily clinical practice, that the best therapeutic results to pembrolizumab precisely occur in those patients consisting of about 7%, of the cases affected by dMMR melanomas; therefore, before choosing the most suitable treatment, the biopsy specimen should be also immunohistochemically tested for DNA MMR proteins.

REFERENCES