Medeniyet Medical Journal 2018;33(1):67-68
doi:10.5222/MMJ.2018.47887

ISSN 2149-2042
e-ISSN 2149-4606

DNA mismatch repair deficiency and melanoma immunotherapy at immunohistochemical glance

Luca RONCATI

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[1]. 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[2]. When this system is defective, the cell are exposed to a series of replication errors in terms of new microsatellites[3]; therefore, a condition of genetic hypermutability and microsatellite instability (MSI) takes place inside the cell itself[4]. For this reason, MSI may result in the occurrence of many tumor histotypes; being more specific, the hereditary nonpolyposis colorectal cancers (Lynch syndrome) are attributed to damaged germline variants in the tumor suppressor genes encoding for one or more DNA MMR proteins[5]. Similarly, the hereditary syndromes Muir-Torre and Turcot are associated with deficient MMR (dMMR) tumors at different location of onset (gut, brain, skin)[6]. Sporadic dMMR cancers are instead characterized by epigenetic alterations that reduce DNA MMR gene expression in most cases[6]. MSI is a frequent condition in malignant melanoma, too[7]. 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[8]. 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[9]. Firstly, implemented by Albert Coons in 1941,[10] over time it has achieved great success for diagnostic purposes (diagnostic IHC), often allowing avoidance of diagnostic disputes[11], then for prognostic ones (prognostic IHC), at the basis of wise choices for a proper patient management[12,13]. Several molecular pathways are altered in skin melanoma and some of these can be targeted in oncotherapy[9]. 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[14]. 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[15]. 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[16]. Pembrolizumab is an anti-Pd1 human monoclonal immunoglobulin G4 capable to block the interaction between Pd1 and Pd-L1 (immune check-

Received: 01.01.2018
Accepted: 28.01.2018
Department of Diagnostic and Clinical Medicine and of Public Health, Institute of Pathology, University of Modena and Reggio Emilia, Modena (MO), Italy
Yazışma adresi: Luca Roncati, Department of Diagnostic and Clinical Medicine and of Public Health, Institute of Pathology, University of Modena and Reggio Emilia, Policlinico Hospital, I-41124 Modena (MO), Italy
e-mail: emailmedical@gmail.com

point blockade), favoring the melanoma cell attack by T cells[17]. In 2017 the Food and Drug Administration has approved the use of pembrolizumab also for unresectable or metastatic solid dMMR tumors[18]. In line with what has been recently hypothesized by other authors[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

1. Iyer RR, Pluciennik A, Burdett V, et al. DNA mismatch repair: functions and mechanisms. Chem Rev. 2006;106:302-23. https://doi.org/10.1021/cr0404794
2. Song H, Ramus SJ, Quaye L, et al. Common variants in mismatch repair genes and risk of invasive ovarian cancer. Carcinogenesis. 2006;27:2235-42. https://doi.org/10.1093/carcin/bgl089
3. Ellegren H. Microsatellites: simple sequences with complex evolution. Nat Rev Genet. 2004;5:435-45. https://doi.org/10.1038/nrg1348
4. Imai K, Yamamoto H. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008;29:673-80. https://doi.org/10.1093/carcin/bgm228
5. Cohen SA, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management. Appl Clin Genet. 2014;7:147-58. https://doi.org/10.2147/TACG.S51483
6. Velter C, Caussade P, Fricker JP, et al. Muir-Torre syndrome and Turcot syndrome. Ann Dermatol Venereol. 2017;144:525-9. https://doi.org/10.1016/j.annder.2017.01.017
7. Kubeček O, Kopecký J. Microsatellite instability in melanoma: a comprehensive review. Melanoma Res. 2016;26:545-50. https://doi.org/10.1097/CMR.0000000000000298
8. Roncati L, Manenti A, Pusiol T, et al. Testosterone aromatization to estradiol in course of ovarian functioning Brenner tumor associated with endometrial carcinoma and endometriosis (Roncati-Manenti triad). Int J Gynecol Cancer. 2016;26:1461-4. https://doi.org/10.1097/IGC.0000000000000779
9. Roncati L, Piscioli F, Pusiol T, et al. Microinvasive radial growth phase of cutaneous melanoma: a histopathological and immunohistochemical study with diagnostic implications. Acta Dermatovenerol Croat. 2017;25:39-45.
10. Coons AH, Creech HJ, Jones RN. Immunological properties of an antibody containing a fluorescent group. Proc Soc Exp Biol Med. 1941;47:200-2. https://doi.org/10.3181/00379727-47-13084P
11. Piscioli F, Pusiol T, Roncati L. Diagnostic disputes regarding atypical melanocytic lesions can be solved by using the term MELTUMP. Turk Patoloji Derg. 2016;32:63-4.
12. Piscioli F, Pusiol T, Roncati L. Wisely choosing thin melanomas for sentinel lymph node biopsy. J Am Acad Dermatol. 2017;76:e25. https://doi.org/10.1016/j.jaad.2016.08.069
13. Piscioli F, Pusiol T, Roncati L. Nowadays a histological subtyping of thin melanoma is demanded for a proper patient management. J Plast Reconstr Aesthet Surg. 2016;69:1563-4. https://doi.org/10.1016/j.bjps.2016.08.026
14. Najem A, Krayem M, Perdrix A, et al. New drug combination strategies in melanoma: current status and future directions. Anticancer Res. 2017;37:5941-53.
15. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42. https://doi.org/10.1111/j.1600-065X.2010.00923.x
16. Wang X, Teng F, Kong L, et al. PD-L1 expression in human cancers and its association with clinical outcomes. Onco Targets Ther. 2016;9:5023-39. https://doi.org/10.2147/OTT.S105862
17. Prasad V, Kaestner V. Nivolumab and pembrolizumab: monoclonal antibodies against programmed cell death-1 (PD-1) that are interchangeable. Semin Oncol. 2017;44:132-5. https://doi.org/10.1053/j.seminoncol.2017.06.007
18. Syn NL, Teng MWL, Mok TSK, et al. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol. 2017;18:e731-e41. https://doi.org/10.1016/S1470-2045(17)30607-1
19. Kim ST, Klempner SJ, Park SH, et al. Correlating programmed death ligand 1 (PD-L1) expression, mismatch repair deficiency, and outcomes across tumor types: implications for immunotherapy. Oncotarget. 2017;8:77415-23. https://doi.org/10.18632/oncotarget.20492
20. Kubecek O, Trojanova P, Molnarova V, et al. Microsatellite instability as a predictive factor for immunotherapy in malignant melanoma. Med Hypotheses. 2016;93:74-6. https://doi.org/10.1016/j.mehy.2016.05.023