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Review

DNA Mismatch Repair System Imbalances in Breast Adenocarcinoma

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Abstract. *DNA mismatch repair system (MMR) is considered a leading genetic mechanism in stabilizing DNA structure and maintaining its function. DNA MMR is a highly conserved system in bacteria, prokaryotic, and eukaryotic cells, and provides the highest protection to DNA by repairing micro-structural alterations. DNA MMR proteins are involved in the detection and repair of intra-nucleotide base-to-base errors inside the complementary DNA strand recognizing the recently synthesized strand from the parental template. During DNA replication, a spectrum of errors including base insertion, deletion, and miss-incorporation negatively affect the molecule's structure and its functional stability. A broad spectrum of genomic alterations such as promoter hyper methylation, mutation, and loss of heterozygosity (LOH) in MMR genes including predominantly hMLH1, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2 lead to their loss of base-to-base error repairing procedure. Microsatellite instability (MSI) refers to the DNA MMR gene alterations that are observed in a variety of malignancies of different histological origins. In the current review, we present the role of DNA MMR deficiency in breast adenocarcinoma, a leading cancer-based cause of death in females worldwide.*

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Breast cancer (BrCa) is the prominent type of cancer in females worldwide and the second leading cause of cancer-related death, behind lung carcinoma (1). Concerning pathology categorization, primary breast carcinoma demonstrates a variety of types including ductal, lobular, medullary, mucinous, adenoid cystic, and papillary correlated to medium or high metastatic potential (2). Regarding its etiology, several socio-demographic and genetic risk factors (*i.e.*, age, chronic smoking, and alcohol consumption), ovarian hormone over-expression/exposure to drug diethylstilbestrol (DES) or radiation therapy, combined or not with reproductive history and potential family history (inherent gene mutations) have been proposed to be involved in its development (3, 4). Additionally, BrCa is characterized by genetic diversity and epigenetic heterogeneity (5, 6). Specifically, altered expression

of crucial molecules such as estrogen (ER) and progesterone (PR) receptors, HER2/neu, ki-67 proliferation marker, and p53 suppressor gene is detected (7). For this reason, BrCa categorization based on these proteins is critical for optimal oncological handling by designing and applying specific targeted and chemotherapeutic regimens. Besides them, new immunotherapy strategies are applied alone or in combination with radiotherapy (8, 9). HER2/ER/PR gene expression signatures are critical for the development of sporadic BrCa, whereas BrCa genes, such as *BRCA1/2,* are involved in hereditary/familial cases (10, 11). Interestingly, other genetic micro-markers include microsatellite instability (MSI), which refers to specific DNA mismatch repair (MMR) genes that are responsible for the detection and repair of nucleotide dissimilarities in the DNA (12). MSI is detected in a variety of malignancies independently of their histological origin (13). In the current molecular review, we describe the function and the role of DNA MMR deficiency in BrCa.

DNA Mismatch Repair System (DNA MMR): Landscape and Mechanisms

DNA is characterized by a high – level structural stability that secures its multiple normal functions. There are different genetic mechanisms that provide a stable micro-environment inside the molecule including DNA MMR, which plays a leading role. DNA MMR is a highly conserved and efficient system in a series of prokaryotic and eukaryotic cells (14). The ability of the corresponding genes to detect and repair DNA base errors is crucial for its homeostasis. The MMR system distinguishes the newly synthesized DNA strand from the parental, which is used as a template. A broad spectrum of intra-nucleotide errors such as base deletion, insertion, and mis-incorporation occur during DNA replication and recombination. Concerning mismatches, they are implicated in a base tautomerization process that takes place in the G2 phase. G/T or A/C pairing that represents frequently detected base abnormalities is repaired by firstly recognizing the deformity, focal excision of the invalid base, and its replacement with the appropriate one. In fact, a significant number of bases (extended to hundreds or thousands of pairs) must be excised from the newly synthesized DNA strand in comparison to the initial template for preventing inappropriate base matching (15).

Significant human DNA MMR gene homologues including *MLH1, MSH2, MSH3, GTBP/MSH6, PMS1*, and *PMS2* are located on chromosomes 2, 3, 5, and 7. Furthermore, *PCNA, RPA, HMGB1, RFC* DNA ligase I, and DNA polymerase delta genes are implicated in DNA structural stability and function, interacting with histone and chromatin domains. Specific genomic alterations such as germline mutations, usually accompanied by allelic loss (loss of heterozygosity-LOH), or epigenetic changes including promoter hypermethylation lead to loss of the expression of MMR genes. For this reason, base errors are not repaired (16). Inherited as well as acquired deficiencies in DNA MMR genes lead to MSI, a genetic phenomenon frequently detected in hereditary (familial) and sporadic colorectal carcinoma (CRC) types.

Microsatellites correspond to nucleotide sequences of 1 to 5 base pairs that are repeated typically 15–30 times and characterized by instability. Based on extensive genetic analyses, thousands of them are detectable throughout the human genome. During DNA replication, an increased microsatellite number is responsible for the formation of small loops in any of the two DNA strands (17, 18). The introns of genes demonstrate a variety of inserted or deleted microsatellites. MSI is used as a very promising, novel biomarker for detecting DNA MMR deficiency in colorectal carcinomas CRCs. Additionally, MSI is detected in a broad spectrum of malignancies characterized by different histo-genetic origin (19). In the current review we focused on DNA MMR deficiency in lung and oral cavity carcinomas to identify mechanistic similarities and differences.

DNA MMR Alterations in BrCa

Alterations or different variants in DNA MMR genes are correlated with an elevated risk for BrCa development. A study group explored the role of specific *MSH2* variants in women without *BRCA1/BRCA2* gene mutations (20). They detected a combination of two mutations (p. Ala272Val and p. Met592Val) and designated them as potentially pathogenic in sub-groups of patients. They also suggested these two *MSH2* gene variants to be analyzed as early genetic biomarkers in women with a family history of BrCa. Additionally, the involvement of *MSH2* in neoplastic transformation of the breast epithelia is under investigation. A study group -focused on *MSH2* function and interactions- analyzed the formation of the MutSα/MutSβ complex in the cytoplasm and nucleus (21). They reported a higher nuclear/cytoplasmic K ratio for MutSα during progression from normal to cancerous cells. For this reason, they proposed MutSα elevated expression as a sensitive biochemical marker for early prediction of BrCa. Furthermore, increased MSH2 protein expression levels have been identified in the mononuclear fraction of the peripheral blood of BrCa patients (22). A study group detected high MSH2 expression in BrCa tissue sections in patients with increased mononuclear concentration associated also with lymph node metastasis. DNA MMR deficiency in familial/hereditary BrCa is correlated to specific single nucleotide polymorphisms (SNPs). A molecular analysis revealed two genetic alterations, MUTYH_rs3219489 and MSH2_rs2303428 variant alleles, which are associated with increased BrCa prevalence (23). Similarly, another study co-analyzed the potential impact of MMR genes (*MLH1, MSH,* and *MSH3*) on BrCa incidence as crucial genetic predisposition factors (24). They observed that XPC-Ala499Val, XPF-Arg415Gln, XPG-Asp1104His, and MLH1-lle219Val SNPs in

MSH2 and *MLH1* increased BrCa risk. Concerning the correlation between DNA MMR gene alterations and the histological origin of malignancies, a study analyzed the role of variations in *MLH1, MSH2,* and *MSH6* in cancerous tissues derived from the colon, breast, ovaries, endometrium, and thyroid (25). They observed that *MSH6* mutations followed by mutations in *MLH1*, *MSH2* demonstrated the highest incidence in breast carcinomas. Additionally, germline monoallelic mutations in *MSH6* and *MHS2* were associated with inherited breast-ovarian carcinoma.

Estrogen/progesterone positive BrCas represent a specific category and the impact of DNA MMR gene mutations is under investigation. A study explored the potential usefulness of MMR gene testing in these tumors (26). Similarly, another study group applied a DNA MMR gene panel (*MLH1, MSH2, MSH6,* and *PMS2*) in familial BrCa cases. They detected eight pathogenic variants in the examined genes (27). Furthermore, MMR-deficient BrCas demonstrated resistance to specific chemotherapeutic agents such as aromatase inhibitors, but sensitivity to others (*i.e.*, palbociclib) (28, 29). A study group showed that MMR-deficient cases characterized by *MSH2, MSH6, MLH1,* and *PMS2* loss of expression are eligible for an alternative treatment protocol based on CDK4 inhibitors (30). In conjunction, MMR-deficiency combined or not with epigenetic silencing of the gene O6-alkylguanine-DNA methyltransferase (*MGMT*) and *BRCA1/2* gene mutations seem to negatively affect the response rates to specific chemotherapeutic agents in sporadic and hereditary BrCas (31). In BrCa cases related to Lynch syndrome (LS), especially in the triple-negative ones, the frequency and impact of DNA MMR deficiency is under investigation. LS is an autosomal dominantly inherited disorder derived from germline mutations in DNA MMR genes. A study group analyzing a significant number of them observed increased MSI and MLH1 promoter hypermethylation (32). Two studies showed higher DNA MMR deficiency in BrCa mutation carriers than in non-carriers (33, 34). Additionally, the involvement of germline mutations in DNA MMR genes in LS cases was the subject of another molecular study. By applying targeted next-generation sequencing (TNGS), a study group explored the mutational profile of *MLH1, MSH2, MSH6, EPCAM*, and *PMS2* genes. They reported a high frequency of mutations in these genes in hereditary BrCa cases (35). Interestingly, another study analyzed LS-BrCa cases in a specific female population (Japanese) and observed a high MSI, especially in ER/PR+/HER2- cases (36). Besides LS-depended BrCa cases, carcinomas that demonstrate inactivation of critical suppressor genes - including phosphatase and tensin homolog (*PTEN*)- also involve DNA MMR deficiency (37, 38). A study group -based on this observation- formed a diagnostic algorithm to evaluate PTEN expression in MMR positive BrCas. Furthermore, specific *MLH1* gene polymorphisms (rs63749795 and rs63749820) lead to MLH1 down-regulation and expression loss correlated to a high risk of BrCa onset (39). Concerning alternative molecules and mechanisms that are implicated in DNA repair, ubiquitination mediated by the ubiquitin-conjugating enzyme E2W (UBE2W) plays a major role in carcinomas including breast (40). A study group reported high UBE2W expression in patients with DNA MMR deficiency and suggested the molecule as a potential reliable biomarker for immune infiltration.

DNA MMR Deficiency in BrCa Immunotherapy Strategies

A variety of targeted therapies – monoclonal antibodies (mAbs) and tyrosine-kinase inhibitors (TKIs), which disrupt signal transduction pathways – have been applied in BrCa patients (41, 42). Besides them, novel immune checkpoint inhibitors that regulate immune system function are considered very promising agents (43). Programmed cell death-1 (*PD-1*) gene - located on chromosome 2 (gene locus: 2q37.3) - encodes a cell surface membrane protein of the immunoglobulin super-family, which acts as an immune-inhibitory receptor implicated in tumor immune escape (44). PD-1 interacts with two potential ligands, PD-L1 and PD-L2 trans-membrane proteins (45). Programmed cell death ligand-1 (PD-L1), also known as CD274 (cytogenetic band: 9p24.1), is expressed in epithelial and hematopoietic cells as well as in thymus gland parenchyma. Furthermore, dendritic cells express PD-L1 modifying self-reactive T cell function. The PD-1/PD-L1 system promotes inhibition of T lymphocyte proliferation, survival, and cytokine release. Additionally, it induces tumor-specific T-dependent apoptosis and $CD4^+$T cell differentiation. In fact, it enhances the resistance of tumor cells to cytotoxic T lymphocyte (CTL) lineage attack. PD-L1 over-expression induces inflammation in malignancies. Malignant cells also escape the host immune system by PD-L1 – mediated suppression of T cell activation (46).

The role of DNA MMR deficiency in anti-PD-L1 immunotherapy strategies is a novel and interesting field for research in BrCa (47). A study group reported low levels of MLH1 and PMS2 protein expression without hypermethylation of *MLH1* gene promoter (48). Because a low MMR deficiency rate was detected in the examined malignancies, they did not propose a routine screening in these patients. Similarly, another study showed a few LS BrCa cases characterized by MMR deficiency, but one of them demonstrated strong response to anti-PD1 therapy (49). Another study group investigated the correlation between MMR-deficiency and PD-L1 in BrCa cases (50). They detected sub-groups of patients with complete or partial loss of MMR and/or high tumor-infiltrating lymphocytes TILs especially in triple-negative BrCas that were considered eligible for immunotherapy. Additionally, a series of studies

explored the impact of DNA MMR deficiency and MSI rates on PD-L1 expression in BrCas (51-54). They reported absence of DNA MMR deficiency and MSI in the examined cases, whereas PD-L1 positivity was prominent in TILs. In addition to these observations, other studies identified extremely low frequency of MSI in these malignancies with loss of MLH1/PMS2 proteins. They also concluded that in high-level TIL BrCas, MSI-H was absent. Furthermore, another study group focused on the role of potential germline mutations in MMR genes in the development of LS-related BrCa. They detected specific mutational signatures in DNA MMR genes correlated to PD-L1 positive cases (54).

In conclusion, a broad spectrum of genomic alterations such as promoter hyper methylation, mutations, and LOH in the MMR genes including predominantly *hMLH1, hMSH2, hMSH3, hMSH6, hPMS1*, and *hPMS2* have been detected in BrCas. These alterations create specific MSI/MMR genetic signatures in subgroups of patients affecting potentially the response rates to targeted/immuno-therapeutic regimens. Understanding the nature and mechanisms of DNA MMR deficiency in BrCa cases, is a very interesting, significant, and promising field in BrCa molecular oncology.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

GIE, ET: design of the study, ET, EF, MA, GIE, DD: manuscript writing: SM, DS, DP, CD: academic advisors: LM, PF, SM: collection and management of references' data. All Authors read and approved the final manuscript.

References

1 Ma F, Laster K and Dong Z: The comparison of cancer gene mutation frequencies in Chinese and U.S. patient populations. Nat Commun *13(1)*: 5651, 2022. PMID: 36163440. DOI: 10.1038/s41467-022-33351-4

2 Tasli F, Cavdar D, Kececi SD, Zengel B, Adibelli ZH, Dal G, Gonen I, Oz O, Yilmaz C, Ozdemir O, Mollamehmetoglu H, Dilek I, Ilhan E and Uslu A: The importance of the pathological perspective in the management of the invasive lobular carcinoma. Breast J *2022*: 2461242, 2022. PMID: 36237576. DOI: 10.1155/2022/2461242

3 Fakhri N, Chad MA, Lahkim M, Houari A, Dehbi H, Belmouden A and El Kadmiri N: Risk factors for breast cancer in women: an update review. Med Oncol *39(12)*: 197, 2022. PMID: 36071255. DOI: 10.1007/s12032-022-01804-x

4 Shao C, Wan J, Lam FC, Tang H, Marley AR, Song Y, Miller C, Brown M, Han J and Adeboyeje G: A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen *63(6)*: 308-316, 2022. PMID: 36054589. DOI: 10.1002/em.22505

5 Whitworth PW, Beitsch PD, Murray MK, Richards PD, Mislowsky A, Dul CL, Pellicane JV, Baron PL, Rahman RL, Lee LA, Dupree BB, Kelemen PR, Ashikari AY, Budway RJ, Lopez-Penalver C, Dooley W, Wang S, Dauer P, Menicucci AR, Yoder EB, Finn C, Blumencranz LE and Audeh W: Genomic classification of HER2-positive patients with 80-gene and 70-gene signatures identifies diversity in clinical outcomes with HER2-targeted neoadjuvant therapy. JCO Precis Oncol *6*: e2200197, 2022. PMID: 36108259. DOI: 10.1200/PO.22.00197

6 Mayrovitz HN, Orrantia-Borunda E, Anchondo-Nuñez P, Acuña-Aguilar LE, Gómez-Valles FO and Ramírez-Valdespino CA: Subtypes of breast cancer. 2022. PMID: 36122153. DOI: 10.36255/exon-publications-breast-cancer-subtypes

7 Lin C, Cui J, Peng Z, Qian K, Wu R, Cheng Y and Yin W: Efficacy of platinum-based and non-platinum-based drugs on triple-negative breast cancer: meta-analysis. Eur J Med Res *27(1)*: 201, 2022. PMID: 36242046. DOI: 10.1186/s40001-022-00839-0

8 Lin PH and Laliotis G: The present and future of clinical management in metastatic breast cancer. J Clin Med *11(19)*: 5891, 2022. PMID: 36233758. DOI: 10.3390/jcm11195891

9 Wang Y and Minden A: Current molecular combination therapies used for the treatment of breast cancer. Int J Mol Sci *23(19)*: 11046, 2022. PMID: 36232349. DOI: 10.3390/ijms231911046

10 Dey P, Wang A, Ziegler Y, Kumar S, Yan S, Kim SH, Katzenellenbogen JA and Katzenellenbogen BS: Estrogen receptor beta 1: A potential therapeutic target for female triple negative breast cancer. Endocrinology *163(12)*: bqac172, 2022. PMID: 36251879. DOI: 10.1210/endocr/bqac172

11 Pavese F, Capoluongo ED, Muratore M, Minucci A, Santonocito C, Fuso P, Concolino P, Di Stasio E, Carbognin L, Tiberi G, Garganese G, Corrado G, Di Leone A, Generali D, Fragomeni SM, D'Angelo T, Franceschini G, Masetti R, Fabi A, Mulè A, Santoro A, Belli P, Tortora G, Scambia G and Paris I: BRCA mutation status in triple-negative breast cancer patients treated with neoadjuvant chemotherapy: a pivotal role for treatment decision-making. Cancers (Basel) *14(19)*: 4571, 2022. PMID: 36230495. DOI: 10.3390/cancers14194571

12 He Y, Zhang L, Zhou R, Wang Y and Chen H: The role of DNA mismatch repair in immunotherapy of human cancer. Int J Biol Sci *18(7)*: 2821-2832, 2022. PMID: 35541922. DOI: 10.7150/ijbs.71714

13 Dal Buono A, Gaiani F, Poliani L, Correale C and Laghi L: Defects in MMR genes as a seminal example of personalized medicine: from diagnosis to therapy. J Pers Med *11(12)*: 1333, 2021. PMID: 34945805. DOI: 10.3390/jpm11121333

14 Yoshioka KI, Kusumoto-Matsuo R, Matsuno Y and Ishiai M: Genomic instability and cancer risk associated with erroneous DNA repair. Int J Mol Sci *22(22)*: 12254, 2021. PMID: 34830134. DOI: 10.3390/ijms222212254

15 Olave MC and Graham RP: Mismatch repair deficiency: The what, how and why it is important. Genes Chromosomes Cancer *61(6)*: 314-321, 2022. PMID: 34837268. DOI: 10.1002/gcc.23015

16 Yang RK, Chen H, Roy-Chowdhuri S, Rashid A, Alvarez H, Routbort M, Patel KP, Luthra R, Medeiros LJ and Toruner GA: Clinical testing for mismatch repair in neoplasms using multiple laboratory methods. Cancers (Basel) *14(19)*: 4550, 2022. PMID: 36230473. DOI: 10.3390/cancers14194550

17 Chung J, Negm L, Bianchi V, Stengs L, Das A, Liu ZA, Sudhaman S, Aronson M, Brunga L, Edwards M, Forster V, Komosa M,

Davidson S, Lees J, Tomboc P, Samuel D, Farah R, Bendel A, Knipstein J, Schneider KW, Reschke A, Zelcer S, Zorzi A, McWilliams R, Foulkes WD, Bedgood R, Peterson L, Rhode S, Van Damme A, Scheers I, Gardner S, Robbins G, Vanan MI, Meyn MS, Auer R, Leach B, Burke C, Villani A, Malkin D, Bouffet E, Huang A, Taylor MD, Durno C, Shlien A, Hawkins C, Getz G, Maruvka YE, Tabori U and International Replication Repair Deficiency Consortium: Genomic microsatellite signatures identify germline mismatch repair deficiency and risk of cancer onset. J Clin Oncol: JCO2102873, 2022. PMID: 36240479. DOI: 10.1200/JCO.21.02873

18 Taieb J, Svrcek M, Cohen R, Basile D, Tougeron D and Phelip JM: Deficient mismatch repair/microsatellite unstable colorectal cancer: Diagnosis, prognosis and treatment. Eur J Cancer *175*: 136-157, 2022. PMID: 36115290. DOI: 10.1016/j.ejca.2022.07.020

19 Hou Y, Peng Y and Li Z: Update on prognostic and predictive biomarkers of breast cancer. Semin Diagn Pathol *39(5)*: 322-332, 2022. PMID: 35752515. DOI: 10.1053/j.semdp.2022.06.015

20 Wu B, Peng Y, Eggert J and Alexov E: Novel genetic markers for early detection of elevated breast cancer risk in women. Int J Mol Sci *20(19)*: 4828, 2019. PMID: 31569399. DOI: 10.3390/ijms20194828

21 Sigley J, Jarzen J, Scarpinato K, Guthold M, Pu T, Nelli D, Low J and Bonin K: Diffusion and binding of mismatch repair protein, MSH2, in breast cancer cells at different stages of neoplastic transformation. PLoS One *12(1)*: e0170414, 2017. PMID: 28125613. DOI: 10.1371/journal.pone.0170414

22 Lira D, Teodoro TR, Pinhal MA, Fonseca FL, Gehrke Fde S, Azzalis LA, Junqueira VB and Alves Bda C: Profile of hMSH2 expression in breast tumors and lymph nodes: a preliminary study. Eur Rev Med Pharmacol Sci *19(17)*: 3229-3233, 2015. PMID: 26400527.

23 Kappil M, Terry MB, Delgado-Cruzata L, Liao Y and Santella RM: Mismatch repair polymorphisms as markers of breast cancer prevalence in the breast cancer family registry. Anticancer Res *36(9)*: 4437-4441, 2016. PMID: 27630279. DOI: 10.21873/anticanres.10987

24 McCullough LE, Santella RM, Cleveland RJ, Millikan RC, Olshan AF, North KE, Bradshaw PT, Eng SM, Terry MB, Shen J, Crew KD, Rossner P Jr, Teitelbaum SL, Neugut AI and Gammon MD: Polymorphisms in DNA repair genes, recreational physical activity and breast cancer risk. Int J Cancer *134(3)*: 654-663, 2014. PMID: 23852586. DOI: 10.1002/ijc.28383

25 Sahin I and Saat H: New perspectives on the recurrent monoallelic germline mutations of DNA repair and checkpoint genes and clinical variability. Genet Test Mol Biomarkers *26(1)*: 17-25, 2022. PMID: 35089076. DOI: 10.1089/gtmb.2021.0108

26 Sajjadi E, Venetis K, Piciotti R, Invernizzi M, Guerini-Rocco E, Haricharan S and Fusco N: Mismatch repair-deficient hormone receptor-positive breast cancers: Biology and pathological characterization. Cancer Cell Int *21(1)*: 266, 2021. PMID: 34001143. DOI: 10.1186/s12935-021-01976-y

27 Nguyen-Dumont T, Steen JA, Winship I, Park DJ, Pope BJ, Hammet F, Mahmoodi M, Tsimiklis H, Theys D, Clendenning M, Giles GG, Hopper JL and Southey MC: Mismatch repair gene pathogenic germline variants in a population-based cohort of breast cancer. Fam Cancer *19(3)*: 197-202, 2020. PMID: 32060697. DOI: 10.1007/s10689-020-00164-7

28 Venetis K, Sajjadi E, Haricharan S and Fusco N: Mismatch repair testing in breast cancer: the path to tumor-specific immuno-oncology biomarkers. Transl Cancer Res *9(7)*: 4060-4064, 2020. PMID: 35117775. DOI: 10.21037/tcr-20-1852

29 Haricharan S, Punturi N, Singh P, Holloway KR, Anurag M, Schmelz J, Schmidt C, Lei JT, Suman V, Hunt K, Olson JA Jr, Hoog J, Li S, Huang S, Edwards DP, Kavuri SM, Bainbridge MN, Ma CX and Ellis MJ: Loss of MutL disrupts CHK2-dependent cell-cycle control through CDK4/6 to promote intrinsic endocrine therapy resistance in primary breast cancer. Cancer Discov *7(10)*: 1168-1183, 2017. PMID: 28801307. DOI: 10.1158/2159-8290.CD-16-1179

30 Cheng AS, Leung SCY, Gao D, Burugu S, Anurag M, Ellis MJ and Nielsen TO: Mismatch repair protein loss in breast cancer: clinicopathological associations in a large British Columbia cohort. Breast Cancer Res Treat *179(1)*: 3-10, 2020. PMID: 31522348. DOI: 10.1007/s10549-019-05438-y

31 Jiang M, Jia K, Wang L, Li W, Chen B, Liu Y, Wang H, Zhao S, He Y and Zhou C: Alterations of DNA damage repair in cancer: from mechanisms to applications. Ann Transl Med *8(24)*: 1685, 2020. PMID: 33490197. DOI: 10.21037/atm-20-2920

32 Wen YH, Brogi E, Zeng Z, Akram M, Catalano J, Paty PB, Norton L and Shia J: DNA mismatch repair deficiency in breast carcinoma: a pilot study of triple-negative and non-triple-negative tumors. Am J Surg Pathol *36(11)*: 1700-1708, 2012. PMID: 22992699. DOI: 10.1097/PAS.0b013e3182627787

33 Lotsari JE, Gylling A, Abdel-Rahman WM, Nieminen TT, Aittomäki K, Friman M, Pitkänen R, Aarnio M, Järvinen HJ, Mecklin JP, Kuopio T and Peltomäki P: Breast carcinoma and Lynch syndrome: molecular analysis of tumors arising in mutation carriers, non-carriers, and sporadic cases. Breast Cancer Res *14(3)*: R90, 2012. PMID: 22691310. DOI: 10.1186/bcr3205

34 Win AK, Lindor NM and Jenkins MA: Risk of breast cancer in Lynch syndrome: a systematic review. Breast Cancer Res *15(2)*: R27, 2013. PMID: 23510156. DOI: 10.1186/bcr3405

35 Nikitin AG, Chudakova DA, Enikeev RF, Sakaeva D, Druzhkov M, Shigapova LH, Brovkina OI, Shagimardanova EI, Gusev OA and Gordiev MG: Lynch syndrome germline mutations in breast cancer: next generation sequencing case-control study of 1,263 participants. Front Oncol *10*: 666, 2020. PMID: 32547938. DOI: 10.3389/fonc.2020.00666

36 Kanaya N, Tanakaya K, Yamasaki R, Arata T, Shigeyasu K, Aoki H, Morito T, Sanaii H, Akagi K and Fujiwara T: Clinicopathological features of breast cancer in Japanese female patients with Lynch syndrome. Breast Cancer *26(3)*: 359-364, 2019. PMID: 30446972. DOI: 10.1007/s12282-018-0931-z

37 Sheehan M, Heald B, Yanda C, Kelly ED, Grobmyer S, Eng C, Kalady M and Pederson H: Investigating the link between lynch syndrome and breast cancer. Eur J Breast Health *16(2)*: 106-109, 2020. PMID: 32285031. DOI: 10.5152/ejbh.2020.5198

38 Lopez G, Noale M, Corti C, Gaudioso G, Sajjadi E, Venetis K, Gambini D, Runza L, Costanza J, Pesenti C, Grossi F, Maggi S, Ferrero S, Bosari S and Fusco N: PTEN expression as a complementary biomarker for mismatch repair testing in breast cancer. Int J Mol Sci *21(4)*: 1461, 2020. PMID: 32098071. DOI: 10.3390/ijms21041461

39 Malik SS, Zia A, Mubarik S, Masood N, Rashid S, Sherrard A, Khan MB and Khadim MT: Correlation of MLH1 polymorphisms, survival statistics, *in silico* assessment and gene downregulation with clinical outcomes among breast cancer cases. Mol Biol Rep *47(1)*: 683-692, 2020. PMID: 31701475. DOI: 10.1007/s11033-019-05175-x

40 Yuan Y, Xiao WW, Xie WH, Li RZ and Gao YH: Prognostic value of ubiquitin E2 UBE2W and its correlation with tumor-infiltrating immune cells in breast cancer. BMC Cancer *21(1)*: 479, 2021. PMID: 33931024. DOI: 10.1186/s12885-021-08234-4

41 Sunshine J and Taube JM: PD-1/PD-L1 inhibitors. Curr Opin Pharmacol *23*: 32-38, 2015. PMID: 26047524. DOI: 10.1016/j.coph.2015.05.011

42 Sharpe AH, Wherry EJ, Ahmed R and Freeman GJ: The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol *8(3)*: 239-245, 2007. PMID: 17304234. DOI: 10.1038/ni1443

43 Caldwell C Jr, Johnson CE, Balaji VN, Balaji GA, Hammer RD and Kannan R: Identification and validation of a PD-L1 binding peptide for determination of PDL1 expression in tumors. Sci Rep *7(1)*: 13682, 2017. PMID: 29057919. DOI: 10.1038/s41598-017-10946-2

44 Okazaki T and Honjo T: PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol *19(7)*: 813-824, 2007. PMID: 17606980. DOI: 10.1093/intimm/dxm057

45 Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V, West AN, Carmona M, Kivork C, Seja E, Cherry G, Gutierrez AJ, Grogan TR, Mateus C, Tomasic G, Glaspy JA, Emerson RO, Robins H, Pierce RH, Elashoff DA, Robert C and Ribas A: PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature *515(7528)*: 568-571, 2014. PMID: 25428505. DOI: 10.1038/nature13954

46 Wang X, Teng F, Kong L and Yu J: PD-L1 expression in human cancers and its association with clinical outcomes. Onco Targets Ther *9*: 5023-5039, 2016. PMID: 27574444. DOI: 10.2147/OTT.S105862

47 Jiang M, Jia K, Wang L, Li W, Chen B, Liu Y, Wang H, Zhao S, He Y and Zhou C: Alterations of DNA damage response pathway: Biomarker and therapeutic strategy for cancer immunotherapy. Acta Pharm Sin B *11(10)*: 2983-2994, 2021. PMID: 34729299. DOI: 10.1016/j.apsb.2021.01.003

48 Arole V, Shafi S, Challa B, Parwani AV, Tozbikian G and Li Z: Evaluating mismatch repair status to screen clinical advanced breast carcinomas for immunotherapy: Experience from a large academic institution. Clin Breast Cancer *22(5)*: e680-e684, 2022. PMID: 35131187. DOI: 10.1016/j.clbc.2022.01.010

49 Schwartz CJ, da Silva EM, Marra A, Gazzo AM, Selenica P, Rai VK, Mandelker D, Pareja F, Misyura M, D'Alfonso TM, Brogi E, Drullinsky P, Razavi P, Robson ME, Drago JZ, Wen HY, Zhang L, Weigelt B, Shia J, Reis-Filho JS and Zhang H: Morphologic and genomic characteristics of breast cancers occurring in individuals with Lynch syndrome. Clin Cancer Res *28(2)*: 404-413, 2022. PMID: 34667028. DOI: 10.1158/1078-0432.CCR-21-2027

50 Özcan D, Lade-Keller J and Tramm T: Can evaluation of mismatch repair defect and TILs increase the number of triple-negative breast cancer patients eligible for immunotherapy? Pathol Res Pract *226*: 153606, 2021. PMID: 34530255. DOI: 10.1016/j.prp.2021.153606

51 Wu S, Shi X, Wang J, Wang X, Liu Y, Luo Y, Mao F and Zeng X: Triple-negative breast cancer: Intact mismatch repair and partial co-expression of PD-L1 and LAG-3. Front Immunol *12*: 561793, 2021. PMID: 33717059. DOI: 10.3389/fimmu.2021.561793

52 Mills AM, Dill EA, Moskaluk CA, Dziegielewski J, Bullock TN and Dillon PM: The relationship between mismatch repair deficiency and PD-L1 expression in breast carcinoma. Am J Surg Pathol *42(2)*: 183-191, 2018. PMID: 28914717. DOI: 10.1097/PAS.0000000000000949

53 Horimoto Y, Thinzar Hlaing M, Saeki H, Kitano S, Nakai K, Sasaki R, Kurisaki-Arakawa A, Arakawa A, Otsuji N, Matsuoka S, Tokuda E, Arai M and Saito M: Microsatellite instability and mismatch repair protein expressions in lymphocyte-predominant breast cancer. Cancer Sci *111(7)*: 2647-2654, 2020. PMID: 32449246. DOI: 10.1111/cas.14500

54 Davies H, Morganella S, Purdie CA, Jang SJ, Borgen E, Russnes H, Glodzik D, Zou X, Viari A, Richardson AL, Børresen-Dale AL, Thompson A, Eyfjord JE, Kong G, Stratton MR and Nik-Zainal S: Whole-genome sequencing reveals breast cancers with mismatch repair deficiency. Cancer Res *77(18)*: 4755-4762, 2017. PMID: 28904067. DOI: 10.1158/0008-5472.CAN-17-1083

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