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Why Don't Immune Checkpoint Inhibitors Work in Colorectal Cancer?

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Abstract

In recent years, immune checkpoint inhibitors have been shown to be effective in treating manifold types of cancer but less robust in Colorectal Cancer (CRC). While, the subgroup of CRC with Microsatellite Instability (MSI); also termed as Mismatch Repair deficient (dMMR), showed a moderate response to Pembrolizumab in a single arm phase II clinical trial, Microsatellite Stable (MSS) cancers were unresponsive. Possible mechanisms that affect immune response in CRC will be reviewed in this article. We will also propose that Histone Deacetylase (HDAC) inhibition may reverse the immune editing commonly seen in advanced CRC and render them sensitive to immune checkpoint blockade.

Keywords: Immune checkpoint blockade; Colorectal cancer; PD1

Abbreviations:

CRC: Colorectal Cancer; MSI: Microsatellite Instability; MSS: Microsatellite Stable; HDAC: Histone Deacetylase; TAP: Transporter associated Antigen Processing; dMMR: Mismatch Repair deficient; MHC: Major Histocompatibility Complex; ER: Endoplasmic Reticulum; LMP: Low Molecule Protein.

Introduction

Immunotherapy, working through immune checkpoint blockade has achieved notable responses in multiple tumor types including malignant melanoma, renal cell carcinoma, non-small cell lung cancer, bladder carcinoma, Hodgkin's lymphoma, triple-negative breast carcinoma as well as head and neck cancer [1]. However, CRC appears to be one of the tumor types that show a poor response to immune checkpoint inhibitors, apart from the MSI CRC subtype which accounts for about 5% [2] of advanced and metastatic CRC [3]. So why don't immune checkpoint inhibitors work in MSS CRC?

In this brief review we will consider the following:

a) Results of clinical trials of CRC with immune checkpoint inhibitors.

b) Mechanisms underlying immune escape by CRC through immunoediting, which is often caused by down regulating Major Histocompatibility Complex (MHC) class I and class II; down regulation of Transporter associated Antigen Processing (TAP) enzymes; decreased expression of co-stimulatory molecules; infiltration of the tumor by regulatory T cells.

c) Hypothesis that HDAC inhibitors reverse immunoediting.

Results of clinical trials with immune checkpoint inhibitors

Two phase I clinical trials of anti PD-1 (BMS936558, Nivolumab) and anti PD-L1 (BMS936559) antibodies were carried out in a variety of cancer types including CRC (19 CRC out of 296 cancer patients and 18 CRC out of 207 cancer patients respectively). Notably, only 1 patient from the metastatic-CRC cohort in the BMS936558 clinical trial, who had a PD-L1 positive tumor, showed a complete response after 6 months' treatment of BMS936558 and had no signs of tumor recurrence after 3 years. This patient's tumor was also dMMR [4-6].

Since somatic mutations have the potential to encode "non-self" immunogenic antigens, it was hypothesized those tumors with mismatch-repair deficiency that can lead to thousands of somatic mutations may be responsive to immune checkpoint inhibitors. 41 patients with or without dMMR advanced cancer were recruited into a phase II clinical trial of Pembrolizumab conducted by Le, et al. Patients were treated with Pembrolizumab intravenously 10 mg/kg every 2 weeks. They were separated into 3 cohorts of dMMR CRC, MMR-proficient CRC and dMMR non-CRC. The primary end point for the first two cohorts was the immune-related objective response rate and the immune-related progression-free survival rate at 20 weeks. The primary endpoint for the third cohort was the immune-related progression-free survival rate at 20 weeks.

The results showed that the 2 groups with MMR-deficient colorectal or non-CRC had the higher rate of immune-related objective response (40% and 71%) and immune-related progression-free survival at 20 weeks (78% and 67%) compared to the MMR-proficient CRC group (0% and 11%).

Interestingly, 1782 versus 73 somatic mutations per tumor in dMMR tumors and MMR-proficient tumors was demonstrated (P=0.007), and higher somatic mutation loads were associated with prolonged progression-free survival (P=0.02). Rash/pruritus, pancreatitis, and thyroiditis/hypothyroidism were found to be the most common treatment-related adverse events, occurring in approximately 10% of patients. This phase II clinical trial proved that patients with mismatch-repair deficient tumors associated with a heavy load of somatic mutations respond to anti-PD1 therapy [3]. Based on this promising study, phase III trials investigating the effect of anti-PD-1 therapy in MSI-H CRC have been initiated.

Mechanisms of cancer immune evasion in CRC

Cancer immunoediting is the term used to describe the dual role of the immune system in host- protection and tumor-sculpting. It consists of 3 phases (also known as the 3Es): Elimination, Equilibrium and Escape [7,8].

In the elimination phase, congenital and adaptive immune cells recognize and destroy the accumulating tumor cells before the clinical manifestations occur. When the tumor cells break through the elimination phase and proceed into the equilibrium state, immunologic mechanisms begin to work to prevent tumor outgrowth [9,10]. Tumors escape due to the ever growing population and the changes in their response to immunoselective pressures and/or to increased tumor-induced immunosuppression or immune system deterioration. [8,11] There are multiple possible mechanisms causing immunoediting: 1) Down regulation of HLA-I and II. 2) Down regulation of antigen processing TAP enzymes. 3) Decreased expression of co-immunostimulatory molecules; and 4) Infiltration of the tumor by regulatory T cells.

Down regulation of human leukocyte antigen class I: According to Menon, et al., over 70% of CRCs undergo a downregulation of human leukocyte antigen class I, the so called human MHC [12]. Thus, tumor cells with downregulated but not completely depleted HLA-1 expression can avoid T cell and NK cell-mediated immune surveillance, and may be to some extent correlated with poor prognosis [13].

Also, a study with large sample numbers (462 tumors) reported that down regulation of MHC-I is an independent marker for poor prognosis in early stage CRC. This implies that if the immune response does occur in early stage disease, it may eliminate micrometastases which have an intact antigen presenting system.

Down regulation of antigen processing tap enzyme: Crucial for the process of translocating peptide from cytoplasm to the Endoplasmic Reticulum(ER), the TAP system is another factor influencing immunoediting. TAP transporters load peptide fragments from tumor cellular antigens onto MHC I molecules. Loaded MHC-I leave the ER and display the antigen on the cell surface, permitting their recognition by CD8+ T lymphocytes, which can induce a cellular immune response and cell destruction. [14].

Ras oncogenic transformation, found in approximately 40% of CRC, is associated with reduced TAP and proteasome subunit Low Molecule Protein (LMP) mRNA expression. This results in incomplete peptide transport and peptide loading of MHC class I molecules, resulting in reduced stability of expression of the MHC class I complex on the cell surface. [15] Down regulation of or depleted TAP1 has been found in different tumor types with frequencies ranging from 10 to 84% [16-20]. Interestingly interferon-gamma [15] and interferon-alpha [21] treatment can enhance expression of TAP, LMP and MHC class I molecules in parental and ras transformed fibroblasts.

Kasajima, et al. explored the *in vivo* association of TAP and MHC class I antigen and their impact on prognosis in CRC. Immunohistochemical assessment of TAP1, TAP2 and MHC class I antigen expression in 336 sporadic colorectal carcinomas was performed in this study (Figure 1). They found TAP1 and TAP2 expression to be significantly associated with MHC class I antigen expression ($P<0.001$). Increased density of CD8 (+) TIL was predominantly found in TAP1, TAP2 and MHC class I antigen-positive cases, and tumors with CD8+ lymphocytic infiltration had an improved prognosis [22].

Decreased expression of co-stimulatory molecules: The interaction between co-stimulatory molecules expressed on the cell surface of antigen presenting and tumor cells and the receptors on immune cells activate a range of intracellular signals to activate T lymphocytes [24,25]. Common co-stimulatory molecules include B7-1/B7-2: CD28/CTLA-4 family and TNF: TNFR family. Different pairs of costimulatory molecules have different ways to interact with each other, for example, one receptor may be activated with one type of ligand while restricted by other type of ligand or one receptor may be linked to two or more ligands [26-28]. Most tumors lack or downregulate the expression of positive costimulatory molecules such as B7-1 (CD80) and B7-2 (CD86) [29-33].

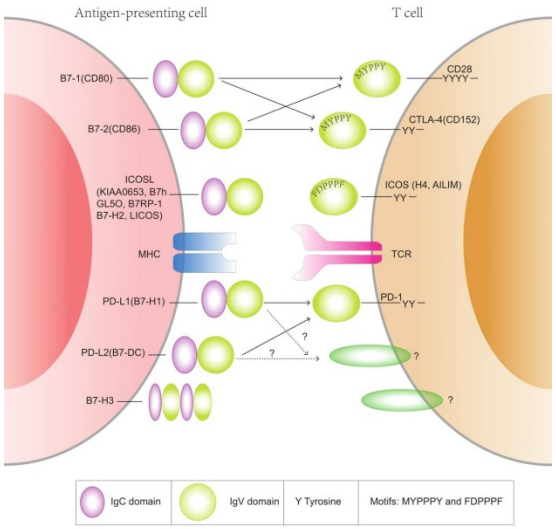

Figure1: Proteins involved in the immune interaction between tumor cells and lymphocytes [23].

Infiltration of the tumor by T regulatory cells: Regulatory T cells act to down regulate effector immune responses. They have a distinct phenotype with the expression of CD4, CD25 and FoxP3. Most studies have concluded that high levels of infiltrating regulatory T cells are correlated with poor prognosis in many kinds of tumors including CRC [34-38]. However, some studies showed that high density infiltration of T reg cells are correlated with an improved outcome in treating cancer [39] which may be explained by differences in methodological sub classification of T reg cells. Both murine models and human *in vitro* models show that depletion of T reg cells induces immune responses against tumor-associated antigens, so it is mechanistically plausible that regulatory T cells are correlated with poor prognosis in CRC [40-43].

Mismatch repair deficiency (MSI)

dMMR or MSI is one of the key genetic mechanisms driving the occurrence and progression of CRC. There are several genes controlling DNA MMR function including MSH2, MLH1. One consequence of dMMR is that these tumor cells carry a very high neo antigen load due to the high frequency of mutations, increasing the

likelihood of immune recognition. Perhaps unsurprisingly, microsatellite unstable colon tumors appear have a strong lymphocyte infiltration [44] and have a significantly better prognosis than MSS CRC, especially in stage II disease [45].

Tumor lymphocytic infiltration

Takemoto, et al. [46] showed that Stroma-Infiltrating Lymphocytes (SIL) were found in approximately the same number in high grade MSI (MSI-H) patients (20%) and low grade MSI (MSI-L) or MSS tumors (12.8%). However, significant differences of Intra-Tumor Cell-Infiltrating Lymphocytes (ITCIL) were shown between MSI-H CRC and MSI-L or MSS CRC patients (41.7% *vs.* 4.3%, respectively ($P<0.001$)). Furthermore, the prognosis of the tumors with higher ITCIL counts was better than the less infiltrated ones. In addition, increased PD-L1 expression has been found at the invasive edge of MSI-H tumors.

All the characteristics mentioned above, as well as the recent definition of highly immunogenic neo-antigens expressed in MSI-H tumor cells, suggest that MSI-H CRCs induce a protective host immune response that may reduce the incidence of metastasis formation and which might explain the better outcome in this patient group [47-49].

Can we reverse immunoediting by treating with HDAC inhibitors?

Researchers have hypothesized that strategies which increase expression of T-cell chemokines and T-cell infiltration of tumors would be capable of enhancing response to PD-1 blockade. There is evidence to suggest that HDAC inhibitors [50,51] are capable of inducing expression of these chemokines in tumor and increasing immune recognition.

It has been reported that increased histone acetylation induced by HDAC inhibitors results in the increase expression of MHC molecules and other molecules involved in antigen processing and presentation [52-55]. Also it can increase expression of tumor antigens recognized by Cytotoxic T Lymphocytes (CTLs) and ligands for NK activating receptors [56,57]. The HDACi romidepsin, induced a strong anti-tumor response against KRAS mutant NSCLC tumors in mice which correlated with T cell infiltration of the tumor, and CD8 T-cell infiltration in human lung tumors has been shown to increase after HDACi vorinostat treatment [58,59]. The combination of the HDAC I depsipeptide and very low concentrations of the cytotoxic antimetabolite 5-fluorouracil (5-FU) induces apoptosis synergistically and up regulates MHC class II in human colon cancer HCT-116 cells [60].

Based on these and many other preclinical study results, several clinical trials have been initiated to evaluate whether the combination of HDAC inhibitors and anti-PD1 therapies can improve tumor responses by enhancing the CD8 T cell infiltration. (NCT02638090, NCT02437136, NCT02697630, NCT01928576, NCT024353620 and NCT02708680) These trials may give an indication if HDAC inhibitors can improve response to anti-PD1 agents in the coming future.

Conclusion

As mentioned in this article, it is the loss of function of cellular immune system that complies possible reason causing no response with checkpoint blockade therapy in CRC. During the cell deterioration process of CRC, the deficiency of immunostimulatory signal presentation and the activation of immunological checkpoints may suppress the immunosurveillance [61]. One clinical approach to targeting the mechanisms that underlie immune evasion in CRC may be to combine immune checkpoint and HDAC inhibitors to restore immunoreactivity and enhance tumor cell kill.

References

1. Sharma P, Allison JP (2015) Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell 161: 205-214.
2. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M (1993) Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis." Nature 363: 558-561.
3. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 372: 2509-2520.
4. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al. (2012) Safety, activity and immune correlates of anti-Pd-1 antibody in cancer. N Engl J Med 366: 2443-2454.
5. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, et al. (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366: 2455-2465.
6. Lipson EJ, Sharfman WH, Drake CG, Wollner Ira, Taube JM, et al. (2013) Durable cancer regression off-treatment and effective reinduction therapy with anti-PD-1 antibody. Clin Cancer Res 19: 462-468.
7. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD, et al. (2002) Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 3: 991-998.
8. Schreiber RD, Old LJ, Smyth MJ (2011) Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 331: 1565-1570.
9. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, et al. (2007) Adaptive immunity maintains occult cancer in an equilibrium state. Nature 450: 903-907.
10. Teng MW, Vesely MD, Duret H, Mclaughlin N, Towne JE, et al. (2012) Opposing roles for IL-23 and IL-12 in maintaining occult cancer in an equilibrium state. Cancer Res 72: 3987-3996.
11. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ (2011) Natural innate and adaptive immunity to cancer. Annu Rev Immunol 29: 235-271.
12. Menon AG, Morreau H, Tollenaar RA, Alphenaar E, Van PM, et al. (2002) Down-regulation of HLA-A expression correlates with a better prognosis in colorectal cancer patients. Lab Invest 82: 1725-1733.
13. Watson NF, Ramage JM, Madjd Z, Spendlove Ian, Ellis IO, et al. (2006) Immunosurveillance is active in colorectal cancer as downregulation but not complete loss of MHC class I expression correlates with a poor prognosis. Int J Cancer 118: 6-10.
14. Abele R, Tampe, R (2004) The ABCs of Immunology: structure and function of Tap, the Transporter Associated with antigen processing. Physiology 19: 216-224.
15. Seliger B, Harders C, Lohmann S, Momburg F, Urlinger S, et al. (1998) Down-regulation of the MHC class I antigen-processing machinery after oncogenic transformation of murine fibroblasts. Eur J Immunol 28: 122-133.
16. Seliger B, Maeurer MJ, Ferrone S (1997) TAP off: tumors on. Immunol Today 18: 292-299.
17. Restifo NP, Esquivel F, Kawakami Y, Yewdell JW, Mule JJ, et al. (1993) Identification of human cancers deficient in antigen processing. J Exp Med 77: 265-272.
18. Murray PG, Constandinou CM, Crocker J, Young LS, Ambinder RF (1998) Analysis of major histocompatibility complex class I, TAP expression and LMP2 epitope sequence in Epstein Barr virus positive Hodgkin's Disease. Blood 92: 2477-2483.

19. Vitale M, Rezzani R, Rodella L, Zauli G, Grigolato P, et al (1998) HLA class I antigen and reansporter associated with antigen processing TAP1 and TAP2 down regulation in high grade primary breast carcinoma lesions. Cancer Res 58: 737-742.
20. Kageshita T, Hirai S, Ono T, Hicklin DJ, Ferrone S (1999) Down-regulation of HLA class I antigen-processing molecules in malignant melanoma: association with disease progression. Am J Pathol 154: 745-754.
21. Heise R, Amann PM, Ensslen S, Marquardt Y, Czaja K, et al. (2016) Interferon alpha signaling and its relevance for the upregulatory effect of transporter proteins associated with antigen processing in patients with malignant melanoma. PLoS One 11: e146325.
22. Kasajima A, Sers C, Sasano H, Johrens K, Stenzinger A, et al. (2010) Down-regulation of the antigen processing machinery is linked to a loss of inflammatory response in colorectal cancer. Hum Pathol 41:1758-1769.
23. Sharpe AH, Freeman GJ (2002) The B7-CD28 super family. Nature Reviews Immunology 2: 116-126.
24. Schwartz RH (1990) A cell culture model for T lymphocyte clonal anergy. Science 248: 1349-1356.
25. Janeway CA, Jr, Bottomly K (1994) Signals and signs for lymphocyte responses. Cell 76: 275-285.
26. Azuma M, Ito D, Yagita DH, Okumura K, Phillips JH, et al. (1993) B70 antigen is a second ligand for CTLA4 and CD28. Nature 366: 76-79.
27. Freeman GJ, Gribben JG, Boussiotis VA, Ng JW, Jr. VA, et al. (1993) Cloning of B7-2: a CTLA-4 counter-receptor that costimulates human T cell proliferation. Science 262: 909-911.
28. Hathcock KS, Laszlo G, Dickler HB, Bradshaw J, Linsley P, et al. (1993) Identification of a CTLA-4 ligand costimulatory for T cell activation. Science 262: 905-907.
29. Nagaraj S, Gabrilovich DI (2008) Tumor escape mechanism governed by myeloid-derived suppressor cells. Cancer Res 68: 2561-2563.
30. Wolfram RM, Budinsky AC, Brodowicz T, Kubista M, Kostler J W, et al. (2000) Defective antigen presentation resulting from impaired expression of costimulatory molecules in breast cancer. Int J Cancer 88: 239-244.
31. Thomas GR, Chen Z, Leukinova E, Waes CV, Wen J (2004) Cytokines IL-1 alpha, IL-6, and GM-CSF constitutively secreted by oral squamous carcinoma induce down-regulation of CD80 costimulatory molecule expression: restoration by interferon gamma. Cancer Immunol Immunother 53: 33-40.
32. Ugurel S, Uhlig D, Pfohler C, Tilgen W, Schadendorf D, et al. (2004) Down-regulation of HLA class II and costimulatory CD86/B7-2 on circulating monocytes from melanoma patients. Cancer Immunol Immunother 53: 551-559.
33. Lindauer M, Rudy W, Guckel B, Doeberitz KM, Meuer SC, et al. (1998) Gene transfer of costimulatory molecules into a human colorectal cancer cell line: requirement of CD54, CD80 and class II MHC expression for enhanced immunogeneity. Immunology 93: 390-397.
34. Carreras J, Lopez-Guillermo A, Fox BC, Colomo L, Martinez A, et al. (2006) High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood 108: 2957-2964.
35. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, et al. (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 10: 942-949.
36. Wolf D, Wolf AM, Rumpold H, Fiegl H, Zeimet AG, et al. (2005) The expression of the regulatory T cell-specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. Clin Cancer Res 11: 8326-8331.
37. Svensson H, Olofsson V, Lundin S, Yakkada C, Bjorck S, et al. (2012) Accumulation of CCR4 CTLA-4 FOXP3CD25 regulatory T cells in colon adenocarcinomas correlate to reduced activation of conventional T cells. PLoS One 7: e30695.
38. Brudvik KW, Henjum K, Aandahl EM, Bjornbeth BA, Tasken K (2012) Regulatory T-cell-mediated inhibition of antitumor immune responses is associated with clinical outcome in patients with liver metastasis from colorectal cancer. Cancer Immunol Immunother 61: 1045-1053.
39. Salama P, Phillips M, Grieu F, Morris M, Zeps N, et al. (2009) Tumor-infiltrating FOXP3+ T regulatory cells show strong prognostic significance in colorectal cancer. J Clin Oncol 27: 186-192.
40. Casares N, Arribillaga L, Sarobe P, Dotor J, Cerio AL, et al. (2003) CD4+/CD25+ regulatory cells inhibit activation of tumor-primed CD4+T cells with IFN-gamma-dependent antiangiogenic activity, as well as long-lasting tumor immunity elicited by peptide vaccination. J Immunol 171: 5931-5939.
41. Taieb J, Chaput N, Schartz N, Roux S, Novault S, et al. (2006) Chemoimmunotherapy of tumors: cyclophosphamide synergizes with exosome based vaccines. J Immunol 176: 2722-2729.
42. Bonertz A, Weitz J, Pietsch DK, Rahbari NH, Schlude C, et al. (2009) Antigen-specific Tregs control T cell responses against a limited repertoire of tumor antigens in patients with colorectal carcinoma. J Clin Invest 119: 3311-3321.
43. Yaqub S, Henjum K, Mahic M, Jahnsen FL, Aandahl EM, et al. (2008) Regulatory T cells in colorectal cancer patients suppress anti-tumor immune activity in a COX-2 dependent manner. Cancer Immunol Immunother 57: 813-821.
44. Smyrk TC, Watson P, Kaul K, Lynch HT (2001) Tumor-infiltrating lymphocytes are a marker for microsatellite instability in colorectal carcinoma. Cancer 91: 2417-2422.
45. Smedt LD, Lemahieu J, Palmans S, Govaere O, Tousseyn T, et al. (2015) Microsatellite instable vs stable colon carcinomas: analysis of tumor heterogeneity, inflammation and angiogenesis. Br J Cancer 113: 500-509.
46. Takemoto N, Konishi F, Yamashita K, Kojima M, Furukawa T, et al. (2004) The correlation of microsatellite instability and tumor-infiltrating lymphocytes in hereditary non-polyposis colorectal cancer (HNPCC) and sporadic colorectal cancers: the significance of different types of lymphocyte infiltration. Jpn J Clin Oncol 34: 90-98.
47. Buckowitz A, Knaebel H-P, Benner A, Blaker H, Gebert J, et al. (2005) Microsatellite instability in colorectal cancer is associated with local lymphocyte infiltration and low frequency of distant metastases. Br J Cancer 92: 1746-1753.
48. Popat S, Hubner R, Houlston RS (2005) Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 23: 609-618.
49. Deschoolmeester V, Baay M, Lardon F, Pauwels P, Peeters M (2011) Immune Cells in Colorectal Cancer: prognostic Relevance and Role of MSI. Cancer Microenviron 4: 377-392.
50. Zheng H, Zhao W, Yan C, Waston CC, Massengill M, et al. (2016) HDAC inhibitors enhance T cell chemokine expression and augment response to PD-1 immunotherapy in lung adenocarcinoma. Clin Cancer Res 22: 4119-4132.
51. Hopewell EL, Zhao W, Fulp WJ, Bronk CC, Lopez AS, et al. (2013) Lung Tumor NF-kappaB signaling promotes T cell-mediated immune surveillance. J Clin Invest 123: 2509-2522.
52. Magner WJ, Kazim AL, Stewart C, Romano MA, Catalano G, et al. (2000) Activation of MHC class I, II, and CD40 gene expression by histone deacetylase inhibitors. J Immunol 165: 7017-7024.
53. Maeda T, Towatari M, Kosugi H, Saito H (2000) Up-regulation of costimulatory/adhesion molecules by histone deacetylase inhibitors in acute myeloid leukemia cells. Blood 96: 3847-3856.
54. Khan AN, Gregorie CJ, Tomasi TB (2008) Histone deacetylase inhibitors induce TAP, LMP, Tapasin genes and MHC class I antigen presentation by melanoma cells. Cancer Immunol Immunother 57: 647-654.
55. Setiadi AF, Omilusik K, David MD, Seipp RP, Hartikainen J, et al. (2008) Epigenetic enhancement of antigen processing and presentation promotes immune recognition of tumors. Cancer Res 68: 9601-9607.
56. Skov S, Pedersen MT, Andresen L, Straten PT, Woetmann A, et al. (2005) Cancer cells become susceptible to natural killer cell killing after exposure to histone deacetylase inhibitors due to glycogen synthase kinase-3-dependent expression of MHC class I-related chain A and B. Cancer Res 65: 11136-11145.

57. Armeanu S, Bitzer M, Lauer UM, Venturelli S, Pathil A, et al. (2005) Natural killer cell-mediated lysis of hepatoma cells via specific induction of NKG2D ligands by the histone deacetylase inhibitor sodium valproate. Cancer Res 65: 6321-6329.

58. Beg AA, Gray JE (2016) HDAC inhibitors with PD-1 blockade: a promising strategy for treatment of multiple cancer types. Epigenomics 8: 1015-1017.

59. Ma T, Galimberti F, Erkmen CP, Memoli V, Chinyengetere F, et al. (2013) Comparing histone deacetylase inhibitor responses in genetically engineered mouse lung cancer models and a window of opportunity trial in patients with lung cancer. Mol Cancer Ther 12:1545-1555.

60. Okada K, Hakata S, Terashima J, Gamou T, Habano W, et al. (2016) Combination of the histone deacetylase inhibitor depsipeptide and 5-fluorouracil upregulates major histocompatibility complex class II and p21 genes and activates caspase-3/7 in human colon cancer HCT-116 cells Oncol Rep 36: 1875-1885.

61. Kroemer G, Galluzzi L, Zitvogel L, Fridman WH (2015) Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy. OncoImmunologgy 4: e1058597.

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