TIM-3, a promising target for cancer immunotherapy

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Abstract: Patients with malignant tumor treated with immunotherapy have received significant clinical benefits over the years. Immune checkpoint blocking agents, such as anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) and anti-programmed cell death protein-1 (anti-PD-1) monoclonal antibodies, have produced impressive clinical results in different types of cancer. T-cell immunoglobulin and mucin domain-3 (TIM-3), another immune checkpoint, could inhibit cancer immunity. Recent studies have highlighted that TIM-3 has an important role to play in T-cell exhaustion and correlates with the outcome of anti-PD-1 therapy. Targeting TIM-3 might be a promising approach for cancer immunotherapy. Here, we review the role of TIM-3 in cancer and clinical trials with TIM-3 inhibitors.

Keywords: immune checkpoint, clinical trial, cancer immunotherapy, T-cell immunoglobulin and mucin domain-3 (TIM-3)

Background

In recent years, cancer immunotherapy, such as programmed death receptor 1 (PD-1) and programmed death-ligand 1 (PD-L1) monoclonal antibodies, has shown promising therapeutic outcomes in cancer.¹⁻⁵ T-cell immunoglobulin mucin-3 (TIM-3) is another important cancer immune checkpoint.⁶ Patients treated with anti-PD-1 or anti-PD-L1 monoclonal antibodies will face the resistance problems. Koyama et al⁶ reported TIM-3 expression was increased when patients faced the anti-PD-1 adaptive resistance.

Introduction to TIM-3

TIM-3, also known as HAVCR2, belongs to the *TIM* gene family. In humans, the TIM family includes TIM-1, TIM-3, and TIM-4 and is located on chromosome 5q33.2. In mice, the TIM family includes TIM-1 to TIM-8 and is located on chromosome 11B1.1.⁷

TIM-3, as a negative regulatory immune checkpoint, is detected in different types of immune cells, including T cells, regulatory T cells (Tregs), dendritic cells (DCs), B cells, macrophages, nature killer (NK) cells, and mast cells.⁷⁻⁹ TIM-3 is a type I membrane protein and consists of 281 amino acids. It comprises an extracellular domain, a single transmembrane domain, and a C-terminal cytoplasmic tail.⁹⁻¹³

TIM-3 has four ligands, including galectin-9 (Gal-9), carcinoembryonic antigen cell adhesion molecule 1 (CEACAM-1), high-mobility group protein B1 (HMGB1), and phosphatidylserine (PS).¹⁴ Gal-9 was the first to be identified. It is a carbohydrate binding protein, specifically recognizing the structure of N-linked sugar chains in the TIM-3 immunoglobulin variable (IgV) domain.¹⁵ TIM-3/Gal-9 can inhibit cancer immunity by negatively regulating T-cell immunity. The connection of the TIM-3 IgV

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domain with Gal-9 can terminate T helper 1 (Th1) immune responses.¹⁰

TIM-3 could induce immunological tolerance.^{10,16} Its molecules are related to asthma, food allergy, and autoimmune disease, such as multiple sclerosis and rheumatoid arthritis.^{7,16} TIM-3 could also inhibit the immune responses of T cells and was associated with immune exhaustion, which induced chronic viral infection.^{12,13,15}

TIM-3 and cancer immunity

TIM-3 inhibited antitumor immunity by mediating T-cell exhaustion.¹⁵ TIM-3+ CD8⁺ T cells exhibit impaired Stat5 and p38 signaling pathway. Blocking the TIM-3 pathway enhanced cancer immunity and increased the production of interferon-gamma (IFN- γ) in T cells.¹⁷ In in vitro and in vivo models, the expression of CD8⁺ TIM-3+ T cells was correlated with PD-1 expression. TIM-3 was constitutively expressed on innate immune cells and could suppress innate antitumor immunity. TIM-3 inhibited the proliferation and effector of cytokine production, such as interleukin-2 (IL-2).^{18–20} PD-1 and TIM-3 positive CD8⁺ T cells produced less IFN- γ than TIM-3 negative CD8⁺ T cells.²¹ Anti-TIM-3 antibodies could also increase IFN- γ of peripheral NK cells.²² Mast cells expressing TIM-3 could be activated through an ITAM-containing receptor for IgE (Fc ϵ RI), using signaling pathways analogous to those in T cells. TIM-3 acts at a receptor-proximal point to enhance Lyn kinase-dependent signaling pathways that modulate both immediate-phase degranulation and late-phase cytokine production downstream of Fc ϵ RI ligation.⁹ TIM-3 could be detected in non-small cell lung cancer (NSCLC),^{22,23} hepatocellular carcinoma (HCC),²⁴ colorectal cancer,^{24–28} cervical cancer,²⁹ ovarian cancer,^{24,30} head and neck cancer,³¹ and so on.

In myelogenous leukemia (AML), upregulated TIM-3 during AML could reduce cytokine production. Co-expression of PD-1 and TIM-3 was correlated with AML progression.¹⁸ In follicular B-cell non-Hodgkin lymphoma, TIM-3 was expressed on nearly 35% of lymph node CD4⁺ and CD8⁺ T cells and could mediate T-cells exhaustion.³² In glioma patients, TIM-3 was correlated with cancer immune escape and might be a potent target.³³ In gastric cancer, TIM-3 could promote disease progression,³⁴ and Gal-9 and TIM-3 expressed on tumor cells might be a potential, independent prognostic factor. Decreased Gal-9 and increased TIM-3 were associated with a poor prognosis in gastric cancer.³⁵ PD-1+ and TIM-3+ CD8⁺ T cells could impair the functioning of CD8⁺ T cells in gastric cancer.^{21,36} In colorectal cancer, upregulation of TIM-3 could restrict

T-cell responses and might participate in tumorigenesis. The expression of TIM-3 might be an independent prognostic factor for colorectal cancer.²⁷ TIM-3 was correlated with the progression of colorectal cancer and could be a potential therapeutic target for the disease.²⁵ PD-1 and TIM-3 could impair surgery colorectal cancer patients' cell-mediated immunity.²⁸ In NSCLC patients, TIM-3 was expressed on about 30% of CD8⁺ tumor-infiltrating lymphocytes (TILs) and 60% of CD4⁺ FoxP3+ TILs. TIM-3+ FoxP3+ Tregs were correlated with the lung cancer stages.³⁷ TIM-3 expression in NK cells was related to disease progression of lung cancer.³⁸ In prostate cancer, TIM-3 could affect disease development and progression.^{39,40} In renal cell carcinoma (RCC), TIM-3 expressed on cancer cells and in myeloid cells could inhibit cancer immunity.⁴¹ In ovarian cancer, TIM-3 could negatively regulate various T-cell subsets. TIM-3 expression on CD4⁺ T cells could serve to predict the outcome of anticancer therapies.³⁰ In cervical cancer, the expression of TIM-3 in tumor cells might be a potential prognostic factor and could promote metastases.²⁹

Targeting TIM-3 in cancer

TIM-3 could be a promising target in cancer because of its expression on a variety of T cells.¹⁶ TIM-3 was also expressed on myeloid cells, such as DCs, macrophages, and monocytes. TIM-3 has an important role in innate immune cell-mediated antitumor immune responses.^{16,42}

An increasing number of preclinical studies have reported that TIM-3 could improve the outcomes of cancer immunotherapy (Table 1).

TIM-3 inhibitors have shown similar efficacy as that of PD-1 inhibitors in preclinical research.⁴⁴ It was reported that PD-1 antibodies may lead to an increase in TIM-3 expression in in vivo models of lung cancer, which showed TIM-3 might be a marker of PD-1 blocking antibody resistance.⁶ PD-1, TIM-3, and LAG-3 were upregulated on tumor-associated antigen-specific T cells in HCC tissues. PD-1, TIM-3, or LAG-3 inhibitors could enhance T cells' response to tumor antigens, and had a synergistic function.⁵² TIM-3+ PD-1+ CD8⁺ TILs inhibited the production of cytokines, such as IFN- γ , tumor necrosis factor-alpha (TNF- α), and IL-2.⁵¹ The combined use of TIM-3 blockade with PD-1 blockade could be more effective than blockade of either the TIM-3 or PD-1 alone.^{6,17–19,43,44,48,49,51,53}

Currently, many clinical trials are focusing on TIM-3 as a new approach to the treatment of cancer (Table 2).

Cancer immunotherapy has shown promising therapeutic outcomes. T-cell checkpoint inhibitor is one of the most promising new therapeutic approaches in cancer. TIM-3

Table I TIM-3 and cancer

Year	Diseases	Conclusions	References
2010	Solid tumors	Combined TIM-3 with PD-1 inhibitor could prevent tumor progression.	19
2010	Melanoma	TIM-3/TIM-3L inhibitor combined with PD-1/PD-L1 inhibitor could reverse T-cell exhaustion and/or dysfunction in advanced melanoma.	43
2011	Cancer	Anti-TIM-3 molecular antibody suppressed tumors by promoting T-cell IFN- γ -mediated antitumor immunity.	44
2011	AML	Combined PD-1/PD-L1 with TIM-3/Gal-9 blockade could prevent CD8 ⁺ T-cell exhaustion in advanced AML.	18
2013	AML	In xenograft models, anti-TIM-3 IgG2a antibody could improve cytotoxic activities and eradicate AML leukemic stem cells.	45
2013	Melanoma	Combined anti-TIM-3 with anti-TIM-4 molecule antibodies could increase the antitumor responses in vivo.	46
2013	Ovarian cancer	Combined anti-TIM-3 and CD137 molecule antibodies significantly inhibited tumor progression.	47
2014	Melanoma	PD-1 combined with TIM-3 blockades could stimulate potential antitumor T-cell responses in melanoma.	48
2015	Gastric cancer	Combined treatments of TIM-3 and CD137, TIM-3 and PD-1, and TIM-3 and CEACAM1 could enhance immune cell response in progression stage cancer. And anti-TIM-3 and anti-TIM-4 molecule antibodies could increase cancer vaccine's efficacy.	49
2015	RCC	TIM-3 expressed on myeloid cells played a critical role in augmenting tumorigenic activities of TIM-3-negative RCC cells. Anti-TIM-3 monoclonal antibody suppressed the cancer cells.	41
2015	Colon cancer	Gal-9/TIM-3 blockade could inhibit the tumor progression in vivo. The blockade increased therapeutic efficacy of cyclophosphamide.	50
2015	Colon cancer	TIM-3 was correlated with colon cancer immune escape.	26
2015	Lung adenocarcinoma	TIM-3 could express on NK cells and was a potential new immune therapy target.	22
2015	Colorectal carcinoma	Higher expression of TIM-3 indicated restriction of T-cell responses.	27
2015	Gastric cancer	TIM-3 expression was correlated with the stages of gastric cancer and was regulated by T-bet.	36
2016	RCC	Blocking the TIM-3 pathway reversed cell proliferation and increased IFN- γ production in varied types of T cell.	17
2016	Colorectal carcinoma	TIM-3/TIM-3L and PD-1/PD-L1 blockade reversed T-cell dysfunction and exhaustion in colorectal cancer.	51
2016	Glioma	Gal-9/TIM-3 pathway was important in immune evasion and could be a potential target in glioma.	33
2017	AML	TIM-3/Gal-9 was a reliable target for AML immune therapy.	20
2017	HCC	Antibodies against PD-L1, TIM-3, or LAG-3 restored responses of HCC-derived T cells to tumor antigens.	52
2017	Gastric cancer	Dual blockade of TIM-3 and PD-1 could improve antitumor function of cancer CD8 ⁺ T cells.	53
2017	Colorectal cancer	TIM-3 was correlated with the progression of colorectal cancer and could be a potential therapeutic target.	25
2017	Prostate cancer	TIM-3 inhibited the immune response in prostate cancer and could be a potential therapeutic target.	40

Abbreviations: TIM-3, T cell immunoglobulin mucin-3; TIM-3L, T cell immunoglobulin mucin-ligand 3; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; IFN- γ , interferon- γ ; Gal-9, galectin-9; AML, acute myeloid leukemia; RCC, renal cell carcinoma; NK, nature killer; HCC, Hepatocellular carcinoma; LAG-3, lymphocyte-activation gene-3.

inhibits antitumor immunity. The roles of TIM-3 in cancer immunity need to be further investigated. New treatment targeting TIM-3 could soon provide a breakthrough in cancer treatment and improve patient outcomes.

Acknowledgment

This study was supported in part by a grant from National Natural Science Foundation of China (81802255), Shanghai Pujiang Program (17PJD036) and a grant from Shanghai

Table 2 Clinical trials of TIM-3 inhibitors

Year	Drug	Phase	Company	Type	Objective	ClinicalTrial.gov identifier
2015	MBG453	I	Novartis Pharmaceuticals (Basel, Switzerland)	Anti-TIM-3	MBG453 given alone or combined with PDR001 in adult patients with advanced malignancies	NCT02608268
2016	TSR-022	I	Tesaro, Inc. (Waltham, MA, USA)	Anti-TIM-3	Dose escalation and cohort expansion study of TSR-022 in advanced solid tumors	NCT02817633
2017	LY3321367	I	Eli Lilly and Company (Indianapolis, IN, USA)	Anti-TIM-3	LY3321367 alone or combined with an anti-PD-L1 antibody in advanced relapsed/refractory solid tumors	NCT03099109
2017	MBG453	I	Novartis Pharmaceuticals	Anti-TIM-3	PDR001 and/or MBG453 in combination with decitabine in AML or high-risk MDS	NCT03066648

Municipal Commission of Health and Family Planning Program (20174Y0131). National key research & development project (2016YFC0902300). Major disease clinical skills enhancement program of three year action plan for promoting clinical skills and clinical innovation in municipal hospitals, Shanghai Shen Kang Hospital Development Center Clinical Research Plan of SHDC (16CR1001A). The fundamental research funds for the central universities.

Disclosure

The authors report no conflicts of interest in this work.

References

- Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255–265.
- Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18(1):31–41.
- Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16(4):375–384.
- Valsecchi ME. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med*. 2015;373(13):1270–1271.
- Thoma C. CheckMate for advanced-stage ccRCC? Nivolumab and cabozantinib aMETEORate poor survival. *Nat Rev Clin Oncol*. 2015;12(12):742.
- Koyama S, Akbay EA, Li YY, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat Commun*. 2016;7:10501.
- Li Z, Ju Z, Frieri M. The T-cell immunoglobulin and mucin domain (Tim) gene family in asthma, allergy, and autoimmunity. *Allergy Asthma Proc*. 2013;34(1):21–26.
- Monney L, Sabatos CA, Gaglia JL, et al. Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. *Nature*. 2002;415(6871):536–541.
- Phong BL, Avery L, Sumpter TL, et al. Tim-3 enhances FcεRI-proximal signaling to modulate mast cell activation. *J Exp Med*. 2015;212(13):2289–2304.
- Cao E, Zang X, Ramagopal UA, et al. T cell immunoglobulin mucin-3 crystal structure reveals a galectin-9-independent ligand-binding surface. *Immunity*. 2007;26(3):311–321.
- Anderson AC, Xiao S, Kuchroo VK. Tim protein structures reveal a unique face for ligand binding. *Immunity*. 2007;26(3):273–275.
- Lee J, Su EW, Zhu C, et al. Phosphotyrosine-dependent coupling of Tim-3 to T-cell receptor signaling pathways. *Mol Cell Biol*. 2011;31(19):3963–3974.
- Ferris RL, Lu B, Kane LP. Too much of a good thing? Tim-3 and TCR signaling in T cell exhaustion. *J Immunol*. 2014;193(4):1525–1530.
- Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. *Immunity*. 2016;44(5):989–1004.
- Zhu C, Sakuishi K, Xiao S, et al. An IL-27/NFIL3 signalling axis drives Tim-3 and IL-10 expression and T-cell dysfunction. *Nat Commun*. 2015;6:6072.
- Freeman GJ, Casanovas JM, Umetsu DT, Dekruyff RH. TIM genes: a family of cell surface phosphatidylserine receptors that regulate innate and adaptive immunity. *Immunol Rev*. 2010;235(1):172–189.
- Cai C, Xu YF, Wu ZJ, et al. Tim-3 expression represents dysfunctional tumor infiltrating T cells in renal cell carcinoma. *World J Urol*. 2016;34(4):561–567.
- Zhou Q, Munger ME, Veenstra RG, et al. Coexpression of Tim-3 and PD-1 identifies a CD8+ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. *Blood*. 2011;117(17):4501–4510.
- Sakuishi K, Apetoh L, Sullivan JM, et al. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *J Exp Med*. 2010;207(10):2187–2194.
- Gonçalves Silva I, Yasinska IM, Sakhnevych SS, et al. The Tim-3-galectin-9 Secretory Pathway is Involved in the Immune Escape of Human Acute Myeloid Leukemia Cells. *EBioMedicine*. 2017;22:44–57.
- Takano S, Saito H, Ikeguchi M. An increased number of PD-1+ and Tim-3+ CD8+ T cells is involved in immune evasion in gastric cancer. *Surg Today*. 2016;46(11):1341–1347.
- Xu L, Huang Y, Tan L, et al. Increased Tim-3 expression in peripheral NK cells predicts a poorer prognosis and Tim-3 blockade improves NK cell-mediated cytotoxicity in human lung adenocarcinoma. *Int Immunopharmacol*. 2015;29(2):635–641.

23. Thommen DS, Schreiner J, Müller P, et al. Progression of lung cancer is associated with increased dysfunction of T cells defined by coexpression of Multiple Inhibitory Receptors. *Cancer Immunol Res.* 2015;3(12):1344–1355.
24. Yan J, Zhang Y, Zhang JP, et al. Tim-3 expression defines regulatory T cells in human tumors. *PLoS One.* 2013;8(3):e58006.
25. Yu M, Lu B, Liu Y, et al. Tim-3 is upregulated in human colorectal carcinoma and associated with tumor progression. *Mol Med Rep.* 2017;15(2):689–695.
26. Zhou E, Huang Q, Wang J, et al. Up-regulation of Tim-3 is associated with poor prognosis of patients with colon cancer. *Int J Clin Exp Pathol.* 2015;8(7):8018–8027.
27. Xu B, Yuan L, Gao Q, et al. Circulating and tumor-infiltrating Tim-3 in patients with colorectal cancer. *Oncotarget.* 2015;6(24):20592–20603.
28. Arai Y, Saito H, Ikeguchi M. Upregulation of TIM-3 and PD-1 on CD4+ and CD8+ T Cells Associated with Dysfunction of Cell-Mediated Immunity after Colorectal Cancer Operation. *Yonago Acta Med.* 2012;55(1):1–9.
29. Cao Y, Zhou X, Huang X, et al. Tim-3 expression in cervical cancer promotes tumor metastasis. *PLoS One.* 2013;8(1):e53834.
30. Wu J, Liu C, Qian S, Hou H. The expression of Tim-3 in peripheral blood of ovarian cancer. *DNA Cell Biol.* 2013;32(11):648–653.
31. Jie HB, Gildener-Leapman N, Li J, et al. Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients. *Br J Cancer.* 2013;109(10):2629–2635.
32. Yang ZZ, Grote DM, Ziesmer SC, et al. IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. *J Clin Invest.* 2012;122(4):1271–1282.
33. Liu Z, Han H, He X, et al. Expression of the galectin-9-Tim-3 pathway in glioma tissues is associated with the clinical manifestations of glioma. *Oncol Lett.* 2016;11(3):1829–1834.
34. Cheng G, Li M, Wu J, et al. Expression of Tim-3 in gastric cancer tissue and its relationship with prognosis. *Int J Clin Exp Pathol.* 2015;8(8):9452–9457.
35. Jiang J, Jin MS, Kong F, et al. Decreased galectin-9 and increased Tim-3 expression are related to poor prognosis in gastric cancer. *PLoS One.* 2013;8(12):e81799.
36. Wang Z, Zhu J, Gu H, et al. The Clinical Significance of Abnormal Tim-3 Expression on NK Cells from Patients with Gastric Cancer. *Immunol Invest.* 2015;44(6):578–589.
37. Gao X, Zhu Y, Li G, et al. TIM-3 expression characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. *PLoS One.* 2012;7(2):e30676.
38. Xu LY, Chen DD, He JY, et al. Tim-3 expression by peripheral natural killer cells and natural killer T cells increases in patients with lung cancer – reduction after surgical resection. *Asian Pac J Cancer Prev.* 2014;15(22):9945–9948.
39. Piao YR, Jin ZH, Yuan KC, Jin XS. Analysis of Tim-3 as a therapeutic target in prostate cancer. *Tumour Biol.* 2014;35(11):11409–11414.
40. Piao Y, Jin X. Analysis of Tim-3 as a therapeutic target in prostate cancer. *Tumour Biol.* 2017;39(7):1010428317716628:101042831771662.
41. Komohara Y, Morita T, Annan DA, et al. The Coordinated Actions of TIM-3 on Cancer and Myeloid Cells in the Regulation of Tumorigenicity and Clinical Prognosis in Clear Cell Renal Cell Carcinomas. *Cancer Immunol Res.* 2015;3(9):999–1007.
42. Chiba S, Baghdadi M, Akiba H, et al. Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. *Nat Immunol.* 2012;13(9):832–842.
43. Fourcade J, Sun Z, Benallaoua M, et al. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. *J Exp Med.* 2010;207(10):2175–2186.
44. Ngiew SF, von Scheidt B, Akiba H, Yagita H, Teng MW, Smyth MJ. Anti-TIM3 antibody promotes T cell IFN- γ -mediated antitumor immunity and suppresses established tumors. *Cancer Res.* 2011;71(10):3540–3551.
45. Kikushige Y, Miyamoto T. TIM-3 as a novel therapeutic target for eradicating acute myelogenous leukemia stem cells. *Int J Hematol.* 2013;98(6):627–633.
46. Baghdadi M, Nagao H, Yoshiyama H, et al. Combined blockade of TIM-3 and TIM-4 augments cancer vaccine efficacy against established melanomas. *Cancer Immunol Immunother.* 2013;62(4):629–637.
47. Guo Z, Cheng D, Xia Z, et al. Combined TIM-3 blockade and CD137 activation affords the long-term protection in a murine model of ovarian cancer. *J Transl Med.* 2013;11:215.
48. Fourcade J, Sun Z, Pagliano O, et al. PD-1 and Tim-3 regulate the expansion of tumor antigen-specific CD8+ T cells induced by melanoma vaccines. *Cancer Res.* 2014;74(4):1045–1055.
49. Cheng L, Ruan Z. Tim-3 and Tim-4 as the potential targets for antitumor therapy. *Hum Vaccin Immunother.* 2015;11(10):2458–2462.
50. Kang CW, Dutta A, Chang LY, et al. Apoptosis of tumor infiltrating effector TIM-3+CD8+ T cells in colon cancer. *Sci Rep.* 2015;5:15659.
51. Liu J, Zhang S, Hu Y, et al. Targeting PD-1 and Tim-3 Pathways to Reverse CD8 T-Cell Exhaustion and Enhance Ex Vivo T-Cell Responses to Autologous Dendritic/Tumor Vaccines. *J Immunother.* 2016;39(4):171–180.
52. Zhou G, Sprengers D, Boor PPC, et al. Antibodies Against Immune Checkpoint Molecules Restore Functions of Tumor-Infiltrating T Cells in Hepatocellular Carcinomas. *Gastroenterology.* 2017;153(4):1107e10–1119.
53. Lu X, Yang L, Yao D, et al. Tumor antigen-specific CD8+ T cells are negatively regulated by PD-1 and Tim-3 in human gastric cancer. *Cell Immunol.* 2017;313:43–51.

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