

TIM-3, a promising target for cancer immunotherapy

Yayi He^{1,*}
Jie Cao^{1,*}
Chao Zhao²
Xuefei Li²
Caicun Zhou¹
Fred R Hirsch³

¹Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai 200433, People's Republic of China; ²Department of Lung Cancer and Immunology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai 200433, People's Republic of China; ³Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

*These authors contributed equally to this work

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

Correspondence: Caicun Zhou
Department of Medical Oncology,
Shanghai Pulmonary Hospital, Tongji
University Medical School Cancer
Institute, Tongji University School of
Medicine, No 507 Zhengmin Road,
Shanghai 200433, People's Republic
of China
Tel +86 65 115 006 3050
Email caicunzhoudr@163.com

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.

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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

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Disclosure

The authors report no conflicts of interest in this work.

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