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 al7 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

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
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 (FcepsilonRI), 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 FcepsilonRI 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,30,32 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 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 1 TIM-3 and cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Diseases</th>
<th>Conclusions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Solid tumors</td>
<td>Combined TIM-3 with PD-1 inhibitor could prevent tumor progression.</td>
<td>19</td>
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<tr>
<td>2010</td>
<td>Melanoma</td>
<td>TIM-3/TIM-3L inhibitor combined with PD-1/PD-L1 inhibitor could reverse T-cell exhaustion and/or dysfunction in advanced melanoma.</td>
<td>43</td>
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<td>2011</td>
<td>Cancer</td>
<td>Anti-TIM-3 molecular antibody suppressed tumors by promoting T-cell IFN-γ-mediated antitumor immunity.</td>
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<tr>
<td>2011</td>
<td>AML</td>
<td>Combined PD-1/PD-L1 with TIM-3/Gal-9 blockade could prevent CD8+ T-cell exhaustion in advanced AML.</td>
<td>18</td>
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<tr>
<td>2013</td>
<td>AML</td>
<td>In xenograft models, anti-TIM-3 IgG2a antibody could improve cytotoxic activities and eradicate AML leukemic stem cells.</td>
<td>45</td>
</tr>
<tr>
<td>2013</td>
<td>Melanoma</td>
<td>Combined anti-TIM-3 with anti-TIM-4 molecule antibodies could increase the antitumor responses in vivo.</td>
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<td>2013</td>
<td>Ovarian cancer</td>
<td>Combined anti-TIM-3 and CD137 molecule antibodies significantly inhibited tumor progression.</td>
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<tr>
<td>2014</td>
<td>Melanoma</td>
<td>PD-1 combined with TIM-3 blockades could stimulate potential antitumor T-cell responses in melanoma.</td>
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<td>2015</td>
<td>Gastric cancer</td>
<td>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.</td>
<td>49</td>
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<td>2015</td>
<td>RCC</td>
<td>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.</td>
<td>41</td>
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<td>2015</td>
<td>Colon cancer</td>
<td>Gal-9/TIM-3 blockade could inhibit the tumor progression in vivo. The blockade increased therapeutic efficacy of cyclophosphamide.</td>
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<tr>
<td>2015</td>
<td>Colon cancer</td>
<td>TIM-3 was correlated with colon cancer immune escape.</td>
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<tr>
<td>2015</td>
<td>Lung adenocarcinoma</td>
<td>TIM-3 could express on NK cells and was a potential new immune therapy target.</td>
<td>22</td>
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<tr>
<td>2015</td>
<td>Colorectal carcinoma</td>
<td>Higher expression of TIM-3 indicated restriction of T-cell responses.</td>
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</tr>
<tr>
<td>2015</td>
<td>Gastric cancer</td>
<td>TIM-3 expression was correlated with the stages of gastric cancer and was regulated by T-bet.</td>
<td>36</td>
</tr>
<tr>
<td>2016</td>
<td>RCC</td>
<td>Blocking the TIM-3 pathway reversed cell proliferation and increased IFN-γ production in varied types of T cell.</td>
<td>17</td>
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<tr>
<td>2016</td>
<td>Colorectal carcinoma</td>
<td>TIM-3/TIM-3L and PD-1/PD-L1 blockade reversed T-cell dysfunction and exhaustion in colorectal cancer.</td>
<td>51</td>
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<td>2016</td>
<td>Glioma</td>
<td>Gal-9/TIM-3 pathway was important in immune evasion and could be a potential target in glioma.</td>
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<tr>
<td>2017</td>
<td>AML</td>
<td>TIM-3/Gal-9 was a reliable target for AML immune therapy.</td>
<td>20</td>
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<td>2017</td>
<td>HCC</td>
<td>Antibodies against PD-L1, TIM-3, or LAG-3 restored responses of HCC-derived T cells to tumor antigens.</td>
<td>52</td>
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<tr>
<td>2017</td>
<td>Gastric cancer</td>
<td>Dual blockade of TIM-3 and PD-1 could improve antitumor function of cancer CD8+ T cells.</td>
<td>53</td>
</tr>
<tr>
<td>2017</td>
<td>Colorectal cancer</td>
<td>TIM-3 was correlated with the progression of colorectal cancer and could be a potential therapeutic target.</td>
<td>25</td>
</tr>
<tr>
<td>2017</td>
<td>Prostate cancer</td>
<td>TIM-3 inhibited the immune response in prostate cancer could be a potential therapeutic target.</td>
<td>40</td>
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</table>

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, galactin-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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**Disclosure**

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