Tim-3 and Tim-4 as the potential targets for antitumor therapy

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Abbreviations: APC, antigen-presenting cells; BTLA, B and T lymphocyte attenuator; CEACAM1, carcinoembryonic antigen cell adhesion molecule 1; CTL, cytotoxicity T lymphocyte; CTLA-4, cytotoxic T lymphocyte antigen-4; DAMPs, danger associated pattern molecules; DCs, dendritic cells; HCC, hepatocellular carcinoma; HMGB1, high mobility group protein B1; LAG-3, lymphocyte activation gene-3; mAbs, monoclonal antibodies; MDSC, myeloid-derived suppressor cells; NK, natural killer cells; NKT, natural killer T cells; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PS, phosphatidylserine; RCC, renal cell cancer; TADC, tumor associated dendritic cells; TAM, tumor associated macrophages; Th1-T TGF-b, transforming growth factor-β; helper type 1 cells; Tim, T-cell immunoglobulin and mucin domain; VEGF, vascular endothelial growth factor

Both Tim-3 and Tim-4 belong to the T-cell immunoglobulin and mucin domain (Tim) gene family, which plays a critical role in immunoregulation. Tim-3 has been suggested as a negative regulator of anti-tumor immunity due to its function on inducing T cells exhaustion in cancer. In addition to its expression on exhausted T cells, Tim-3 also has been reported to up-regulate on nature killer (NK) cells and promote NK cells functionally exhausted in cancer. While Tim-3 selectively expression on most types of leukemia stem cells, it promotes the progression of acute myeloid leukemia. Recently, data from experimental models of tumor discovered that Tim-3 and Tim-4 up-regulation on tumor associated dendritic cells and macrophages attenuated the anti-tumor effects of cancer vaccines and chemotherapy. Moreover, co-blockage of Tim-3 and PD-1, Tim-3 and CD137, Tim-3 and carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) could enhance cell-mediated immunity in advanced tumor, and combined treatment with anti-Tim-3 and anti-Tim-4 mAbs further increase the efficacy of cancer vaccines. The therapeutic manipulation of TIM-3 and TIM-4 may provide a novel strategy to improve the clinical efficacy of cancer immunotherapy.

Introduction

The T-cell immunoglobulin and mucin domain (Tim) gene family was discovered in 2001, which plays a critical role in immunoregulation.1 The Tim gene family comprises of 8 members (TIM-1–8) on mouse chromosome 11B1.1 and 3 members (TIM-1, TIM-3, and TIM-4) on human chromosome 5q33.2.2 Tim-3 is expressed on many types of immune cells, including T cells, dendritic cells (DCs), macrophages, nature killer cells (NK), cancer stem cells, and so on.3 TIM-3 is previously known as a receptor for galectin-9 and phosphatidylserine (PS), it may induce the apoptosis of T cells, enhance the secretion of pro-inflammatory cytokines such as TNF by DCs and NK cells, and promote the phagocytosis of apoptotic cells by monocytes and macrophages through interaction with its ligands.4,5 Recently, carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1), another well-known molecule expressed on activated T cells and involved in T-cell inhibition, was discovered as a heterophilic ligand for TIM-3, and their interaction had a crucial role in regulating autoimmunity.6 Unlike Tim-3, Tim-4 is exclusively expressed on antigen-presenting cells (APCs),7 and serves as a critical sensor for controlling the functions of naive and activated T cells and phagocytosis of apoptotic cells by APCs through interaction with PS.8,9

Indeed, Tim-3 has been reported as a negative regulator of anti-tumor immunity. The expression of Tim-3 on T cells in cancer may induce T cell exhaustion, and promote the expansion of immunosuppressive CD4+FoxP3+ regulatory T (Treg) cells and CD11b+Gr-1+ myeloid suppressor cells (MDSC).10 Recent reports also showed that TIM-3, as a surface molecule, is selectively expressed on leukemia stem cells (LSCs) in acute myeloid leukemia (AML), and as such it can be a good target in eradicating AML stem cells, leaving normal hematopoietic stem cells intact.11-13 In addition, Tim-3 has also been reported to up-regulate on tumor associated dendritic cells (TADC) and macrophages (TAM), and attenuate the antitumor effects of cancer vaccines.4 (Fig. 1). The expression of Tim-4 on TAM could mediate degradation of dying tumor cells by autophagy, reduce antigen presentation and impaired cytotoxicity T lymphocyte (CTL) responses, and suppress the antitumor effects of chemotherapy.14 Co-blockage of Tim-3 with other negative checkpoint regulators expressed on T cells, such as programmed death-1 (PD-1) and CD137, would enhance cell-mediated immunity in advanced tumor, and combined treatment with anti-Tim-3 and anti-Tim-4 mAbs further increase the efficacy of cancer vaccines.
Tim-3 was discovered nearly 10 y ago as a molecule expressed on IFN-γ-producing CD4+ T helper type 1 (Th1) and CD8+ T cytotoxic type 1 (Tc1) cells, and induced T cell apoptosis through interaction with its ligand galectin-9. And then, several studies have identified TIM-3 as an important immune regulator in the tumor microenvironment due to its negative regulation on various T-cell subsets. Within the tumor microenvironment, a cross-talk between the infiltrating cells may occur conditioning the characteristic of the in situ immune response. CD4+ or CD8+ Tumor-Induced Senescent T cells may promote production of pro-inflammatory cytokines (TNF, IL-1β and IL-6) and angiogenic factors (MMP-9, VEGF-A and IL-8) by CD14+ monocytes/macrophages (Mo/Ma), and Tim-3 and CD40 are involved in this modulation.15

In addition, a synergistic action between negative checkpoint regulators expressed on T cells may also exist. The expression of negative checkpoint regulator PD-1 and TIM-3 impairing cell-mediated immunity was observed in advanced melanoma and colorectal cancer.16,17 Co-blockage of Tim-3 and PD-1 could enhance the expansion and function of tumor antigen–specific CD8+ T cells in vitro and in vivo, induce tumor rejection in experimental models and enhance the vaccine effect in patients with advanced melanoma.18,19 New treatment targeting TIM-3 and PD-1 on CD4+ and CD8+ T cells may provide a breakthrough treatment to cancer patients. In a murine model of ovarian cancer, co-blockage of Tim-3 and CD137 was able to prevent the tumor progression in advanced established tumor by increasing the number of CD4+ and CD8+ cells and decreasing immunosuppressive CD4+FoxP3+ regulatory T (Treg) cells and CD11b+Gr-1+ MDSC.20 Also, co-blockade of CEACAM1 and TIM-3 leads to enhancement of anti-tumor immune responses with improved elimination of tumors in mouse colorectal cancer models.6 Other negative checkpoint regulators expression on tumor-infiltrating lymphocytes, such as cytotoxic T lymphocyte antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3) and BTLA (B and T lymphocyte attenuator) also negatively regulate antitumor immunity in tumor microenvironments, the effects of co-blockage of them with Tim-3 still need further investigation.21-23

**Tim-3 and TIM-4 on TADC and TAM**

Despite Tim-3 and Tim-4 expressed by DCs and macrophages promote the phagocytosis of apoptotic cells through interaction with PS, little is known about what regulates Tim-3 and Tim-4 expression. Tumor microenvironments play a determinant role in tumor survival, suppressing responsiveness to anticancer drugs and accelerating subsequent tumor growth, thus may be responsible for the expression of Tim-3 and Tim-4 on tumor infiltrating cells. Chiba et al pointed out that in tumor microenvironments, tumor-derived immunoregulatory factors such as IL-10 and vascular endothelial growth factor (VEGF) promoted Tim-3 expression on DCs alone or together, in a dose-dependent manner, and the mechanisms used by tumor cells to induce their expression of TIM-3 distinct from those used by DCs.4 When upregulation on TADC, TIM-3 directly interacted with high mobility group protein B1 (HMGB1) and suppressed nucleic acid-mediated activation of an effective antitumor immune response. Recently, Yan et al showed that, Tim-3 expression on TAM in hepatocellular carcinoma (HCC) is induced by tumor-derived signals, including transforming growth factor-β (TGF-β). In turn, TAM promotes the growth of HCC by secretion of soluble factors such as interleukin-6 (IL-6). Additionally, Tim-3 inhibits the activation of tumor-specific CD8+ T cells. Inhibition of Tim-3 could target HCC from 2 angles, first by blocking growth promotion mediated by TAM and second by releasing CD8+ T cell cytotoxicity.24,25 While Baghdadi et al also found that danger associated pattern molecules (DAMPs) such as HMGB1, HSP90 (heat shock protein 90), MSU (monosodium urate), S100A8, and ATP (apprase) released from dying or stressed tumor cells treated with chemotherapeutic drugs could promote TIM-4 expression on macrophages and DCs.14

Autophagy is an important homeostatic cellular recycling mechanism responsible for degrading unnecessary or dysfunctional cellular organelles and proteins in all living cells,26 and has an important role in cancer-cell resistance to anticancer therapies such as radiation, chemotherapy, and some other targeted therapies.27-29 In the study of Baghdadi et al, they pointed out the
mechanism of cancer-cell resistance to chemotherapy. After rec-
ognition of DAMPs from dying or stressed tumor cells by che-
motherapy, TIM-4 up-regulated on TAM and directly interacted
with AMPKa1, thus promoted phosphorylation of ULK1 at
Ser555, recruited Atg13/FIP200 and initiated autophagic vesicle
formation and activated autophagy mediated degradation of
ingested tumors, leading to reduced antigen presentation and
impaired cytotoxicity T lymphocyte (CTL) responses (Fig. 2).
Consistently, blockage of the TIM-4-AMPKa1-autophagy path-
way augmented the antitumor effect of chemotherapeutics by
enhancing tumor-specific CTL responses. So, targeting of the
TIM-4-AMPKa1 interaction may constitute a unique strategy
for augmenting antitumor immunity and improving cancer
chemotherapy.14

Both TIM-3 and TIM-4 attenuate the antitumor effect of
cancer vaccines, a combined treatment with anti-TIM-3 and
anti-TIM-4 mAbs may further increase the efficacy of cancer vac-
cines and chemotherapy. In established B16 melanoma, combin-
ing anti-TIM-3 and anti-TIM-4 mAbs markedly increased
vaccine-induced antitumor responses by increasing the numbers
and effector functions of both NK cells and CD8+ T cells.30
The therapeutic manipulation of TIM-3 and TIM-4 may pro-
vide a novel strategy to improve the clinical efficacy of cancer
immunotherapy. Taken together, these findings identify TIM3
and Tim-4 as potential targets for inducing antitumor immunity
in conjunction with DNA vaccines and/or immunogenic chem-
otherapy in clinical settings.

Other roles of Tim-3 in tumor
Tim-3 also functions as a human NK-cell co-receptor to
enhance IFN-γ production, which has important implications
for the control of infectious disease and cancer.31 Meanwhile,
NK-cell responses may be negatively regulated when NK cells
encounter target cells expressing cognate ligands of Tim-3.32 For
patients with metastatic melanoma, expression of Tim-3 on NK
cells induce functionally impaired/exhausted NK cells, and Tim-
3 blockage reversed this exhausted phenotype, thus Tim-3–tar-
geted therapies may be an effective method to restore antitumor
immunity.33

In the studies of Kikushige et al, Tim-3 is selectively expressed
on LSCs in most types of AML, with the exception of acute pro-
myelocytic leukemia, not on normal hematopoietic stem cells
(HSCs). Although it is not surprising in mouse models reconsti-
tuted with human AML LSCs or human hematopoietic stem
cells, a human TIM-3 mouse IgG2a antibody with complement-
dependent and antibody-dependent cellular cytotoxic activities
eradicates AML LSCs in vivo without affecting normal human
hematopoiesis.11-13 Thus, TIM-3 may serve as one of the promis-
ting targets to eradicate AML LSCs. Jajosky et al also pointed out
that, RepSox (a reprogramming tool and inhibitor of transform-
ing growth factor-β receptor 1) accelerated loss of Tim-3 from
the surface of AML cells by inhibiting TGF-β signaling.34

Tim-3 as human cancer prognostic factor
The expression of TIM-3 on T cells was poor clinic pathologi-
cal parameters such as nodal metastasis and advanced cancer
stages in gastric cancer,35 lung cancer,36 cervical cancer37 and
ovarian cancer.38 The ectopic expression of TIM-3 in tumor cells
has been suggested as a potential, independent prognostic factor
for patients with lung cancer,36 cervical cancer37 and prostate
cancer.39 The Tim-3/galectin-9 signaling pathway mediates T-
cell senescence was also involved in patients with hepatitis B virus
(HBV)-associated HCC, thus it has been a potential immuno-
therapeutic target.40

In addition, polymorphisms in TIM-3 gene were showed to
be associated with various cancers. Subjects carrying +4259TG
genotype had a significantly higher risk of NSCLC, pancreatic
cancer and renal cell carcinoma compared to the wide-type geno-
type.41-43 TIM3–1516 genotypes GT or TT may differentially
and interactively predispose cirrhosis and HCC in chronic HBV
infection.44 The relationship between TIM3–1516 polymorphic
genotype and the distant metastasis of gastric cancer was also

![Figure 2. Tim-4 expression on tumor associated macrophages mediates degradation of dying tumor cells by autophagy. Danger associated pattern molecules (DAMPs) released from dying or stressed tumor cells treated with chemotherapeutic drugs such as high mobility group protein B1 (HMGB1), heat shock protein 90 (HSP90) and apyrase (ATP) promote TIM-4 expression on macrophage. After recognition of DAMPs released from dying or stressed tumor cells with chemotherapy, TIM-4 expression on TAM directly interacts with AMPKa1, thus promotes phosphorylation of ULK1 at Ser555, which is critical to recruit Atg13/FIP200 and initiate autophagic vesicle formation and activates autophagy mediated degradation of ingested tumors, leading to reduced antigen presentation and impaired antitumor immune responses.](image-url)
found. Overall, the results suggest that TIM-3 may play important roles in regulating the prognosis of these diseases.

Conclusion and future perspectives
Despite the fact that TIM-3 expression on various T cell subsets could negatively regulate the antitumor immunity in patients with cancer, the expression of TIM-3 on NK cells and TADC, and the expression of TIM-4 on TAM also attenuates the cell-mediated antitumor effects in established tumors. In addition, the expression of TIM-3 on LSCs also promotes the progression of AML. New treatment targeting TIM-3 and PD-1, TIM-3 and CD137, Tim-3 and CEACAM1, Tim-3 and other negative checkpoin regulators on T cells, Tim-3 on NK cells and LSCs, and combined chemotherapy or cancer vaccines with mAb to Tim-3 or Tim-4 may provide a breakthrough in the treatment for the patients with advanced cancer. Since polymorphisms in TIM-3 may play important roles in regulating the prognosis of various cancers, the mechanisms behind this still need further investigation.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
LC carried out collection and assembly of data, and manuscript writing. ZHR conceived of the review and helped to draft the manuscript, and gave final approval of manuscript. All authors read and approved the final manuscript.

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