



# T-cell immunoglobulin and mucin-domain containing-3 in malignant cancers

Yun Xu\*, Xiping Jiang\*, Yaqing Huang

Department of Gynecology, The Third Affiliated Hospital of Soochow University, Changzhou 213003, China

*Contributions:* (I) Conception and design: Y Xu, X Jiang; (II) Administrative support: Y Xu, X Jiang; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

\*These authors contributed equally to this work.

*Correspondence to:* Yun Xu, MD. Department of Gynecology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou 213003, China. Email: czyunxu@163.com.

**Abstract:** Immune checkpoints are one of the key factors comprising the extensive network of the human immune system. Immune checkpoints ensure T-cell homeostasis, activation and differentiation. The checkpoint T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) plays an important role in immune system. Tim-3 is a member of TIM family and can negatively regulate T helper 1 (Th1) immunity. A literature search for Tim-3 was performed via PubMed. It is suggested that the overexpression of Tim-3 is correlated with poorer prognosis for multiple cancers. Co-expression of Tim-3 and other immune checkpoints has been revealed. Blockade of Tim-3 exerts antitumor function and may have synergistic activity being alone or combined with anti-PD-1 antibody or chemotherapy. Thus, Tim-3 is a promising target for cancer immunotherapy.

**Keywords:** T-cell immunoglobulin and mucin-domain containing-3 (Tim-3); human cancer; anti-Tim-3 antibody; cancer immunotherapy

Submitted Feb 03, 2017. Accepted for publication Apr 12, 2017.

doi: 10.21037/tcr.2017.05.08

**View this article at:** <http://dx.doi.org/10.21037/tcr.2017.05.08>

## Introduction

Since the successful application of anti-CTLA-4 antibody in prolongation of the survival of treated advanced metastatic melanoma patients (1), studies focusing on anti-tumor immunotherapy have been processing towards persuading greater achievements through blocking inhibitory immune checkpoints. By now, inhibition of three immune checkpoints has demonstrated potent anti-tumor abilities, which involves PD-1, PD-L1 and CTLA-4 (2). Presently, another checkpoint molecule, T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) is being more and more investigated for the sake of its promising performance in preclinical tumor settings.

Tim-3 shares a common structure with the other TIM family members consisting of an N-terminal IgV domain

followed by a mucin domain, a transmembrane domain, and a cytoplasmic tail. Originally, Tim-3 was identified as an inhibitory receptor of T cells selectively expressed on interferon (IFN)- $\gamma$ -producing CD4<sup>+</sup> T helper 1 (Th1) and CD8<sup>+</sup> T cytotoxic 1 (Tc1) T cells, also by natural killer (NK) cells, macrophages, endothelial cell, etc., but not Th2 cells (3). Many studies have shown that in tumors, Tim-3 expression is upregulated on the majority of effector T cells (4), but not on naive T-cells (5). Furthermore, Tim-3 influences tumor outcome by its function on myeloid cells and cancer stem cells (4). Moreover, studies have demonstrated that Tim-3 is co-expressed with other inhibitory receptors, including BTLA, LAG-3, KRLG-1, 2B4, CD160, PD-1 and CTLA-4 (6).

Unlike anti-CTLA-4 or anti-PD-1/PD-L1 cancer immunotherapy, studies on the inhibition of Tim-

3 are currently ongoing and are about to enter clinical development. The number of studies on Tim-3 is much less than that of PD-1/PD-L1 and CTLA-4. In this work, we reviewed the Tim-3 expression and its function in various cancers and provided evidences for Tim-3 blockade as an antitumor treatment modality.

The lymphocytes, separated from the paratumor tissues from patients with ovarian cancer, consist of significantly larger proportion of Tim-3<sup>+</sup>CD4<sup>+</sup> T cells (7). And patients who develop recurrent ovarian cancer have a remarkable higher proportion of Tim-3<sup>+</sup>CD4<sup>+</sup> T cells than that at the time of diagnosis (8). Tumor-derived Tim-3<sup>+</sup>CD4<sup>+</sup> T cells often display an incompetent ability of secreting interleukin (IL)-2 and IFN- $\gamma$ , while with higher expression of CD25, Foxp3, CTLA-4 and GITR comparing with their Tim-3<sup>+</sup>CD4<sup>+</sup> counterparts. Tumor-derived Tim-3<sup>+</sup>CD4<sup>+</sup> T cells significantly suppress the proliferation of autologous CD8<sup>+</sup> T cells (7).

### Tim-3 expression on immune cells

Tim-3 over-expression on innate immunocytes, including CD4<sup>+</sup> Th1 cells, CD4<sup>+</sup>Th2 cells, CD8<sup>+</sup> Tc cells, regulatory T cells (Tregs), has been observed in a few tumors. Tim-3 on tumor-associated immunocytes and tumor cells possesses oncogenic potential (9). The co-expression of Tim-3 with other inhibitory molecules such as PD-1 and CEACAM1 indicates T cell exhaustion in tumor (10). Tim-3 expression also defines highly suppressive Tregs in both human and mouse tumors (6,11,12). T cells co-expressing multiple checkpoints display defects in cell cycle and secretion of cytokines including IFN- $\gamma$ , IL-2 and tumor necrosis factor (TNF) (13,14).

In a gastric tumor bearing mouse model, Tim-3 level on NK cells increase along with tumor growth (15). Tim-3 expression on CD8<sup>+</sup> T cells as well as NK cells from patients with gastric cancer is significantly higher than that from healthy controls (15). Tim-3 induces CD8<sup>+</sup> T cells to produce less IFN- $\gamma$  (16). And PD-1 is significantly co-expressed with Tim-3 on CD8<sup>+</sup> T cells (13).

In non-small-cell lung cancer (NSCLC) patients, Tim-3 is highly upregulated in CD4<sup>+</sup> and CD8<sup>+</sup> tumor-infiltrating lymphocytes (TILs), with a 60–70% co-expression rate with FOXP3 (6). In patients' peripheral blood, Tim-3 expression is negligible on T cells but obviously increased on NK cells (11,17). After surgical resection of the primary tumor, Tim-3 level is effectively reduced (17).

Tim-3<sup>+</sup>CD4<sup>+</sup> (6) and Tim-3<sup>+</sup>CD8<sup>+</sup> (18) T cells are

frequently detected at higher levels in patients with colorectal cancer than in healthy controls. Additionally, these cell types are also found at higher frequency in tumor tissues than in peritumoral tissues and in peripheral blood (18). T-cells with low Tim-3 expression have less production of IFN- $\gamma$  (18). Tumor-derived Tim-3<sup>+</sup>CD4<sup>+</sup> T cells can inhibit the proliferation of CD8<sup>+</sup> T cells *in vitro* (6).

Tim-3 is a biomarker in melanoma for histiocytic and dendritic cells (19). Tim-3 is expressed on mast cells in melanomas (20), and often co-expressed with PD-1 are on CD8<sup>+</sup> TILs in mice bearing transplanted tumor, and co-expressed with NY-ESO-1 in patients with advanced melanoma (21).

Tim-3 expression was induced on CD14<sup>+</sup> monocytes upon long-term stimulation with renal cell cancer (RCC) cells, and Tim-3-expressing myeloid cells augment tumorigenic activities of Tim-3-negative RCC cells. Tim-3 expression is upregulated in patients with more IL-10-producing B cells (22).

Generally, Tim-3 is a marker of the dysfunctional subgroups of CD8<sup>+</sup> T cells. Tim-3 is upregulated on lymphocytes in cancer patients and tumor-bearing animals. And this upregulation is associated with T cell exhaustion.

### Tim-3 expression on tumor cells

#### Gastric cancer

In gastric cancer patients, Tim-3 is positively expressed in 60% of tumor tissues (15,16), significantly more than that in the corresponding peritumoral tissues (3,12). In gastric cancer patients, significantly greater numbers of Tim-3<sup>+</sup>CD8<sup>+</sup> T cells were observed in the tumor tissues than in peripheral blood (4).

*H. pylori* are considered a key contributor to gastric cancer development. Increased Tim-3 levels are found in *H. pylori* infected mice. In 104 gastric cancer patients tested for *H. pylori*, no correlation between *H. pylori* infection and Tim-3 expression was observed (12). However, there are opposite observations regarding with the association between *H. pylori* infection and Tim-3 expression. In one study, there seems to be an independent relevance of *H. pylori* infection and Tim-3 expression (6).

Higher Tim-3 expression has been reported in adults no younger than 60 years old, in male patients, and in patients with venous infiltration (12). Tim-3 expression on NK cells are associated with advanced tumor stage (15). In gastric cancer patients, higher Tim-3 level in Tregs and CD8<sup>+</sup> T

cells is associated with poorer prognosis (9,23). Positive Tim-3 status in tumor tissue is associated with a shorter overall survival (OS), suggesting that Tim-3 expression could be an independent prognostic marker (12).

At the mRNA level, the -1516 G/T, one polymorphism in Tim-3 gene, is associated with distant tumor metastasis. Furthermore, there is a close association between the TTGCT haplotype and higher risk of gastric cancer (24).

### **NSCLC**

In patients with NSCLC, Tim-3-expressing CD4<sup>+</sup> and CD8<sup>+</sup> T cells produce reduced amount of cytokines, such as IL-2, TNF, and IFN- $\gamma$ , comparing to those in their Tim-3 counterparts (6). These kinds of T cells are less proliferative responding to antigen and may promote tumor development. Interestingly, Tim-3 expression on CD4<sup>+</sup> TILs, but not on CD8<sup>+</sup> TILs, correlates with poor clinicopathological parameters of NSCLC, such as nodal metastasis and advanced cancer stages (6,25).

Researchers found that Tim-3 overexpression on TILs is more frequently associated with advanced stages (III/IV) than those at early stage disease (I/II) (17). The 5-year survival rate is significantly lower in patients with moderate to strong Tim-3 expression in TILs than those with weak/negative Tim-3 expression (1).

At the mRNA level, patients with +4259 T/G, one polymorphism in Tim-3 gene, have nearly 3 folds of increased risk and a significantly shorter OS comparing with patients with wild-type Tim-3 (26). Thus, Tim-3 expression level on TILs could be an independent prognostic predictor for NSCLC.

### **Colorectal cancer**

Tim-3 also plays a role in the development of colorectal cancer, with significantly higher expression observed in stage III/IV patients than that in stage I/II ones (4). Increasing Tim-3 level in patients undergoing surgical resection of colorectal tumors could restore T-cell-mediated immunity. Significantly higher expression of Tim-3<sup>+</sup> T cells has been found in postoperative patients, which indicates decrease in IFN- $\gamma$  secretion (27). These data suggest that Tim-3 might be an indicator in monitoring immune function in patients with colorectal cancer. Besides, coblockade of Tim-3 and CAEAM-1 enhances anti-tumor reactions, resulting in obliteration of tumor cells in an animal model (28).

### **Ovarian cancer**

Tim-3 expression increases in CD4<sup>+</sup> and CD8<sup>+</sup> T cells in ovarian cancer patients than those in control subjects (8). Tim-3 level in tumor-infiltrating Tregs is positively associated with tumor size (29). Significantly higher Tim-3 expressions are observed in both CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells in patients with stage III/IV or with tumor grade G3 than those with stage I/II or a lower tumor grade (11).

Tim-3 is involved in progression of multiple subtypes of ovarian cancer (30). Blockade of Tim-3 is able to revert Treg-mediated suppression. Ovarian tumor-infiltrating Tregs with Tim-3-dependent pattern are more immunosuppressive than their counterparts in peripheral blood. Blocking Tim-3 significantly can revert Treg-mediated inhibition of CD8<sup>+</sup> T cell inflammation (29). Combination of anti-CD137 antibody and anti-Tim-3 antibody can significantly inhibit the growth of ovarian cancer cells in mouse model, and 60% of those tumor-bearing mice have a long-term survival (31).

### **Hepatocellular carcinoma (HCC)**

Tim-3<sup>+</sup> T cells are increased in patients with HBV-associated HCC (6,11,32), and engage in T-cell dysfunction and exhaustion during persistent HBV infection and HCC development (33). Tim-3/galectin-9 signaling pathway mediates T-cell senescence in HBV-associated HCC (23). SNP rs25855 is associated with a reduced probability of HBV-associated HCC (34), while Tim-3-1516 genotypes G/T is associated with a higher risk in the development of HCC (35).

Tim-3 expression in tumor-associated macrophages (TAMs) (36) and TILs (32) is strongly associated with higher tumor grades and a shorter OS of patients with HCC. Moreover, Tim-3 interference in macrophages significantly inhibited the alternative activation of macrophages and suppressed HCC cell growth both *in vitro* and *in vivo* (36).

### **Leukemia**

Tim-3 is expressed on leukemia stem cells (LSCs) in acute myelocytic leukemia (AML), but not in acute promyelocytic leukemia (APL) or normal hematopoietic stem cells (HSCs) (37). Separation of HSCs from LSCs can be differentiated based on Tim-3 expression in the majority

of AML specimens. Tim-3<sup>+</sup> population contain majorly functional LSCs (38). Blockage with anti-Tim-3 selectively targets LSCs of AML without attacking normal HSCs (37,38).

At the mRNA level, miR34a promoted proliferation and migration and inhibited apoptosis of AML cells, which were associated with the changes of Tim-3 levels (39).

The median proportion of Tim-3<sup>+</sup> myeloblasts and average fluorescence intensity of Tim-3 are less in non-cancerous specimens from whom with no recent chemotherapy comparing with AML, but not significantly different as comparing to non-leukemic myeloblasts in the post-chemotherapy setting (40).

Tim-3 and PD-1 are co-expressed and increased levels are found during disease progression (4). PD-1<sup>+</sup>Tim-3<sup>+</sup>CD8<sup>+</sup> T cells and PD-L1 and galectin-9 expressing AML cells are all lack in producing cytokines including IL-2, TNF- $\alpha$  and IFN- $\gamma$ , and in PD-L1 and galectin-9 expressing AML cells. Combined inhibition of Tim-3/galectin-9 and PD-1/PD-L1 pathways may be beneficial to patients with advanced AML, which will be confirmed in a clinical trial.

### Melanoma

Melanoma is not a common cancer compared to the other tumor types described above. However, there has been great interest in assessing the efficacy of immunotherapies in melanoma patients (19,41).

Higher Tim-3 level is associated with thickness and mitotic rate of the tumor, as well as ulceration and late stage disease (28). Tim-3 can facilitate the survival of melanoma cells in peripheral circulation and metastatic colonization of the lung, resulting in additional metastatic foci (2).

Blockade of Tim-3 may prevent the metastatic spread of melanoma (42). Blockade of Tim-3 also enhances T cell function (2). Combination use with anti-PD-1/PD-L1/BTLA/Tim-4 antibodies (21,41,43) has demonstrated synergistic effects against melanoma *in vitro*. Moreover, chemotherapy also demonstrated effectiveness in mice that were administered anti-Tim-3 (44). This combinational therapeutic strategy may be suitable for melanoma patients who do not respond to certain monotherapy.

### Prostate cancer

Tim-3 promotes the tumorigenesis of prostate cancer through its regulation on immune cells. Tim-3 expression on both CD4<sup>+</sup> and CD8<sup>+</sup> T cells are significantly higher

in prostate intraepithelial neoplasia, followed by localized disease, and metastatic prostate cancer (45,46). Higher expression of Tim-3 on T cells is associated with higher nuclear grades, higher PSA levels, higher Gleason scores (45), later stages, pulmonary metastasis, shorter and recurrence-free survival, as well as shorter progression-free survival (PFS) times (46), while increased number of Tim-3<sup>+</sup> NK cells is potential predictor of longer OS (47). Blocking Tim-3 in prostate cancer cells inhibited their proliferation and invasiveness (46).

### RCC

Zhu *et al.* (48) also pointed out that IL-27 induces nuclear factor, interleukin 3 regulated (NFIL3), which promoted permissive chromatin remodeling of the Tim-3 locus and induced Tim-3 expression together with the immunosuppressive cytokine IL-10. Tim-3 is also expressed on TILs in RCC (49). Tim-3 co-expressed with PD-1 on CD8<sup>+</sup>T cells is associated with an unsatisfactory clinical outcome in RCC (50).

At the mRNA level, TTG (+4259, -1516 and -574) is associated with RCC (51).

Decreased Tim-3 levels inhibited the tumorigenic potential of clear cell renal cell carcinoma (ccRCC) cells *in vitro* and *in vivo*, and also the proliferation and invasiveness of these cells (52). In patients with ccRCC, Tim-3 is expressed on tumor cells and CD204<sup>+</sup> TAMs. The role for Tim-3 in facilitating invasive potential of ccRCC cells by either activating GATA3 or inhibiting GATA3 (53). Suppression of downstream GATA3 is an important mechanism by which Tim-3 triggered metastasis in ccRCC cell lines.

In patients with ccRCC, Tim-3 expression was higher in ccRCC tissue than in the normal renal tissue. Higher Tim-3 level is positively associated with an increased number of TAMs and a shorter PFS (52,54). Furthermore, the drug resistance to sunitinib and mTOR inhibitors is in part due to elevated Tim-3 levels (54).

### Perspective

Tim-3 is presently under early evaluation as an interesting checkpoint. It has been well established that Tim-3/galectin-9 interaction inhibits Th1 responses and induces peripheral tolerance. More importantly, Tim-3 is now recognized as having a crucial role in the induction of T cell exhaustion during the progression of tumors. Moreover, the

upregulation of Tim-3 often predicts worse prognosis of cancer patients (55). The benefit of blocking Tim-3 is being explored. Here, we provide a review on Tim-3 discussing the signaling pathway and antitumor immunotherapy. Its selective expression in tumor tissue, along with its role in multiple mechanisms of immunosuppression, highlights its value as a target for cancer immunotherapy.

Important future steps toward harnessing Tim-3 for anticancer immunotherapy will be to elucidate the signals. The unique features of Tim-3, together with accumulating preclinical data, strongly support the use of Tim-3—targeted therapies in combinatorial modalities with other checkpoint-based therapies to achieve objective responses in cancer patients. The combination therapy with Tim-3 and PD-1 blockade has shown efficacy in different animal models. Clinically, Tim-3 could be an independent prognostic predictor in multiple malignancies. Besides, we also reviewed the genotypes of Tim-3 in various cancers. However, further studies are warranted to understand the association between genotypes and Tim-3 expression.

Preclinical data suggests that Tim-3-targeted treatment and in combination with other immunotherapies could be a potential treatment strategy for cancer patients. Additionally, it is encouraging that immunosuppressive treatment does not hamper the efficacy of immune checkpoint blockade (56). Currently, there are three ongoing clinical trials for evaluating the anti-Tim-3 antibodies as a monotherapy or in combination with anti-PD-1 antibody for treating advanced solid tumors (anti-Tim-3 antibodies TSR-022 and MBG453) or with decitabine for treating AML (anti-Tim-3 antibody MBG453). Though these trials are still on their ways, it is reasonable to believe that blockade of Tim-3 signaling may be a highly effective means for the treatment of cancer where T cell exhaustion is a barrier in mounting an effective immune response. Additional collaboration between basic scientists and physicians is needed to achieve the results from Tim-3-aimed studies from bench to bedside.

### Acknowledgments

*Funding:* This work was supported by grants from Society Development Plans, Department of Science and Technology Changzhou (CJ20159018 to Dr. Y Xu).

### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.05.08>).

The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

### References

1. Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. *Nat Immunol* 2009;10:1185-92.
2. Nishimura H, Nose M, Hiai H, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999;11:141-51.
3. da Silva IP, Gallois A, Jimenez-Baranda S, et al. Reversal of NK-cell exhaustion in advanced melanoma by Tim-3 blockade. *Cancer Immunol Res* 2014;2:410-22.
4. Anderson AC. Tim-3, a negative regulator of anti-tumor immunity. *Curr Opin Immunol* 2012;24:213-6.
5. Baitsch L, Legat A, Barba L, et al. Extended co-expression of inhibitory receptors by human CD8 T-cells depending on differentiation, antigen-specificity and anatomical localization. *PLoS One* 2012;7:e30852.
6. Yan J, Zhang Y, Zhang JP, et al. Tim-3 expression defines regulatory T cells in human tumors. *PLoS One* 2013;8:e58006.
7. Yang X, Jiang X, Chen G, et al. T cell Ig mucin-3 promotes homeostasis of sepsis by negatively regulating the TLR response. *J Immunol* 2013;190:2068-79.
8. Wu J, Liu C, Qian S, et al. The expression of Tim-3 in peripheral blood of ovarian cancer. *DNA Cell Biol* 2013;32:648-53.
9. Jan M, Chao MP, Cha AC, et al. Prospective separation of normal and leukemic stem cells based on differential

- expression of TIM3, a human acute myeloid leukemia stem cell marker. *Proc Natl Acad Sci U S A* 2011;108:5009-14.
10. Zhu S, Lin J, Qiao G, et al. Tim-3 identifies exhausted follicular helper T cells in breast cancer patients. *Immunobiology* 2016;221:986-93.
  11. 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:e30676.
  12. Sakuishi K, Ngiew SF, Sullivan JM, et al. TIM3+FOXP3+ regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. *Oncoimmunology* 2013;2:e23849.
  13. Zhou Q, Munger ME, Veenstra RG, et al. Coexpression of Tim-3 and PD-1 identifies a CD8<sup>+</sup> T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. *Blood* 2011;117:4501-10.
  14. 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;207:2187-94.
  15. 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:e81799.
  16. Takano S, Saito H, Ikeguchi M. An increased number of PD-1<sup>+</sup> and Tim-3<sup>+</sup> CD8<sup>+</sup> T cells is involved in immune evasion in gastric cancer. *Surg Today* 2016;46:1341-7.
  17. 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;15:9945-8.
  18. Zhao X, Zhang Z, Li H, et al. Cytokine induced killer cell-based immunotherapies in patients with different stages of renal cell carcinoma. *Cancer Lett* 2015;362:192-8.
  19. Dorfman DM, Hornick JL, Shahsafaie A, et al. The phosphatidylserine receptors, T cell immunoglobulin mucin proteins 3 and 4, are markers of histiocytic sarcoma and other histiocytic and dendritic cell neoplasms. *Hum Pathol* 2010;41:1486-94.
  20. Wiener Z, Kohalmi B, Poczta P, et al. TIM-3 is expressed in melanoma cells and is upregulated in TGF-beta stimulated mast cells. *J Invest Dermatol* 2007;127:906-14.
  21. Fourcade J, Sun Z, Benallaoua M, et al. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8<sup>+</sup> T cell dysfunction in melanoma patients. *J Exp Med* 2010;207:2175-86.
  22. Cai C, Zhang J, Li M, et al. Interleukin 10-expressing B cells inhibit tumor-infiltrating T cell function and correlate with T cell Tim-3 expression in renal cell carcinoma. *Tumour Biol* 2016;37:8209-18.
  23. Shen P, Yue R, Tang J, et al. Preferential Tim-3 expression on Treg and CD8(+) T cells, supported by tumor-associated macrophages, is associated with worse prognosis in gastric cancer. *Am J Transl Res* 2016;8:3419-28.
  24. Cao B, Zhu L, Zhu S, et al. Genetic variations and haplotypes in TIM-3 gene and the risk of gastric cancer. *Cancer Immunol Immunother* 2010;59:1851-7.
  25. Zhuang X, Zhang X, Xia X, et al. Ectopic expression of TIM-3 in lung cancers: a potential independent prognostic factor for patients with NSCLC. *Am J Clin Pathol* 2012;137:978-85.
  26. Bai J, Li X, Tong D, et al. T-cell immunoglobulin- and mucin-domain-containing molecule 3 gene polymorphisms and prognosis of non-small-cell lung cancer. *Tumour Biol* 2013;34:805-9.
  27. Arai Y, Saito H, Ikeguchi M. Upregulation of TIM-3 and PD-1 on CD4<sup>+</sup> and CD8<sup>+</sup> T Cells Associated with Dysfunction of Cell-Mediated Immunity after Colorectal Cancer Operation. *Yonago Acta Med* 2012;55:1-9.
  28. Huang YH, Zhu C, Kondo Y, et al. CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. *Nature* 2015;517:386-90.
  29. Bu M, Shen Y, Seeger WL, et al. Ovarian carcinoma-infiltrating regulatory T cells were more potent suppressors of CD8(+) T cell inflammation than their peripheral counterparts, a function dependent on TIM3 expression. *Tumour Biol* 2016;37:3949-56.
  30. Blasius AL, Beutler B. Intracellular toll-like receptors. *Immunity* 2010;32:305-15.
  31. 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.
  32. Li H, Wu K, Tao K, et al. Tim-3/galectin-9 signaling pathway mediates T-cell dysfunction and predicts poor prognosis in patients with hepatitis B virus-associated hepatocellular carcinoma. *Hepatology* 2012;56:1342-51.
  33. Li Z, Liu Z, Zhang G, et al. TIM3 gene polymorphisms in patients with chronic hepatitis B virus infection: impact on disease susceptibility and hepatocellular carcinoma traits. *Tissue Antigens* 2012;80:151-7.
  34. Liao J, Zhang Q, Liao Y, et al. Association of T-cell immunoglobulin and mucin domain-containing molecule 3 (Tim-3) polymorphisms with susceptibility and disease progression of HBV infection. *PLoS One* 2014;9:e98280.
  35. Li Z, Li N, Zhu Q, et al. Genetic variations of PD1 and TIM3 are differentially and interactively associated with the development of cirrhosis and HCC in patients with

- chronic HBV infection. *Infect Genet Evol* 2013;14:240-6.
36. Yan W, Liu X, Ma H, et al. Tim-3 fosters HCC development by enhancing TGF-beta-mediated alternative activation of macrophages. *Gut* 2015;64:1593-604.
  37. Kikushige Y, Miyamoto T. TIM-3 as a novel therapeutic target for eradicating acute myelogenous leukemia stem cells. *Int J Hematol* 2013;98:627-33.
  38. Kikushige Y, Shima T, Takayanagi S, et al. TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. *Cell Stem Cell* 2010;7:708-17.
  39. Wang Y, Cheng Q, Liu J, et al. Leukemia Stem Cell-Released Microvesicles Promote the Survival and Migration of Myeloid Leukemia Cells and These Effects Can Be Inhibited by MicroRNA34a Overexpression. *Stem Cells Int* 2016;2016:9313425.
  40. Roth CG, Garner K, Eyck ST, et al. TIM3 expression by leukemic and non-leukemic myeloblasts. *Cytometry B Clin Cytom* 2013;84:167-72.
  41. 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;62:629-37.
  42. Wu FH, Yuan Y, Li D, et al. Endothelial cell-expressed Tim-3 facilitates metastasis of melanoma cells by activating the NF-kappaB pathway. *Oncol Rep* 2010;24:693-9.
  43. Fourcade J, Sun Z, Pagliano O, et al. CD8(+) T cells specific for tumor antigens can be rendered dysfunctional by the tumor microenvironment through upregulation of the inhibitory receptors BTLA and PD-1. *Cancer Res* 2012;72:887-96.
  44. Patel J, Bozeman EN, Selvaraj P. Taming dendritic cells with TIM-3: another immunosuppressive strategy used by tumors. *Immunotherapy* 2012;4:1795-8.
  45. Piao YR, Jin ZH, Yuan KC, et al. Analysis of Tim-3 as a therapeutic target in prostate cancer. *Tumour Biol* 2014;35:11409-14.
  46. Piao YR, Piao LZ, Zhu LH, et al. Prognostic value of T cell immunoglobulin mucin-3 in prostate cancer. *Asian Pac J Cancer Prev* 2013;14:3897-901.
  47. Jochems C, Tucker JA, Tsang KY, et al. A combination trial of vaccine plus ipilimumab in metastatic castration-resistant prostate cancer patients: immune correlates. *Cancer Immunol Immunother* 2014;63:407-18.
  48. 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.
  49. Fend L, Gatard-Scheikl T, Kintz J, et al. Intravenous injection of MVA virus targets CD8<sup>+</sup> lymphocytes to tumors to control tumor growth upon combinatorial treatment with a TLR9 agonist. *Cancer Immunol Res* 2014;2:1163-74.
  50. Granier C, Dariane C, Combe P, et al. Tim-3 Expression on Tumor-Infiltrating PD-1<sup>+</sup>CD8<sup>+</sup> T Cells Correlates with Poor Clinical Outcome in Renal Cell Carcinoma. *Cancer Res* 2017;77:1075-82.
  51. Cai C, Wang L, Wu Z, et al. T-cell immunoglobulin- and mucin-domain-containing molecule 3 gene polymorphisms and renal cell carcinoma. *DNA Cell Biol* 2012;31:1285-9.
  52. Yuan J, Jiang B, Zhao H, et al. Prognostic implication of TIM-3 in clear cell renal cell carcinoma. *Neoplasma* 2014;61:35-40.
  53. Zheng H, Guo X, Tian Q, et al. Distinct role of Tim-3 in systemic lupus erythematosus and clear cell renal cell carcinoma. *Int J Clin Exp Med* 2015;8:7029-38.
  54. 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;3:999-1007.
  55. Taipale K, Liikanen I, Juhila J, et al. Chronic Activation of Innate Immunity Correlates With Poor Prognosis in Cancer Patients Treated With Oncolytic Adenovirus. *Mol Ther* 2016;24:175-83.
  56. Postow MA. Managing immune checkpoint-blocking antibody side effects. *Am Soc Clin Oncol Educ Book* 2015:76-83.

**Cite this article as:** Xu Y, Jiang X, Huang Y. T-cell immunoglobulin and mucin-domain containing-3 in malignant cancers. *Transl Cancer Res* 2017;6(3):613-619. doi: 10.21037/tcr.2017.05.08