REVIEW

Immune regulation by Tim-3 [version 1; peer review: 2 approved]

Hridesh Banerjee, Lawrence P. Kane

Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA

V1 First published: 14 Mar 2018, 7(F1000 Faculty Rev):316
<https://doi.org/10.12688/f1000research.13446.1>

Latest published: 14 Mar 2018, 7(F1000 Faculty Rev):316
<https://doi.org/10.12688/f1000research.13446.1>

Abstract

T-cell immunoglobulin and mucin domain 3 (Tim-3) is a transmembrane protein that in both mice and humans has been shown to possess various functions in a context-dependent manner. Thus, Tim-3 has been associated with both inhibitory and co-stimulatory function, depending in part on the specific cell type and immune response course. Though originally described on T cells, Tim-3 is now known to be expressed by both lymphoid and non-lymphoid cells within the immune system and even by non-immune cells. In addition, though widely thought of as a negative regulator of immunity, Tim-3 has been shown in more recent studies to have a positive function on both myeloid and lymphoid cells, including T cells. Tim-3 is often expressed at a high level on exhausted T cells in tumors and chronic infection and may engage in crosstalk with other so-called “checkpoint” molecules such as PD-1. Thus, Tim-3 has emerged as a possible therapeutic target, which is being actively explored both pre-clinically and clinically. However, recent research suggests a more complex *in vivo* role for this protein, compared with other targets in this area.

Keywords

T cell activation, T cell exhaustion, immunotherapy

Open Peer Review

Approval Status

	1	2
version 1		
14 Mar 2018		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Mario A. Ostrowski**, Institute of Medical Science, Toronto, Ontario, Canada
2. **MeiRong Du**, Hospital of Obstetrics and Gynecology, Fudan University Shanghai Medical College, Shanghai, China

Any comments on the article can be found at the end of the article.

Corresponding author: Lawrence P. Kane (lkane@pitt.edu)

Author roles: **Banerjee H:** Writing – Original Draft Preparation, Writing – Review & Editing; **Kane LP:** Funding Acquisition, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Work on Tim-3 in Lawrence P. Kane's lab is funded by National Institutes of Health award CA206517. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

Copyright: © 2018 Banerjee H and Kane LP. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Banerjee H and Kane LP. **Immune regulation by Tim-3 [version 1; peer review: 2 approved]** F1000Research 2018, 7(F1000 Faculty Rev):316 <https://doi.org/10.12688/f1000research.13446.1>

First published: 14 Mar 2018, 7(F1000 Faculty Rev):316 <https://doi.org/10.12688/f1000research.13446.1>

Introduction

T-cell immunoglobulin and mucin domain 3 (Tim-3) (gene name *Havcr2*)¹ is an immunoglobulin (Ig) and mucin domain family cell-surface molecule that was originally identified on CD4 helper 1 (Th1) and CD8 T cytotoxic 1 (Tc1) cells². Initial studies on the role of Tim-3 in the murine experimental autoimmune encephalomyelitis (EAE) model suggested an inhibitory function on Th1 responses and regulation of macrophage activation and function. Blocking of Tim-3 can lead to the development of spontaneous autoimmunity, at least in some settings³. Corroborating an inhibitory function for Tim-3 is the fact that antibodies against Tim-3 have been shown to enhance anti-viral and anti-tumor T-cell responses, as described below. However, Tim-3 is now known to also be expressed by regulatory T (Treg) cells and innate immune cells such as dendritic cells (DCs), natural killer (NK) cells, monocytes, macrophages, and mast cells. Tim-3 is often referred to as a checkpoint receptor and exhaustion marker; however, Tim-3 has been seen to function differentially, in a context-dependent manner, and now is speculated to have both positive and inhibitory functions⁴⁻⁶. Here, we will discuss existing evidence for these positive and negative effects of Tim-3 on immune responses and highlight some important unanswered questions.

Tim-3 structure and ligands

Tim-3 belongs to the Ig super family, with an N-terminal IgV domain, followed by a mucin-like domain that has sites for glycosylation. This is followed by sites for N-linked glycosylation and a single transmembrane domain. The C-terminal cytoplasmic domain does not have any known inhibitory motifs but has five tyrosine residues, two of which have been shown to be phosphorylated and critical for Tim-3-mediated signaling. The IgV domain of Tim-3 consists of two anti-parallel beta sheets that are attached to each other by a disulfide bond. An additional disulfide bond stabilizes the IgV domain and reorients the CC' loop toward the FG loop, thus forming a unique ligand-binding pocket^{4,7}.

In humans, shedding of the ecto domain of Tim-3 can take place because of disintegrin and metalloproteases ADAM10 (a disintegrin and metalloprotease 10) and ADAM17. In the absence of the intracellular cytoplasmic domain of Tim-3, this shedding cannot occur, suggesting a role for the cytoplasmic domain of Tim-3 in its cleavage by ADAM10 and ADAM17. Although the relevance of this observation for Tim-3-mediated signaling is not well understood, Tim-3 shedding has been observed with CD14⁺ monocytes, in response to lipopolysaccharide stimulation, and in T cells, in the setting of graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplant. Plasma levels of soluble Tim-3 were also found to be elevated in patients with GVHD⁸. Tim-3 shedding by ADAM10 has also been observed in untreated HIV patients, and this correlates with disease progression⁹.

At this point, four distinct ligands have been reported to bind to Tim-3 in different contexts. These are galectin-9 (Gal-9), high-mobility group protein B1 (HMGB1), carcinoembryonic antigen cell adhesion molecule 1 (Ceacam-1), and

phosphatidylserine (PtdSer). Gal-9 was the first reported ligand for Tim-3 and was shown to induce apoptosis in Th1 cells¹⁰, although Gal-9 can bind to other receptors on the cell surface as well¹¹. Interaction of PtdSer with Tim-3 has been shown to play a role in the clearing of apoptotic bodies and also helps in antigenic cross-presentation, although it should be noted that the affinity of PtdSer for Tim-3 is significantly weaker than for other TIM proteins¹². Ceacam-1 is the most recently identified ligand for Tim-3 and can form a heterodimer with Tim-3 as well as interacting with Tim-3 *in trans*¹³. HMGB1 is highly expressed by tumor-infiltrating DCs. In tumors, Tim-3 therefore competes with nucleic acid binding to HMGB1 and lowers the transport of nucleic acids to the endosomes, thereby dampening the innate immune response to tumor-associated nucleic acid¹⁴. Liver-primed CD8⁺ Tim-3⁺ cells were also shown to suppress anti-viral immunity in a Gal-9-independent and HMGB1-dependent manner¹⁵. As discussed below, antibodies to Tim-3 are actively being explored as therapeutics. Although these are often referred to as “blocking” antibodies, their ability to block the interaction of Tim-3 with its various ligands is not always documented directly.

Regulation of Tim-3 expression and function

Transcriptional control of Tim-3 during acute and chronic infection and in tumors is an area of active research. Nuclear factor of activated T cells (NFAT) signaling has been shown to play a role in CD8⁺ T-cell regulation of Tim-3¹⁶. T-bet is another transcription factor that has been shown to have a positive effect on Tim-3 expression during T-cell activation¹⁷, whereas the same factor appears to have a negative effect in exhausted T cells¹⁸. Tim-3 expression has also been shown to be regulated by at least three transcription factors: NFIL3, T-bet, and STAT3. In one report, the authors showed that interleukin-10 (IL-10) and IL-27 together can lead to epigenetic changes in the *Havcr2* locus¹⁹, further supporting the notion that, along with T-cell receptor (TCR) stimulus, cytokines and other extrinsic factors may have differential effects on Tim-3 expression and function.

Tim-3 is generally co-expressed with other checkpoint receptors in settings of T-cell exhaustion in both tumors and chronic infection in both humans and mice²⁰. However, mechanisms by which TCR, and other factors, regulate the expression of Tim-3 during acute versus chronic stimulation are not well defined. Similarly, in tumors, although a significant population of tumor-infiltrating T cells express Tim-3, it is not known what factors in the tumor microenvironment, along with tumor antigen, play a role in the upregulation of Tim-3 on effector and Treg cells.

Tim-3 signaling

Although initially Tim-3 was found to have an inhibitory function, based on its expression on exhausted T cells and in an autoimmunity model, there is still little direct proof of this concept. There are also some reports which prove that Tim-3 in certain cases may play a co-stimulatory enhancing function. High ectopic expression of Tim-3 on T-cell lines has also been shown to have increased activation based on increased NFAT/AP-1 and nuclear factor-kappa B (NF-κB) reporter assays and enhanced

levels of cytokines²¹ and higher phospho-S6 levels. One possible explanation for contradicting reports with respect to Tim-3 function in T cells relates to the expression of Ceacam-1 along with Tim-3. Thus, it has been suggested that Tim-3 inhibitory function is dependent on the co-expression of Ceacam-1 in both tumors and autoimmune disease¹³. Another factor which may play an important role, and which complicates the characterization of Tim-3 signaling *in vivo*, is that Tim-3 is also expressed in other cell types.

Multiple tyrosine molecules in the cytoplasmic tail of Tim-3 do not form any recognizable inhibitory motifs. Nonetheless, *in silico* characterization of these sites predicts that they can be substrates for phosphorylation by multiple tyrosine kinases. Indeed, several studies have now shown that tyrosine residues in the cytoplasmic tails of Tim-3 can be phosphorylated^{21,22}. Both the Src family kinases Fyn and Lck and the Tec family tyrosine kinase Itk have been reported to have a role in Tim-3 cytoplasmic domain phosphorylation. Owing to the involvement of multiple kinases and multiple phosphorylation sites in the Tim-3 cytoplasmic domain, distinct binding of different Tim-3 ligands or antibodies may bring about different outcomes. However, this possibility needs to be explored further.

In support of a possible co-stimulatory function, Tim-3 expression during acute lymphocytic choriomeningitis virus (LCMV) infection is associated with a better short-term effector T-cell response, though possibly at the cost of memory T-cell formation. Furthermore, the absence of Tim-3 leads to defective Akt/mTOR signaling²³; however, in the chronic LCMV T-cell exhaustion model, Tim-3 expression was sufficient to dampen the anti-PD-1 rescue of T-cell responses, thereby suggesting crosstalk of PD-1 and Tim-3 in exhausted T cells²³, as discussed above. Supporting this finding is the recent report by Gorman and Colgan that acute stimulation in response to LCMV infection leads to upregulation of Tim-3 in persisting Th1-type CD4 cells, and these cells also show enhanced effector functions both *in vitro* and *in vivo*²⁴.

Bat3 is an adapter molecule that has also been shown to act as an inhibitor of Tim-3 signaling by directly binding to the Tim-3 cytoplasmic tail in a Gal-9-reversible manner. Switch of binding of the cytoplasmic domain of Tim-3 from Bat3 to Fyn is speculated to play a role in determining whether Tim-3 signaling positively or negatively affects TCR signaling²⁵. It has also been reported that Tim-3 can co-localize with transmembrane phosphatases such as CD45 and CD148 and that recruitment of Tim-3 to the immunological synapse may lead to destabilization of the synapse and dampening of TCR signaling²⁶. During early pregnancy, in decidual NK cells, Gal-9/Tim-3 signaling has been shown to be important and beneficial for the maintenance of pregnancy²⁷.

Tim-3 and innate immunity

Tim-3 is known to be expressed on certain innate immune cells, including NK cells, macrophages, DCs, and mast cells. Tim-3 has been found to be expressed by all mature NK cells, and immature NK cells upregulate Tim-3 upon maturation²⁸. Studies on *in vitro*

cultured NK cells suggest a co-stimulatory function for Tim-3. In tumors, Tim-3 expression is associated with poor prognosis and suppression of anti-tumor function. Blockade of Tim-3 reverses the exhaustion phenotype of NK cells in certain tumor models^{29,30}. Tim-3 is constitutively expressed on mast cells and enhances proximal FcεRI signaling, leading to degranulation and cytokine release upon antigen crosslinking, suggesting a co-stimulatory function of Tim-3 in mast cells³¹.

Tim-3 is expressed on DCs and in tumors was shown to suppress the response to nucleic acid ligands for TLR3, TLR7, and TLR9 and cytosolic sensors to DNA and RNA by impairing HMGB1-mediated recruitment of nucleic acids to endosomes¹⁴. In DCs, Tim-3 has also been shown to inhibit activation and maturation via Btk and c-Src to prevent NF-κB signaling³². A recent article also shows that, during chronic HIV infection, Tim-3 may play a role in the dysfunction of plasmacytoid DCs by interfering with TLR signaling via the recruitment of IRF7 and p85 to lysosomes³³.

Tim-3 is expressed on macrophages and, in various disease models, has been associated with inhibitory function³⁴. More recently, Tim-3 has been shown to act as a negative regulator of the NLRP3 inflammasome by dampening NF-κB responses in mouse peritoneal macrophages³⁵. The authors further showed that tyrosines 256 and 263 near the Tim-3 C-terminus are necessary for NLRP3 inhibition by Tim-3 and, in a model of peritonitis blockade of Tim-3, led to increased pathology. Finally, a recent report also suggests a role for Tim-3 in regulating the resolution of inflammation in an acute lung injury model through effects of Tim-3⁺ Treg cells on macrophage polarization³⁶.

Tim-3 and tumors

Tim-3 is expressed on a significantly higher proportion of tumor-infiltrating lymphocytes compared with its expression in peripheral lymphoid compartments^{1,37}. Tim-3 upregulation, along with upregulation of other checkpoint receptors, is associated with CD8 T-cell exhaustion. In melanoma, upregulation of Tim-3, along with PD-1, marks a highly non-responsive population of CD8 T cells¹. Tim-3 has also been shown to be expressed on tumor antigen-specific T cells in the peripheral blood of patients with various tumors. In mouse models, various types of tumors have been shown to be affected differently in terms of the efficacy of Tim-3 antibody treatment. While there are reports in which anti-Tim-3 antibody treatment did not lead to any inhibition of tumor growth³⁸, there are other studies in which anti-Tim-3 antibody did lead to a slowing of tumor progression by promoting type I anti-tumor immunity³⁹. It has also been reported that Tim-3⁺ T cells in head and neck cancer are resistant to PD-1 blockade alone and that there is crosstalk between Tim-3 and PD-1 in CD8 T cells via PI3K/AKT signaling⁴⁰. It has also been reported that in a head and neck cancer model, increased resistance to cetuximab is associated with increased PD-1 and Tim-3 expression on tumor-infiltrating lymphocytes⁴¹, further suggesting the need for a multi-dimensional approach to cancer treatment. Thus, a combination of anti-Tim-3 treatment with other anti-checkpoint receptors and co-receptor receptors is a

potentially attractive immunotherapy for cancer. However, it should be noted that how these combination therapies work mechanistically is still under-explored.

In addition to effector T cells, Tim-3 is highly expressed on tumor-infiltrating Treg cells across multiple types of tumors⁴². A higher frequency of Tim-3⁺ tumor-infiltrating lymphocyte Treg cells is also associated with poor patient survival³⁷. Consistent with this, Tim-3⁺ tumor Treg cells may be more suppressive than Tim-3⁻ Treg cells from the same tumors⁴³. In head and neck tumors, Tim-3⁺ Treg cells have also been shown to express higher levels of co-inhibitory molecules such as CTLA-4 and CD39, along with higher levels of FoxP3, CD25, granzyme B, and PD-1. Some tissue-resident Treg cells have also been reported to upregulate Tim-3⁴⁴, which has been shown to play a role in tissue homeostasis and repair⁴⁵, but the exact role of Tim-3 in these tissue Treg cells is still not clear. Treg cells are also known to express Tim-3 during allograft rejection, in which it has been shown that Tim-3-expressing Treg cells are short-lived⁴⁶. This raises a question about the status of Tim-3-expressing Treg cells in tumors, as it was recently reported that apoptotic Treg cells in the tumor microenvironment may have a more important suppressive function than live Treg cells via an inhibitory effect of ATP on both antigen-presenting cells and effector T cells⁴⁷.

With regard to non-T cells, Tim-3 is expressed by tumor-associated macrophages in response to tumor-derived factors such as transforming growth factor-beta (TGF- β)⁴⁸. In addition, Tim-3 low M1 macrophages can upregulate Tim-3 and become M2 macrophages in the tumor microenvironment, directly dampening macrophage function⁴⁹. It should be noted that a direct role for Tim-3 in M2 macrophages has not been reported. NK cells are also known to play a significant role in tumor clearance, and tumor-associated NK cells constitutively express Tim-3. These NK cells also show an exhausted phenotype, and anti-Tim-3 treatment, as discussed above, leads to the reversal of exhaustion in some tumors. Tim-3 function and regulation in NK tumor immunity are still relatively under-studied, compared with T cells, so future studies may reveal additional layers of Tim-3-mediated crosstalk in tumor immune responses involving NK cells.

There is increasing evidence that Tim-3 can also be expressed by tumor cells themselves^{50–52}. The expression of Tim-3 on tumor cells may lead to tumor progression by multiple mechanisms, including direct suppression of CD4 T-cell function and inhibition of IL-6–STAT3 signaling and by directly promoting tumor metastasis⁵². Given the expression of Tim-3 in multiple cell types in different tumor models, it would be very interesting to explore how anti-Tim-3 alone, or in combination with other anti-checkpoint receptor modalities, affects various subpopulations of Tim-3-expressing cells. A more in-depth discussion about the possible roles of Tim-3 in tumors can be found in recent reviews^{53,54}.

Tim-3 and pregnancy

A possible role for Tim-3 in pregnancy was first reported by Zhao *et al.*, who showed that Tim-3 was upregulated by peripheral blood monocytes (but not T or B cells)⁵⁵. This group also reported that abnormal Tim-3 levels during pregnancy are associated with pregnancy loss, although it should be noted that a later report suggested that the expression of Tim-3 by peripheral blood CD8 T cells and NK cells was associated with lower cytokine production cytotoxicity⁵⁶. In pregnant mice, cells from the decidua show high expression of both PD-1 and Tim-3, and these T cells also had higher proliferative capacity and cytokine-producing ability. Treatment of pregnant mice with anti-PD-1 or anti-Tim-3 (or both) leads to pregnant mice becoming highly susceptible to pregnancy loss. The number and function of Tim-3⁺PD-1⁺ T cells were also seen to be affected in cases of recurrent miscarriage⁵⁷. In addition, PD-1 and Tim-3 have been shown to induce Th2 bias at the maternal–fetal interface⁵⁸. The interaction of Gal-9 and Tim-3 was also shown to play a role at the maternal–fetal interface by directly affecting decidual NK cell function^{59,60}. Furthermore, Tim-3-expressing peripheral NK cells were shown to have immunosuppressive function, resulting in the production of anti-inflammatory cytokines and the induction of Treg cells⁵⁷. Significantly, in cases of recurrent miscarriage, Tim-3 expression and function on NK cells were found to be defective^{59,60}. In addition, Tim-3 could protect decidual stromal cells from Toll-like receptor-mediated apoptosis and inflammatory reactions and promotes Th2 bias at the maternal–fetal interface⁵⁸. Thus, these studies demonstrate that Tim-3 plays important roles in establishing and maintaining the immune-tolerant environment both at the maternal–fetal interface and in the peripheral blood, resulting in successful pregnancy.

Tim-3 and infectious disease

The role of Tim-3 during infection was first reported in HIV-infected patients, in whom CD8⁺ T cells were shown to express Tim-3 and were functionally exhausted⁶¹. Tim-3 expression also directly correlated with viral load and was inversely correlated with the use of highly active anti-retroviral therapy. *In vitro* peptide stimulation in the presence of anti-Tim-3 antibody also led to the restoration of cytokine function and proliferation of HIV-specific T cells. Tim-3, along with PD-1, is also highly expressed on mouse and human exhausted T cells in LCMV⁶², hepatitis B virus⁶³, Friend virus, and hepatitis C virus⁶⁴ infection. It should be noted that Tim-3, along with PD-1, is associated with terminally exhausted T cells and that in some cases anti-Tim-3, along with anti-PD-L1 antibody, leads to the restoration of cytotoxic function and reduction of viral titer⁶².

Recent work in our lab highlights an additional role of Tim-3 as a determinant of effector versus memory T-cell differentiation in acute viral infection, consistent with the observation that Tim-3 is rapidly expressed by activated T cells in response to acute LCMV challenge²³. This raises an interesting question

regarding the possibility of differential regulation and function of Tim-3 in acute versus chronic infection. Thus, in acute infection, there appears to be a co-stimulatory role for Tim-3, leading to differences in mTOR signaling, whereas in the case of chronic infection, Tim-3 marks exhausted cells and may play a direct role in dampening T-cell responses. Alternatively, it is worth considering that the expression of Tim-3 by exhausted T cells represents a last-ditch effort by the immune system to salvage some function from these cells. Further support for a positive role for Tim-3 in driving mTOR activation comes from a recent study of human T cells⁶⁵.

Consistent with a positive role for Tim-3 in at least some infections, Tim-3 expression by human T cells during *Mycobacterium tuberculosis* (MTb) infection is associated with increased effector function⁶⁶. For reasons that are unclear, a more recent report, using a mouse model, concluded that Tim-3 helps to maintain T-cell exhaustion on T cells during MTb infection⁶⁷. The same authors previously reported an indirect mechanism for Tim-3 in both mouse and human MTb infection, whereby Tim-3 expressed by T cells interacts with Gal-9, which in turn stimulated the antibacterial function of macrophages^{68,69}. Thus, as described elsewhere in this review, significant attention will need to be paid to the effects of Tim-3 on not only T cells but also other cell types that can express this protein. In *Listeria monocytogenes* infection, Tim-3 expression has been shown to correlate positively with an effector phenotype of T cells, and Tim-3 expression has been directly demonstrated to enhance CD8 T-cell responses in this model⁵.

Tim-3 and immunotherapy

Establishment of Tim-3 as an exhaustion marker, in both tumors and chronic infection, makes Tim-3 an attractive target for immunotherapy. In mouse tumor models where PD-1 blockade is only partially efficacious, the combination of Tim-3 and PD-1 therapy has been shown to be more effective as a treatment, leading to better tumor regression^{38,39}. In the case of chronic infection, combined blockade of Tim-3 and PD-1 led to improved CD8 T-cell response and viral control⁶². Adaptive resistance to PD-1 monotherapy has been associated with the upregulation of other checkpoint receptors and is a current challenge in the field⁷⁰, including crosstalk between PD-1 and Tim-3 in exhausted/effector T cells⁴⁰. Combined blockade of Tim-3 along with other checkpoint receptors such as PD-1 and CTLA-4 therefore may be an important therapeutic approach. Long-term protection has also been observed in a murine tumor model when Tim-3 monoclonal antibody was combined with agonist antibodies against the co-stimulatory molecule CD137 on T cells⁷¹. Pursuant to a better mechanistic understanding of how anti-Tim-3 antibodies might function in tumor therapy, a recent report showed that previously described antibodies to human or mouse

anti-Tim-3 seem to work by blocking the interaction of Tim-3 with PtdSer and Ceacam-1⁷².

Recently, the use of chimeric antigen receptor (CAR) T cells was approved by the US Food and Drug Administration as a therapy to treat B-cell lymphoma. Despite some success of CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia and B-cell malignancies, there is limited efficacy of CAR T cells in solid tumors. One of the probable reported causes of this is the ability of the tumor microenvironment to induce CAR T-cell exhaustion, leading to PD-1 and Tim-3 expression after initial waves of expansion⁵⁶. It has also been reported that tonic CAR T receptor signaling triggered by antigen-independent clustering can lead to early exhaustion of CAR T cells through the upregulation of Tim-3, PD-1, and LAG-3⁷³. This further highlights the rationale for exploring anti-Tim-3 therapy, along with other therapeutic approaches, for the treatment of cancer.

Although Tim-3 has been shown to be a promising therapeutic target, a recent report suggests that anti-Tim-3 treatment can lead to more severe inflammation and peribronchiolar fibrosis due to defective clearance of apoptotic bodies⁷⁴, consistent with the notion that Tim-3 is a receptor for PtdSer on apoptotic cells. Therefore, more detailed and systematic study is needed to determine other potential side effects of anti-Tim-3 antibody treatment.

Summary

Although Tim-3 was first described as an inhibitory receptor on T cells, it is now known to be expressed by different immune and non-immune cell types. In addition, Tim-3 has now been shown to possess either negative or positive function in various settings, depending on the cell type and physiological or pathological context. All of these findings suggest that current efforts to translate Tim-3 as a target for immunotherapy of cancer will be more complicated than other targets with more limited expression (for example, CTLA-4 and PD-1). Nonetheless, they also indicate that there is more interesting biology surrounding Tim-3 that remains to be deconvolved and that may lead to unanticipated applications for this protein as a therapeutic target.

Competing interests

The authors declare that they have no competing interests.

Grant information

Work on Tim-3 in Lawrence P. Kane's lab is funded by National Institutes of Health award CA206517.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. **F** 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): 2175–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
2. **F** 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): 536–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
3. **F** Sánchez-Fueyo A, Tian J, Picarella D, *et al.*: **Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance.** *Nat Immunol.* 2003; **4**(11): 1093–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
4. 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): 1525–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. **F** Gorman JV, Starbeck-Miller G, Pham NL, *et al.*: **Tim-3 directly enhances CD8⁺ T cell responses to acute *Listeria monocytogenes* infection.** *J Immunol.* 2014; **192**(7): 3133–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
6. 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): 2289–304.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. **F** Anderson AC, Anderson DE, Bregoli L, *et al.*: **Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells.** *Science.* 2007; **318**(5853): 1141–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
8. Möller-Hackbarth K, Dewitz C, Schweigert O, *et al.*: **A disintegrin and metalloprotease (ADAM) 10 and ADAM17 are major sheddases of T cell immunoglobulin and mucin domain 3 (Tim-3).** *J Biol Chem.* 2013; **288**(48): 34529–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. **F** Clayton KL, Douglas-Vail MB, Nur-ur Rahman AK, *et al.*: **Soluble T cell immunoglobulin mucin domain 3 is shed from CD8⁺ T cells by the sheddase ADAM10, is increased in plasma during untreated HIV infection, and correlates with HIV disease progression.** *J Virol.* 2015; **89**(7): 3723–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
10. Zhu C, Anderson AC, Schubart A, *et al.*: **The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity.** *Nat Immunol.* 2005; **6**(12): 1245–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Su EW, Bi S, Kane LP: **Galectin-9 regulates T helper cell function independently of Tim-3.** *Glycobiology.* 2011; **21**(10): 1258–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. DeKruyff RH, Bu X, Ballesteros A, *et al.*: **T cell/transmembrane, Ig, and mucin-3 allelic variants differentially recognize phosphatidylserine and mediate phagocytosis of apoptotic cells.** *J Immunol.* 2010; **184**(4): 1918–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. **F** Huang YH, Zhu C, Kondo Y, *et al.*: **CEACAM1 regulates TIM-3-mediated tolerance and exhaustion.** *Nature.* 2015; **517**(7534): 386–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
14. **F** 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): 832–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
15. Dolina JS, Braciale TJ, Hahn YS: **Liver-primed CD8⁺ T cells suppress antiviral adaptive immunity through galectin-9-independent T-cell immunoglobulin and mucin 3 engagement of high-mobility group box 1 in mice.** *Hepatology.* 2014; **59**(4): 1351–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. **F** Martinez GJ, Pereira RM, Åijö T, *et al.*: **The transcription factor NFAT promotes exhaustion of activated CD8⁺ T cells.** *Immunity.* 2015; **42**(2): 265–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. Anderson AC, Lord GM, Dardalhon V, *et al.*: **T-bet, a Th1 transcription factor regulates the expression of Tim-3.** *Eur J Immunol.* 2010; **40**(3): 859–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. **F** Kao C, Oestreich KJ, Paley MA, *et al.*: **Transcription factor T-bet represses expression of the inhibitory receptor PD-1 and sustains virus-specific CD8⁺ T cell responses during chronic infection.** *Nat Immunol.* 2011; **12**(7): 663–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
19. **F** 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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
20. Zehn D, Wherry EJ: **Immune Memory and Exhaustion: Clinically Relevant Lessons from the LCMV Model.** *Adv Exp Med Biol.* 2015; **850**: 137–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. 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): 3963–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. van de Weyer PS, Muehlfeit M, Klose C, *et al.*: **A highly conserved tyrosine of Tim-3 is phosphorylated upon stimulation by its ligand galectin-9.** *Biochem Biophys Res Commun.* 2006; **351**(2): 571–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Avery L, Szymczak-Workman AL, Kane LP: **(Tim-3 co-stimulation promotes short-term effector T cells, restricts memory precursors and is dispensable for T cell exhaustion.** *bioRxiv* 179002 [Preprint]. August 22 2017.
[Publisher Full Text](#)
24. **F** Gorman JV, Colgan JD: **Acute stimulation generates Tim-3-expressing T helper type 1 CD4 T cells that persist *in vivo* and show enhanced effector function.** *Immunology.* 2018.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. Rangachari M, Zhu C, Sakuishi K, *et al.*: **Bat3 promotes T cell responses and autoimmunity by repressing Tim-3-mediated cell death and exhaustion.** *Nat Med.* 2012; **18**(9): 1394–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Clayton KL, Haaland MS, Douglas-Vail MB, *et al.*: **T cell Ig and mucin domain-containing protein 3 is recruited to the immune synapse, disrupts stable synapse formation, and associates with receptor phosphatases.** *J Immunol.* 2014; **192**(2): 782–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. **F** Li YH, Zhou WH, Tao Y, *et al.*: **The Galectin-9/Tim-3 pathway is involved in the regulation of NK cell function at the maternal-fetal interface in early pregnancy.** *Cell Mol Immunol.* 2016; **13**(1): 73–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
28. Nielsen N, Ødum N, Ursø B, *et al.*: **Cytotoxicity of CD56^{bright} NK cells towards autologous activated CD4⁺ T cells is mediated through NKG2D, LFA-1 and TRAIL and dampened via CD94/NKG2A.** *PLoS One.* 2012; **7**(2): e31959.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Gallois A, Silva I, Osman I, *et al.*: **Reversal of natural killer cell exhaustion by TIM-3 blockade.** *Oncotarget.* 2015; **6**(12): e946365.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. 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**(5): 410–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Phong B, Avery L, Menk AV, *et al.*: **Cutting Edge: Murine Mast Cells Rapidly Modulate Metabolic Pathways Essential for Distinct Effector Functions.** *J Immunol.* 2017; **198**(2): 640–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Maurya N, Gujar R, Gupta M, *et al.*: **Immunoregulation of dendritic cells by the receptor T cell Ig and mucin protein-3 via Bruton's tyrosine kinase and c-Src.** *J Immunol.* 2014; **193**(7): 3417–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. **F** Schwartz JA, Clayton KL, Mujib S, *et al.*: **Tim-3 is a Marker of Plasmacytoid Dendritic Cell Dysfunction during HIV Infection and Is Associated with the Recruitment of IRF7 and p85 into Lysosomes and with the Submembrane Displacement of TLR9.** *J Immunol.* 2017; **198**(8): 3181–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. Ocaña-Guzman R, Torre-Bouscoulet L, Sada-Ovalle I: **TIM-3 Regulates Distinct Functions in Macrophages.** *Front Immunol.* 2016; **7**: 229.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. **F** Wang W, Shi Q, Dou S, *et al.*: **Negative regulation of Nod-like receptor protein 3 inflammasome activation by T cell Ig mucin-3 protects against peritonitis.** *Immunology.* 2018; **153**(1): 71–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. **F** Liu X, Jiang S, Zhang Q, *et al.*: **Tim-3 Regulates Tregs' Ability to Resolve the Inflammation and Proliferation of Acute Lung Injury by Modulating Macrophages Polarization.** *Shock.* 2017.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. **F** 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): 2187–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. Ngio SF, von Scheidt B, Akiba H, *et al.*: **Anti-TIM3 antibody promotes T cell IFN-γ-mediated antitumor immunity and suppresses established tumors.** *Cancer Res.* 2011; **71**(10): 3540–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Shayan G, Srivastava R, Li J, *et al.*: **Adaptive resistance to anti-PD1 therapy by**

- Tim-3 upregulation is mediated by the PI3K-Akt pathway in head and neck cancer.** *Oncimmunology*. 2016; 6(1): e1261779.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Jie HB, Srivastava RM, Argiris A, *et al.*: **Increased PD-1⁺ and TIM-3⁺ TILs during Cetuximab Therapy Inversely Correlate with Response in Head and Neck Cancer Patients.** *Cancer Immunol Res*. 2017; 5(5): 408–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 42. Yan J, Zhang Y, Zhang JP, *et al.*: **Tim-3 expression defines regulatory T cells in human tumors.** *PLoS One*. 2013; 8(3): e58006.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Sakuishi K, Ngiow SF, Sullivan JM, *et al.*: **TIM3⁺FOXP3⁺ regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer.** *Oncimmunology*. 2013; 2(4): e23849.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Panduro M, Benoist C, Mathis D: **Tissue Tregs.** *Annu Rev Immunol*. 2016; 34: 609–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 45. **F** Burzyn D, Kuswanto W, Kolodin D, *et al.*: **A special population of regulatory T cells potentiates muscle repair.** *Cell*. 2013; 155(6): 1282–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 46. **F** Gupta S, Thornley TB, Gao W, *et al.*: **Allograft rejection is restrained by short-lived TIM-3⁺PD-1⁺FOXP3⁺ Tregs.** *J Clin Invest*. 2012; 122(7): 2395–404.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 47. **F** Maj T, Wang W, Crespo J, *et al.*: **Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor.** *Nat Immunol*. 2017; 18(12): 1332–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 48. **F** Yan W, Liu X, Ma H, *et al.*: **Tim-3 fosters HCC development by enhancing TGF- β -mediated alternative activation of macrophages.** *Gut*. 2015; 64(10): 1593–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 49. **F** Jiang X, Zhou T, Xiao Y, *et al.*: **Tim-3 promotes tumor-promoting M2 macrophage polarization by binding to STAT1 and suppressing the STAT1-miR-155 signaling axis.** *Oncimmunology*. 2016; 5(9): e1211219.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 50. Wiener Z, Kohalmi B, Pocza P, *et al.*: **TIM-3 is expressed in melanoma cells and is upregulated in TGF-beta stimulated mast cells.** *J Invest Dermatol*. 2007; 127(4): 906–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. Shang Y, Li Z, Li H, *et al.*: **TIM-3 expression in human osteosarcoma: Correlation with the expression of epithelial-mesenchymal transition-specific biomarkers.** *Oncol Lett*. 2013; 6(2): 490–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 52. Huang X, Bai X, Cao Y, *et al.*: **Lymphoma endothelium preferentially expresses Tim-3 and facilitates the progression of lymphoma by mediating immune evasion.** *J Exp Med*. 2010; 207(3): 505–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. Du W, Yang M, Turner A, *et al.*: **TIM-3 as a Target for Cancer Immunotherapy and Mechanisms of Action.** *Int J Mol Sci*. 2017; 18(3): pii: E645.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. Das M, Zhu C, Kuchroo VK: **Tim-3 and its role in regulating anti-tumor immunity.** *Immunol Rev*. 2017; 276(1): 97–111.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 55. Zhao J, Lei Z, Liu Y, *et al.*: **Human pregnancy up-regulates Tim-3 in innate immune cells for systemic immunity.** *J Immunol*. 2009; 182(10): 6618–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. **F** Meggyes M, Lajko A, Palkovics T, *et al.*: **Feto-maternal immune regulation by TIM-3/galectin-9 pathway and PD-1 molecule in mice at day 14.5 of pregnancy.** *Placenta*. 2015; 36(10): 1153–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 57. **F** Wang S, Li Y, Piao H, *et al.*: **PD-1 and Tim-3 pathways are associated with regulatory CD8⁺ T-cell function in decidua and maintenance of normal pregnancy.** *Cell Death Dis*. 2015; 6: e1738.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 58. **F** Wang S, Zhu X, Xu Y, *et al.*: **Programmed cell death-1 (PD-1) and T-cell immunoglobulin mucin-3 (Tim-3) regulate CD4⁺ T cells to induce Type 2 helper T cell (Th2) bias at the maternal-fetal interface.** *Hum Reprod*. 2016; 31(4): 700–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 59. **F** Li Y, Zhang J, Zhang D, *et al.*: **Tim-3 signaling in peripheral NK cells promotes maternal-fetal immune tolerance and alleviates pregnancy loss.** *Sci Signal*. 2017; 10(498): pii: eaah4323.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 60. Li Y, Li D, Du M: **TIM-3: a crucial regulator of NK cells in pregnancy.** *Cell Mol Immunol*. 2017; 14(11): 948–950.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. **F** Jones RB, Ndhlovu LC, Barbour JD, *et al.*: **Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection.** *J Exp Med*. 2008; 205(12): 2763–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 62. Jin H, Anderson AC, Tan WG, *et al.*: **Cooperation of Tim-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection.** *Proc Natl Acad Sci U S A*. 2010; 107(33): 14733–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. **F** Liu Y, Gao L, Liang X, *et al.*: **Role of Tim-3 in hepatitis B virus infection: An overview.** *World J Gastroenterol*. 2016; 22(7): 2294–303.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 64. **F** Golden-Mason L, Palmer BE, Kassam N, *et al.*: **Negative immune regulator Tim-3 is overexpressed on T cells in hepatitis C virus infection and its blockade rescues dysfunctional CD4⁺ and CD8⁺ T cells.** *J Virol*. 2009; 83(18): 9122–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 65. **F** Sabins NC, Chornoguz O, Leander K, *et al.*: **TIM-3 Engagement Promotes Effector Memory T Cell Differentiation of Human Antigen-Specific CD8 T Cells by Activating mTORC1.** *J Immunol*. 2017; 199(12): 4091–102.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 66. Qiu Y, Chen J, Liao H, *et al.*: **Tim-3-expressing CD4⁺ and CD8⁺ T cells in human tuberculosis (TB) exhibit polarized effector memory phenotypes and stronger anti-TB effector functions.** *PLoS Pathog*. 2012; 8(11): e1002984.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 67. **F** Jayaraman P, Jacques MK, Zhu C, *et al.*: **TIM3 Mediates T Cell Exhaustion during *Mycobacterium tuberculosis* Infection.** *PLoS Pathog*. 2016; 12(3): e1005490.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 68. **F** Jayaraman P, Sada-Ovalle I, Beladi S, *et al.*: **Tim3 binding to galectin-9 stimulates antimicrobial immunity.** *J Exp Med*. 2010; 207(11): 2343–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 69. Sada-Ovalle I, Chávez-Galán L, Torre-Bouscoulet L, *et al.*: **The Tim3-galectin 9 pathway induces antibacterial activity in human macrophages infected with *Mycobacterium tuberculosis*.** *J Immunol*. 2012; 189(12): 5896–902.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 70. **F** 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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 71. 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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 72. **F** Sabatos-Peyton CA, Nevin J, *et al.*: **Blockade of Tim-3 binding to phosphatidylserine and CEACAM1 is a shared feature of anti-Tim-3 antibodies that have functional efficacy.** *Oncimmunology*. 2017; 7: e1385690.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 73. Meggyes M, Miko E, Polgar B, *et al.*: **Peripheral blood TIM-3 positive NK and CD8⁺ T cells throughout pregnancy: TIM-3/galectin-9 interaction and its possible role during pregnancy.** *PLoS One*. 2014; 9: e92371.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 74. **F** Isshiki T, Akiba H, Nakayama M, *et al.*: **Cutting Edge: Anti-TIM-3 Treatment Exacerbates Pulmonary Inflammation and Fibrosis in Mice.** *J Immunol*. 2017; 199: 3733–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. MeiRong Du

Laboratory for Reproductive Immunology, Hospital of Obstetrics and Gynecology, Fudan University Shanghai Medical College, Shanghai, China

Competing Interests: No competing interests were disclosed.

2. Mario A. Ostrowski

University of Toronto, Institute of Medical Science, Toronto, Ontario, Canada

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research