Hindawi Publishing Corporation
Journal of Immunology Research
Volume 2016, Article ID 8605134, 6 pages
http://dx.doi.org/10.1155/2016/8605134

Review Article

Immune Regulation and Antitumor Effect of TIM-1

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Received 18 February 2016; Revised 10 April 2016; Accepted 28 April 2016

Academic Editor: Bin Zhang

T cells play an important role in antitumor immunity, and the T cell immunoglobulin domain and the mucin domain protein-1 (TIM-1) on its surface, as a costimulatory molecule, has a strong regulatory effect on T cells. TIM-1 can regulate and enhance type 1 immune response of tumor association. Therefore, TIM-1 costimulatory pathways may be a promising therapeutic target in future tumor immunotherapy. This review describes the immune regulation and antitumor effect of TIM-1.

1. Introduction

Immune suppression is an important factor for immune evasion of tumor. Generally, the immune systems of tumor patients often have excessive inhibitory functions, which are induced by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), or the secretion of immunosuppressive cytokines, such as tumor growth factor-β (TGF-β) and interleukin-10 (IL-10). These conditions constitute an extremely favorable microenvironment for tumor progression [1–4]. Therefore, it is important to find novel targets for reversing immunosuppression microenvironment.

The identification of new classes of costimulatory molecules provides new exciting opportunities for inducing and enhancing effective endogenous immune response to cancer. TIM-1, a key member and costimulatory molecule in the T cell immunoglobulin mucin (TIM) family, is expressed on the surface of T cells. It can promote the activation and proliferation of T cells and the secretion of cytokines, which play critical roles in tumor immunity [5–9]. Our preliminary studies have shown that TIM-1 may be a novel candidate tumor therapeutic costimulatory molecule, because it may directly enhance the functions of $CD8^+$ T cells and/or NK cells, as well as altering the tumor microenvironment for more effective antitumor immune response (data not shown). This review tries to describe how TIM-1 regulates immune function and takes part in antitumor immune responses and illustrates the mechanism of immune regulation.

2. Structure and Basic Function of TIM-1

In human, there are three members (TIM-1, TIM-3, and TIM-4) located in the human chromosome 5q33.2 region. In mouse, the TIM family consists of eight members (TIMs 1–8) located in the 11B1.1 region of chromosome. The human and mouse TIM family genes are highly homologous [8, 10]. Like other TIM members, TIM-1 is similar in structure to the type 1 membrane protein, which consists of an N-terminal Cys-rich immunoglobulin variable- (IgV-) like domain, a mucin-like domain, a transmembrane domain, and an intracellular tail [11, 12]. The intracellular tail of TIM-1 contains tyrosine phosphorylation motifs that are involved in transmembrane signal [8, 13–15].

The expression of human TIM-1 was first detected in damaged kidney and named human kidney injury molecule-1 (KIM-1) [16–19]. Previous studies have indicated that *in vivo* TIM-1 gene mutations in human and mouse are associated with some allergic diseases [8, 20]. Abnormal expression of TIM-1 is related to some autoimmune diseases [21–27]. In recent years, study found that TIM-1 is mainly expressed on the surfaces of $CD4^+$ T cells, $CD8^+$ T cells, NK cells,

macrophages, DCs, B cells, and mast cells [28]. Moreover, it is also found that TIM-1 is expressed in lymphoid tissues [8, 29] and confirmed that TIM-1 can promote the production of cytokines and enhance the antigen induced immune response of T cells [30–35]. Therefore, TIM-1 may be a potential costimulatory molecule to enhance antitumor immune response [8, 23, 35–38].

3. Immune Regulation of TIM-1

TIM-1 is a highly efficient costimulatory molecule, which can enhance the formation of CD3-TCR with agonistic anti-TIM-1 antibody involved in the activation of T cells [7, 8, 37, 39]. The main ligands of TIM-1 are TIM-4 and phosphatidylserine (PS) [36, 40, 41]. TIM-4 is expressed on the surface of antigen presenting cells (APCs) such as macrophages and dendritic cells, working as an endogenous ligand of TIM-1 [5, 42, 43]. TIM-4 can promote T cell activation, proliferation, and cytokine production by binding to TIM-1, which mediates the positive regulation of T cells and triggers the immune response with costimulatory effect [30, 40]. PS is another important ligand of TIM-1 and can activate NKT cells by binding to TIM-1 on the surface of NKT cells [12, 44, 45]. In addition, P-selectin and S-selectin are also potential ligands for TIM-1 and may play roles in inflammation and autoimmune diseases. This signal pathway is closely related to the migration of Th1 and Th17 cells in blood vessels [38, 46].

The biological function of TIM-1 mainly depends on lymphocytes. TIM-1 in $CD4^+$ T cells can upregulate the activation signal of T cells by interacting with T cell receptor (TCR), which promotes the synergistic effect of TIM-1 [8, 47]. In immune regulation, the positive and negative regulation of TIM-1 are essential for the maintenance of immune homeostasis. The immune regulation of TIM-1 mainly depends on its ligands [8]. It has been reported that agonistic TIM-1 mAbs (clone 3B3 and clone 1H8.2) augment T cell-mediated immune responses, whereas an antagonistic antibody inhibits immune responses through regulatory B cells [48]. Agonistic TIM-1 monoclonal antibody can promote the proliferation of $CD8^+$ T cells *in vitro* and enhance their biological function [49]. The different effects of agonistic and antagonistic TIM-1 mAbs *in vivo* may be due to the fact that different TIM-1 mAbs deliver qualitatively and quantitatively different signals to T cells and B cells. The TIM-1 signaling on B cells is important in maintaining normal homeostasis of the immune system and preventing systemic autoimmunity [50, 51]. In $CD4^+$ T cells, the TIM-1 molecules bound with agonistic TIM-1 mAbs [39] or other agonistic ligands can produce a strong costimulation signal to activate T cells, promote the differentiation and proliferation of T cells *in vivo*, activate the production of cytokines, and enhance the antigen induced immune response of T cells [30–34]. Previous studies have found that the inhibition of TIM-1 signal of $CD4^+$ T cell can reduce the level of white blood cells and the production of inflammatory mediators, which can reduce the tissue damage caused by excessive inflammatory reactions [30, 35, 52, 53].

The negative regulation of immune function of TIM-1 in B cells plays a key role in preventing immune rejection [51, 54]. The inhibition of TIM-1-Fc signaling inhibits the differentiation and function of $CD4^+$ T cells and further reduces chronic rejection reactions [55]. Zhang et al. have found that the suppression of the TIM-1 signal in $CD4^+$ T cells can inhibit the activity of macrophages and reduce the injury of transplanted liver in a mouse model [56]. TIM-1 is also a key molecule in the regulation of immune rejection of allogeneic transplantation [49], and functional deficiency of TIM-1 is also one of the mechanisms of autoimmune diseases [50]. The expressions of TIM-3 and TIM-1 on the surface of mouse mast cells promote the secretion of IL-13, IL-6, and IL-4, indicating that mast cells also regulate immune function through TIM members [57]. Study also found that the inhibition of TIM-1 signal can reduce infiltration of T cells into allergic skin tissues and tissues of autoimmune diseases [38], and deficiency of TIM-1 reduces the incidence of allergic asthma in a mouse model [58]. Therefore, TIM-1 may also be related to the molecular mechanism of allergic diseases.

4. TIM-1 for Cancer Immunity

Type 1 immune response, mediated by Th1 cells, cytotoxic T lymphocytes (CTLs), NK cells, NKT cells, and gamma delta T cells, is considered as a critical component of cell-mediated immunity against tumor. $CD8^+$ T cells are important T cell subsets in specific immune response. They are the final effector cells to kill tumor and inhibit tumor progression *in vivo*, which are widely used in tumor adoptive immunotherapy [59, 60]. In human, the presence of Th1 cells and CTLs in tumor can be a favorable prognostic indicator [61]. However, many tumor infiltrating Th1 and $CD8^+$ T cells are in a status of nonresponsiveness due to local and systemic mechanisms of immune suppression in cancer patients as well as in tumor-bearing mice and even play a protective role for tumor [62, 63]. The lack of costimulation of type 1 lymphocytes is the major mechanism underlying tumor-induced immune tolerance [64, 65]. Thus, agonistic antibodies against costimulatory receptors such as 4-1BB and CD40 have shown promising antitumor effects in various preclinical tumor models, which are evaluated in clinical trials. The costimulation signal plays an important role in $CD8^+$ T cells [64]. In the model of acute renal injury induced by cisplatin, blocking of TIM-1 signal can significantly reduce the number of $CD8^+$ T cells and inhibit the secretion of IFN-γ, indicating that TIM-1 costimulation signal can enhance the effect of $CD8^+$ T cells [66].

In the TIM family, to date, it has been confirmed that TIM-3 is related to tumor [67, 68] and found that the expression of TIM-3 has an important influence on tumor microenvironment [69, 70]. However, we still have a lot of unknowns regarding the effects of tumor immunity of TIM-1. There are only a few articles that can be retrieved, which are about antitumor effect of TIM-1 [5, 6], but it has been determined that TIM-1 can promote the proliferation and differentiation of T cells by binding to different agonistic ligands [15, 30, 40, 71]. A study has demonstrated that TIM-1 tyrosine phosphorylation can recruit the PI3K adaptors p85, which stimulates the activation and function of T cells [15].

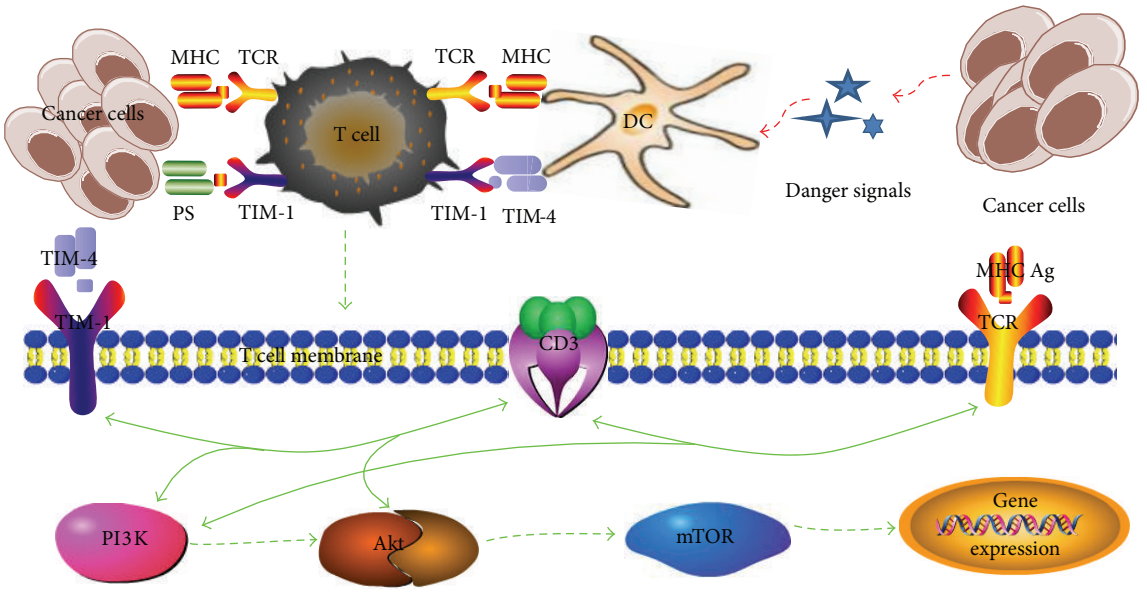

Figure 1: Tumor cells release signals, which are received by dendritic cells (DCs). Tumor antigens are processed to MHC antigens and then presented to the T cell receptor (TCR) for activation. TIM-4 (or phosphatidylserine) on DCs binds to TIM-1 on T cells to form the CD3-TCR complex, which participates in TCR-mediated T cell activation and initiates the intracellular PI3K signal pathway. PI3K signal pathway consists of the interaction between TIM-1 and ligands, tyrosine phosphorylation of the intracellular region of TIM-1, the recruitment of PI3K, the activation of Akt by PI3K, and the activation of mTOR by Akt. Activated mTOR can regulate the biological functions of T cells.

In tumor microenvironment, the effector cells, such as $CD8^+$ T cells, directly participate in immune response and can enhance antigen recognition, proliferation, and differentiation of other effector cells.

Ligation of the transmembrane protein TIM-1 can costimulate T cell activation by the PI3K signaling pathway. Agonistic antibodies to TIM-1 are also capable of inducing T cell activation without additional stimuli; PI3K is an important factor in mediating TIM-1 signaling [15]. It has been known that the PI3K/Akt/mTOR signaling pathway plays a crucial role in the regulation of cell growth, proliferation, and metabolism. The immune cells and tumor cells compete for energy. The activation of some signaling molecules closely related to energy metabolism regulates T cell activation, differentiation, and function and further enhances the antigen recognition, proliferation, and the differentiation of T cells. So far, PI3K/Akt/mTOR signaling pathway is a target of tumor therapy [72–77].

The transcription factor T-bet/Eomes is involved in the regulation of $CD8^+$ T cell function and induces the differentiation of $CD8^+$ T cells to effector and central memory T cells [78, 79]. The expression level of TIM-1 and T-bet/Eomes has important effects on regulating the biological function of T cells, and the expression of T-bet is closely related to the prognosis of tumor patients [24, 80]. We have analyzed 152 cases of gastric cancer patients and found that the expression of T-bet is closely related to the survival of tumor patients. The number of T-bet positive T cells in tumor tissues has a significant effect on the prognosis of the patients [81]. T-bet/Eomes, which stimulates the activation and differentiation of $CD8^+$ T cells, is significantly upregulated in the tumor of the third day after radiofrequency ablation (RFA), and the expression level of TIM-1 in infiltrating $CD8^+$ T cells is significantly upregulated. In T-bet/Eomes double knockout tumor model mice, it has been found that the expression of TIM-1 is very low in infiltrating $CD8^+$ T cells stimulated by tumor antigen, and in wild type mice it is significantly upregulated (data not shown). At present, TIM-1 is considered to improve the secretion of some cytokines such as IL-4 and IFN-γ [82]. Type 1 immune response of TIM-1-mediated T cell activation is associated with tumor immunity through transcription factor T-bet/Eomes [71, 83] and the PI3K signal pathway [15] (Figure 1).

5. Prospect

We speculate that TIM-1, a new costimulatory candidate molecule for tumor treatment, not only directly enhances the antitumor effect of $CD8^+$ T cells and NK cells but also changes the tumor microenvironment to induce more effective antitumor immune response. As a target molecule, it may have a good application prospect in clinical cancer research. In addition, agonistic anti-TIM-1 monoclonal antibody or other ligands can enhance the function of T cells [39, 82], increase $CD8^+$ T cells and NK cells, reduce MDSC in tumor tissues, and inhibit tumor growth (data not shown). It is important to define the mode of action and determine whether $CD8^+$ T cells and NK cells mediate the antitumor effect of agonistic TIM-1 mAbs *in vivo*. These may provide a theoretical basis to construct a new tumor therapy model of TIM-1 signal interference.

Competing Interests

There are no potential competing interests to disclose.

Acknowledgments

This work was supported by grants from the National Key Technology R&D Program (no. 2015BAI12B12) and the National Natural Science Foundation of China (nos. 81171653, 31428005, 31570877, and 31570908).

References

[1] I. Silvestri, S. Cattarino, A. M. Aglianò, G. Collalti, and A. Sciarra, "Beyond the immune suppression: the immunotherapy in prostate cancer," *BioMed Research International*, vol. 2015, Article ID 794968, 9 pages, 2015.

[2] K. H. Parker, D. W. Beury, and S. Ostrand-Rosenberg, "Myeloid-derived suppressor cells: critical cells driving immune suppression in the tumor microenvironment," *Advances in Cancer Research*, vol. 128, pp. 95–139, 2015.

[3] D. J. Silver, M. Sinyuk, M. A. Vogelbaum, M. S. Ahluwalia, and J. D. Lathia, "The intersection of cancer, cancer stem cells, and the immune system: therapeutic opportunities," *Neuro-Oncology*, vol. 18, no. 2, pp. 153–159, 2016.

[4] L. Chen, J. V. Heymach, F. X.-F. Qin, and D. L. Gibbons, "The mutually regulatory loop of epithelial-mesenchymal transition and immunosuppression in cancer progression," *OncoImmunology*, vol. 4, no. 5, Article ID e1002731, 2015.

[5] H.-W. Sun, C. Wu, H.-Y. Tan, and Q.-S. Wang, "A new development of FG-CC′ siRNA blocking interaction of Tim-1 and Tim-4 can enhance DC vaccine against gastric cancer," *Hepato-Gastroenterology*, vol. 59, no. 120, pp. 2677–2682, 2012.

[6] S. Xiao, B. Zhu, H. Jin et al., "Tim-1 stimulation of dendritic cells regulates the balance between effector and regulatory T cells," *European Journal of Immunology*, vol. 41, no. 6, pp. 1539–1549, 2011.

[7] W. Soo Hoo, E. R. Jensen, A. Saadat et al., "Vaccination with cell immunoglobulin mucin-1 antibodies and inactivated influenza enhances vaccine-specific lymphocyte proliferation, interferon-gamma production and cross-strain reactivity," *Clinical & Experimental Immunology*, vol. 145, no. 1, pp. 123–129, 2006.

[8] R. Rodriguez-Manzanet, R. Dekruyff, V. K. Kuchroo, and D. T. Umetsu, "The costimulatory role of TIM molecules," *Immunological Reviews*, vol. 229, no. 1, pp. 259–270, 2009.

[9] C. Mariat, N. Degauque, S. Balasubramanian et al., "Tim-1 signaling substitutes for conventional signal 1 and requires costimulation to induce T cell proliferation," *The Journal of Immunology*, vol. 182, no. 3, pp. 1379–1385, 2009.

[10] V. K. Kuchroo, D. T. Umetsu, R. H. DeKruyff, and G. J. Freeman, "The TIM gene family: emerging roles in immunity and disease," *Nature Reviews Immunology*, vol. 3, no. 6, pp. 454–462, 2003.

[11] Y. Uchida, B. Ke, S. Cecilia et al., "The emerging role of t cell immunoglobulin mucin-1 in the mechanism of liver ischemia and reperfusion injury in the mouse," *Hepatology*, vol. 51, no. 4, pp. 1363–1372, 2010.

[12] R. H. DeKruyff, X. Bu, A. Ballesteros et al., "T cell/transmembrane, Ig, and mucin-3 allelic variants differentially recognize phosphatidylserine and mediate phagocytosis of apoptotic cells," *The Journal of Immunology*, vol. 184, no. 4, pp. 1918–1930, 2010.

[13] S. Xiao, C. R. Brooks, R. A. Sobel, and V. K. Kuchroo, "Tim-1 is essential for induction and maintenance of IL-10 in regulatory B cells and their regulation of tissue inflammation," *The Journal of Immunology*, vol. 194, no. 4, pp. 1602–1608, 2015.

[14] M. L. Curtiss, B. S. Hostager, E. Stepniak et al., "Fyn binds to and phosphorylates T cell immunoglobulin and mucin domain-1 (Tim-1)," *Molecular Immunology*, vol. 48, no. 12-13, pp. 1424–1431, 2011.

[15] A. J. de Souza, J. S. Oak, R. Jordanhazy, R. H. DeKruyff, D. A. Fruman, and L. P. Kane, "T cell Ig and mucin domain-1-mediated T cell activation requires recruitment and activation of phosphoinositide 3-kinase," *The Journal of Immunology*, vol. 180, no. 10, pp. 6518–6526, 2008.

[16] J. V. Bonventre, "Kidney injury molecule-1 (KIM-1): a specific and sensitive biomarker of kidney injury," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 68, no. 241, pp. 78–83, 2008.

[17] J. V. Bonventre, "Kidney injury molecule-1: a translational journey," *Transactions of the American Clinical and Climatological Association*, vol. 125, pp. 293–299, 2014.

[18] A. K. Ajay, T.-M. Kim, V. Ramirez-Gonzalez, P. J. Park, D. A. Frank, and V. S. Vaidya, "A bioinformatics approach identifies signal transducer and activator of transcription-3 and checkpoint kinase 1 as upstream regulators of kidney injury molecule-1 after kidney injury," *Journal of the American Society of Nephrology*, vol. 25, no. 1, pp. 105–118, 2014.

[19] T. Ichimura, C. R. Brooks, and J. V. Bonventre, "Kim-1/Tim-1 and immune cells: shifting sands," *Kidney International*, vol. 81, no. 9, pp. 809–811, 2012.

[20] J. J. McIntire, S. E. Umetsu, O. Akbari et al., "Identification of Tapr (an airway hyperreactivity regulatory locus) and the linked Tim gene family," *Nature Immunology*, vol. 2, no. 12, pp. 1109–1116, 2001.

[21] S.-C. Chae, Y.-R. Park, J.-H. Song, S.-C. Shim, K.-S. Yoon, and H.-T. Chung, "The polymorphisms of Tim-1 promoter region are associated with rheumatoid arthritis in a Korean population," *Immunogenetics*, vol. 56, no. 10, pp. 696–701, 2005.

[22] S.-C. Chae, J.-H. Song, S.-C. Shim, K.-S. Yoon, and H.-T. Chung, "The exon 4 variations of Tim-1 gene are associated with rheumatoid arthritis in a Korean population," *Biochemical and Biophysical Research Communications*, vol. 315, no. 4, pp. 971–975, 2004.

[23] M. Khademi, Z. Illés, A. W. Gielen et al., "T cell Ig- and mucin-domain-containing molecule-3 (TIM-3) and TIM-1 molecules are differentially expressed on human Th1 and Th2 cells and in cerebrospinal fluid-derived mononuclear cells in multiple sclerosis," *The Journal of Immunology*, vol. 172, no. 11, pp. 7169–7176, 2004.

[24] X.-M. Zhang, N.-N. Shan, Y. Hu, and X. Wang, "Expression of TIM-1 and TIM-3 in spleen mononuclear cells and their role in Th1 polarization in primary immune thrombocytopenia patients," *Zhonghua Xue Ye Xue Za Zhi*, vol. 34, no. 7, pp. 614–617, 2013.

[25] X. Z. Cai, W. Y. Huang, Y. Qiao et al., "Downregulation of TIM-3 mRNA expression in peripheral blood mononuclear cells from patients with systemic lupus erythematosus," *Brazilian Journal of Medical and Biological Research*, vol. 48, no. 1, pp. 77–82, 2015.

[26] J. A. Shim, E.-S. Lee, B. Choi, and S. Sohn, "The role of T cell immunoglobulin mucin domains 1 and 4 in a herpes simplex

virus-induced Behçet's disease mouse model," *Mediators of Inflammation*, vol. 2013, Article ID 903948, 13 pages, 2013.

[27] K. Zheng, G. Xu, X. Lu, J. Zhang, and P. Zhang, "Expression and polymorphisms of T cell immunoglobulin domain and mucin domain protein-1 in thymoma with or without myasthenia gravis," *Oncology Letters*, vol. 8, no. 1, pp. 317–322, 2014.

[28] Z. Li, Z. Ju, and M. Frieri, "The T-cell immunoglobulin and mucin domain (Tim) gene family in asthma, allergy, and autoimmunity," *Allergy and Asthma Proceedings*, vol. 34, no. 1, pp. e21–e26, 2013.

[29] S. Hu, Y. Xie, N. Zhou et al., "Expression of T-cell immunoglobulin- and mucin-domain-containing molecules-1 and -3 (Tim-1 and Tim-3) in *Helicobacter pylori* infection," *Helicobacter*, vol. 16, no. 5, pp. 373–381, 2011.

[30] O. Schweigert, C. Dewitz, K. Möller-Hackbarth et al., "Soluble T cell immunoglobulin and mucin domain (TIM)-1 and -4 generated by A Disintegrin And Metalloprotease (ADAM)-10 and -17 bind to phosphatidylserine," *Biochimica et Biophysica Acta—Molecular Cell Research*, vol. 1843, no. 2, pp. 275–287, 2014.

[31] S. E. Umetsu, W.-L. Lee, J. J. McIntire et al., "TIM-1 induces T cell activation and inhibits the development of peripheral tolerance," *Nature Immunology*, vol. 6, no. 5, pp. 447–454, 2005.

[32] I. D. Sizing, V. Bailly, P. McCoon et al., "Epitope-dependent effect of anti-murine TIM-1 monoclonal antibodies on T cell activity and lung immune responses," *Journal of Immunology*, vol. 178, no. 4, pp. 2249–2261, 2007.

[33] X. Liu, X. Cui, D. Yuan et al., "Altered expression of T cell Immunoglobulin-Mucin (Tim) molecules in peripheral blood mononuclear cells in aplastic anemia," *Cancer Cell International*, vol. 14, article 144, 2014.

[34] J. Lin, L. Chen, and L. P. Kane, "Murine Tim-1 is excluded from the immunological synapse," *F1000Research*, vol. 1, article 10, 2012.

[35] M. L. Curtiss, J. V. Gorman, T. R. Businga et al., "Tim-1 regulates Th2 responses in an airway hypersensitivity model," *European Journal of Immunology*, vol. 42, no. 3, pp. 651–661, 2012.

[36] C. Santiago, A. Ballesteros, L. Martínez-Muñoz et al., "Structures of T cell immunoglobulin mucin protein 4 show a metal-ion-dependent ligand binding site where phosphatidylserine binds," *Immunity*, vol. 27, no. 6, pp. 941–951, 2007.

[37] L. L. Binné, M. L. Scott, and P. D. Rennert, "Human TIM-1 associates with the TCR complex and up-regulates T cell activation signals," *The Journal of Immunology*, vol. 178, no. 7, pp. 4342–4350, 2007.

[38] S. Angiari, T. Donnarumma, B. Rossi et al., "TIM-1 glycoprotein binds the adhesion receptor P-selectin and mediates T cell trafficking during inflammation and autoimmunity," *Immunity*, vol. 40, no. 4, pp. 542–553, 2014.

[39] S. Xiao, N. Najafian, J. Reddy et al., "Differential engagement of Tim-1 during activation can positively or negatively costimulate T cell expansion and effector function," *The Journal of Experimental Medicine*, vol. 204, no. 7, pp. 1691–1702, 2007.

[40] J. H. Meyers, S. Chakravarti, D. Schlesinger et al., "TIM-4 is the ligand for TIM-1, and the TIM-1-TIM-4 interaction regulates T cell proliferation," *Nature Immunology*, vol. 6, no. 5, pp. 455–464, 2005.

[41] N. Kobayashi, P. Karisola, V. Peña-Cruz et al., "TIM-1 and TIM-4 glycoproteins bind phosphatidylserine and mediate uptake of apoptotic cells," *Immunity*, vol. 27, no. 6, pp. 927–940, 2007.

[42] M. Miyanishi, K. Tada, M. Koike, Y. Uchiyama, T. Kitamura, and S. Nagata, "Identification of Tim4 as a phosphatidylserine receptor," *Nature*, vol. 450, no. 7168, pp. 435–439, 2007.

[43] N. Nurtanio and P.-C. Yang, "Role of TIM-4 in innate or adaptive immune response," *North American Journal of Medical Sciences*, vol. 3, no. 5, pp. 217–221, 2011.

[44] S. Moller-Tank, A. S. Kondratowicz, R. A. Davey et al., "Role of the phosphatidylserine receptor TIM-1 in enveloped-virus entry," *Journal of Virology*, vol. 87, no. 15, pp. 8327–8341, 2013.

[45] H.-H. Lee, E. H. Meyer, S. Goya et al., "Apoptotic cells activate NKT cells through T cell Ig-like mucin-like-1 resulting in airway hyperreactivity," *Journal of Immunology*, vol. 185, no. 9, pp. 5225–5235, 2010.

[46] S. Angiari and G. Constantin, "Regulation of T cell trafficking by the T cell immunoglobulin and mucin domain 1 glycoprotein," *Trends in Molecular Medicine*, vol. 20, no. 12, pp. 675–684, 2014.

[47] A. J. de Souza, T. B. Oriss, K. J. O'Malley, A. Ray, and L. P. Kane, "T cell Ig and mucin 1 (TIM-1) is expressed on *in vivo*-activated T cells and provides a costimulatory signal for T cell activation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 47, pp. 17113–17118, 2005.

[48] Q. Ding, M. Yeung, G. Camirand et al., "Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice," *Journal of Clinical Investigation*, vol. 121, no. 9, pp. 3645–3656, 2011.

[49] N. Degauque, C. Mariat, J. Kenny et al., "Immunostimulatory Tim-1-specific antibody deprograms Tregs and prevents transplant tolerance in mice," *Journal of Clinical Investigation*, vol. 118, no. 2, pp. 735–741, 2008.

[50] S. Xiao, C. R. Brooks, C. Zhu et al., "Defect in regulatory B-cell function and development of systemic autoimmunity in T-cell Ig mucin 1 (Tim-1) mucin domain-mutant mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 30, pp. 12105–12110, 2012.

[51] S. Sattler, G.-S. Ling, D. Xu et al., "IL-10-producing regulatory B cells induced by IL-33 (BregIL-33) effectively attenuate mucosal inflammatory responses in the gut," *Journal of Autoimmunity*, vol. 50, pp. 107–122, 2014.

[52] S. Rong, J.-K. Park, T. Kirsch et al., "The TIM-1:TIM-4 pathway enhances renal ischemia-reperfusion injury," *Journal of the American Society of Nephrology*, vol. 22, no. 3, pp. 484–495, 2011.

[53] S. Balasubramanian, S. K. Kota, V. K. Kuchroo, B. D. Humphreys, and T. B. Strom, "TIM family proteins promote the lysosomal degradation of the nuclear receptor NUR77," *Science Signaling*, vol. 5, no. 254, article ra90, 2012.

[54] K. M. Lee, J. I. Kim, R. Stott et al., "Anti-CD45RB/anti-TIM-1-induced tolerance requires regulatory B cells," *American Journal of Transplantation*, vol. 12, no. 8, pp. 2072–2078, 2012.

[55] X. Shi, M. Zhang, F. Liu et al., "Tim-1-Fc suppresses chronic cardiac allograft rejection and vasculopathy by reducing IL-17 production," *International Journal of Clinical and Experimental Pathology*, vol. 7, no. 2, pp. 509–520, 2014.

[56] Y. Zhang, H. Ji, X. Shen et al., "Targeting TIM-1 on CD4 T cells depresses macrophage activation and overcomes ischemia-reperfusion injury in mouse orthotopic liver transplantation," *American Journal of Transplantation*, vol. 13, no. 1, pp. 56–66, 2013.

[57] S. Nakae, M. Iikura, H. Suto et al., "TIM-1 and TIM-3 enhancement of Th2 cytokine production by mast cells," *Blood*, vol. 110, no. 7, pp. 2565–2568, 2007.

[58] H. Y. Kim, Y.-J. Chang, Y.-T. Chuang et al., "T-cell immunoglobulin and mucin domain 1 deficiency eliminates airway hyperreactivity triggered by the recognition of airway cell death," *Journal of Allergy and Clinical Immunology*, vol. 132, no. 2, pp. 414–425.e6, 2013.

[59] D. Coe, C. Addey, M. White, N. Harwood, J. Dyson, and J.-G. Chai, "Distinct in vivo CD8 and CD4 T cell responses against normal and malignant tissues," *Cancer Immunology, Immunotherapy*, vol. 62, no. 1, pp. 101–112, 2013.

[60] J. Jiang, C. Wu, and B. Lu, "Cytokine-induced killer cells promote antitumor immunity," *Journal of Translational Medicine*, vol. 11, no. 1, article 83, 2013.

[61] J. Galon, A. Costes, F. Sanchez-Cabo et al., "Type, density, and location of immune cells within human colorectal tumors predict clinical outcome," *Science*, vol. 313, no. 5795, pp. 1960–1964, 2006.

[62] W. Zou, "Immunosuppressive networks in the tumour environment and their therapeutic relevance," *Nature Reviews Cancer*, vol. 5, no. 4, pp. 263–274, 2005.

[63] W. Zou, "Regulatory T cells, tumour immunity and immunotherapy," *Nature Reviews Immunology*, vol. 6, no. 4, pp. 295–307, 2006.

[64] E. Bremer, "Targeting of the tumor necrosis factor receptor superfamily for cancer immunotherapy," *ISRN Oncology*, vol. 2013, Article ID 371854, 25 pages, 2013.

[65] X. Zang and J. P. Allison, "The B7 family and cancer therapy: costimulation and coinhibition," *Clinical Cancer Research*, vol. 13, no. 18, part 1, pp. 5271–5279, 2007.

[66] Y. Nozaki, D. J. Nikolic-Paterson, H. Yagita, H. Akiba, S. R. Holdsworth, and A. R. Kitching, "Tim-1 promotes cisplatin nephrotoxicity," *American Journal of Physiology—Renal Physiology*, vol. 301, no. 5, pp. F1098–F1104, 2011.

[67] Y. Cao, X. Zhou, X. Huang et al., "Correction: Tim-3 expression in cervical cancer promotes tumor metastasis," *PLoS ONE*, vol. 11, no. 3, Article ID e0152830, 2016.

[68] X. Gao, J. Yang, Y. He, and J. Zhang, "Quantitative assessment of TIM-3 polymorphisms and cancer risk in Chinese Han population," *Oncotarget*, vol. 7, no. 24, pp. 35768–35775, 2016.

[69] C. Cai, Y.-F. Xu, Z.-J. Wu et al., "Tim-3 expression represents dysfunctional tumor infiltrating T cells in renal cell carcinoma," *World Journal of Urology*, vol. 34, no. 4, pp. 561–567, 2016.

[70] J. Patel, E. N. Bozeman, and P. Selvaraj, "Taming dendritic cells with TIM-3: another immunosuppressive strategy used by tumors," *Immunotherapy*, vol. 4, no. 12, pp. 1795–1798, 2012.

[71] H. S. Kim, H. S. Kim, C. W. Lee, and D. H. Chung, "T cell Ig domain and mucin domain 1 engagement on invariant NKT cells in the presence of TCR stimulation enhances IL-4 production but inhibits IFN-γ production," *Journal of Immunology*, vol. 184, no. 8, pp. 4095–4106, 2010.

[72] K. N. Pollizzi and J. D. Powell, "Integrating canonical and metabolic signalling programmes in the regulation of T cell responses," *Nature Reviews Immunology*, vol. 14, no. 7, pp. 435–446, 2014.

[73] S. S. Chang, "Re: MPDL3280A (Anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer," *The Journal of Urology*, vol. 194, no. 4, p. 956, 2015.

[74] H. Park, Y. Kim, J.-W. Sul et al., "Synergistic anticancer efficacy of MEK inhibition and dual PI3K/mTOR inhibition in castration-resistant prostate cancer," *Prostate*, vol. 75, no. 15, pp. 1747–1759, 2015.

[75] F. Wang, Y. Mao, Q. You, D. Hua, and D. Cai, "Piperlongumine induces apoptosis and autophagy in human lung cancer cells through inhibition of PI3K/Akt/mTOR pathway," *International Journal of Immunopathology and Pharmacology*, vol. 28, no. 3, pp. 362–373, 2015.

[76] Q. Zhang, H. Zhu, X. Xu, L. Li, H. Tan, and X. Cai, "Inactivated Sendai virus induces apoptosis and autophagy via the PI3K/Akt/mTOR/p70S6K pathway in human non-small cell lung cancer cells," *Biochemical and Biophysical Research Communications*, vol. 465, no. 1, pp. 64–70, 2015.

[77] S. Raha, S. Yumnam, G. E. Hong et al., "Naringin induces autophagy-mediated growth inhibition by downregulating the PI3K/Akt/mTOR cascade via activation of MAPK pathways in AGS cancer cells," *International Journal of Oncology*, vol. 47, no. 3, pp. 1061–1069, 2015.

[78] G. Li, Q. Yang, Y. Zhu et al., "T-bet and eomes regulate the balance between the effector/central memory T cells versus memory stem like T cells," *PLoS ONE*, vol. 8, no. 6, Article ID e67401, 2013.

[79] J. R. Fergusson, M. H. Hühn, L. Swadling et al., "$CD161^{int}CD8+$ T cells: a novel population of highly functional, memory CD8+ T cells enriched within the gut," *Mucosal Immunology*, vol. 9, no. 2, pp. 401–413, 2015.

[80] G. Xu, L. Cheng, W. Wen et al., "Inverse association between T-cell immunoglobulin and mucin domain-1 and T-bet in a mouse model of allergic rhinitis," *Laryngoscope*, vol. 117, no. 6, pp. 960–964, 2007.

[81] L.-J. Chen, X. Zheng, Y.-P. Shen et al., "Higher numbers of T-bet+ intratumoral lymphoid cells correlate with better survival in gastric cancer," *Cancer Immunology, Immunotherapy*, vol. 62, no. 3, pp. 553–561, 2013.

[82] E. W. Su, J. Y. Lin, and L. P. Kane, "TIM-1 and TIM-3 proteins in immune regulation," *Cytokine*, vol. 44, no. 1, pp. 9–13, 2008.

[83] Z. Wang, J. Zhu, H. Gu et al., "The clinical significance of abnormal Tim-3 expression on NK cells from patients with gastric cancer," *Immunological Investigations*, vol. 44, no. 6, pp. 578–589, 2015.