Review Article **OPEN ACCESS**

Role of TIM-4 in innate or adaptive immune response

Natasha Nurtanio, Ping-Chang Yang

Department of Pathology & Molecular Medicine, McMaster University, Hamilton, ON, Canada.

Citation: Nurtanio N, Yang P-C. Role of TIM-4 in innate or adaptive immune response. **North Am J Med Sci** 2011; 3: 217-221.
Doi: 10.4297/najms.2011.3217
Availability: www.najms.org
ISSN: 1947 – 2714

Abstract

Human being living in constant contact with microbes and pathogen and in the process has developed a recognition pattern of pathogenic structure in the immune cells. The gut lumen has high density of microbes thus the immune response is slightly tolerable to certain microbes, known as commensal flora. These microbes along with other innocuous agents do not cause any inflammation response normally, and are considered as harmless by the immune cells. In immune hypersensitivity condition, such as colitis or food allergy, this mechanism is disturbed. T cell immunoglobulin and mucin domain (TIM)-4 is a phosphatidylserine receptor expressed in mature antigen presenting cells. It is shown that TIM-4 and its ligand TIM-1 are associated in intestinal immune response. However the characteristic of TIM-4 sometimes seems to be two-faced and there is a possibility that TIM-4 also bind to other ligands.

Keywords: TIM-4; Inflammation; Immunity.

Correspondence to: Dr. Ping-Chang Yang, Room T3303, 50 Charlton Ave East, Hamilton, ON, Canada. Tel: (905) 522-1155 ext. 32934. Fax: (905) 540-6593. Email: yangp@mcmaster.ca

Thriving in a sea of microbes

All along in millions of years, the interaction between immune cells and the micro environment intertwined each other in an inseparable relationship. Human immune cells build up their recognition database of microbe's antigens as well as how to cease pathogenic microorganism invasion then pass it on to the next generations. Similarly microbes at times changes their antigenic structure to evade recognition and destruction from immune cells, and those that survived the screening process also pass on their genomic structure as a new strain of species [1]. This relationship goes on and on for as long as the human history and, like a scale, it skewed each time changes happened in either side of the hand. However, not all microbes are harmful to the body; some microbes are classified as commensal or harmless residents, this population even offers protection from other pathogenic microbes[2,3].Interestingly, the commensal microorganism sometimes shares the same general antigenic features like any other pathogenic microbes but was not attacked by the immune cells [4]. The mechanism of how the immune cells differentiate between pathogen and harmless microbes need more in depth exploration, but the cause behind the phenomena is that the pathogenic microbes express a structure called pathogen-associated molecular patterns (PAMPs) which are easily recognized by the immune cells [5, 6].

The immune system is consists of innate and adaptive immune responses. Innate immune response works as a first liner in confronting pathogen invasion, these cells responds very fast and kill anything that is marked as threat to the body; adaptive immune response is more antigen-specific, however, works slower and takes time to be developed. Pattern recognition receptor (PRR), a compartment that binds to PAMPS, from the innate immune system responded to antigens then triggered adaptive immune response through multiple pathways [5, 7-9]. In general, adaptive immune response will be halted if innate pathway is sufficient to cover the damage caused by pathogens immediately and usually the response is not a systemic one. If the damage cannot be compensated by these cells, then these immune cells will eventually send signals and release cytokines to recruit more cells to the site; meanwhile antigen presenting cells (APCs) which also express PRR will be responsible to carry on the antigenic information to T lymphocytes and start the

adaptive immune response. Once those T cells receive the antigenic information it can be activated and proliferate with an antigenic-specific site expressed on their surface. Some of them will induce B lymphocytes activation to produce antigenic-specific antibodies, and some will migrate out to the infected sites for pathogen eradication[10, 11]. Mostly activated cells will become apoptotic soon after they finish their task, only a small amount of these cells will become memory cells and keep all the antigenic information for later use. So when there is a second exposure with the same antigen in the future, rapid response will follow and more cells will be released to the site [12, 13].

In the gut: more tolerable

Immune protection in the gut is considered to be more tolerable compared to other places [3, 8]. There are billions of microbes ingested into the intestinal lumen daily. To protect the intestinal mucosa from harmful pathogen, a tight junction is built in the surface of the lumen by the intestinal epithelial cells (IECs). These cells also produce mucus to lubricate and trap the pathogen on the surface preventing it to cross the barrier. Apart from physical barrier, an ample amount of soluble Immunoglobulin A (IgA) is secreted to the lumen daily to keep control of the microorganism population. IECs also express PRR and have the ability to recruit immune cells when bind to PAMPs from the pathogen inside the lumen [7, 14, 15]. However the professional APCs in the gut, dendritic cells (DCs) and macrophage, seemingly more tolerant to luminal microbes in sending alert and phagocyting them compared to APCs from other sites. It is even thought that when the immune cells are no longer tolerant to commensal microbes then unwanted inflammation occurs, such as that in colitis [3, 16]. Immune over-reactivity is a condition where immune cells over-react toward innocuous agents, whether self cells or harmless microbes [1]. Food allergy is another type of intestinal immune over-reactivity. It happens when an incompletely digested protein breaks through a leak in the intestinal barrier, captured by an APC and flagged as an antigen then presented to the T cells, henceforth that certain proteins will be classified as pathogens and thus at the second exposure antigen-specific antibodies flood the intestinal lumen to cause unwanted protection and inflammation [17, 18].

In 2001, McIntire et al found a gene family related to a Mendelian trait known as T cell and Airway phenotype regulator (Tapr) which has a restricted immunoglobulin variable domain and mucin domain. The gene family is found expressed on T cells so hence called T cell immunoglobulin and mucin domain (TIM) [19]. Up until now there are 3 TIM subtype discovered in human (TIM-1, TIM-3, and TIM-4), and 8 in mice (TIM1 to TIM8) [20]. In this review, we will discuss mainly about TIM-4 and another member related to it. In the association with natural selection over thousands of years, TIM-4 molecule has been through positive natural selection pressure along with other immunoglobulin superfamily gene like CD3, CD4, CD48 and several others [21], indicating that TIM-4 plays a role in either innate or adaptive immune response.

Role of TIM-4 in immunity

TIM-4, previously known as SMUCKLER, gene is conserved in human and mouse APCs unlike other TIM gene family which is expressed mainly in T cells. TIM-4 expression in APCs is restricted only to certain subtypes that express CD11c+ and CD11b+ [22, 23]. TIM-4 has the ability to engage TIM-1 and co-stimulate T cell proliferation in activated T cells[24-26]. TIM-1 expression is present in any activated T cells, especially TH2[24, 27]. Feng *et al*. found that disruption of TIM-1 and TIM-4 binding with anti-TIM-1 antibody and with TIM-4 interfered gene expression can deplete TH2 and allergic response in peanut allergy mice model [28]. However in another study, Meyer at al discovered that TIM-4 fusion protein induce an increase of T cells proliferation but in lower concentration it inhibited T cells response [24]. Other findings show that in vivo administration of TIM-4 antibody apparently induced TH1 cells proliferation and that TIM-4 fusion protein is able to induce an increase of interferon gamma (IFN-g) and tumor necrosis factor-alpha (TNF-a) rate in vitro [22, 29, 30]. Albacker et al found that over-expressed TIM-4 in APCs decreased antigenic specific T cell activity [29], while Mizui et al found that blocking TIM-4 will increase antigenic specific T cell activity but decrease inflammation and T cell proliferation rate [30].

Apart from that, like other members of the TIM gene, TIM-4 is also a phosphatidylserine (PS) receptor that enhances phagocytosing activity of apoptotic cells by macrophages to maintain the homeostasis [12, 29, 31]. For instance, blocking of the PS receptor in APCs will consequently produce negative effect in peritoneal macrophage phagocytosing activity. PS expressed on the surface of an apoptotic cell is a signal that attracts APCs for immediate clearance or else too much linger will eventually cause auto-immunity reaction and chronic inflammation[13]. After phagocytosing, APCs will release transforming growth factor beta (TGF-b) that plays a part in inducing regulatory T (Treg) cells proliferation. In the gut, Treg cells are responsible to maintain immune tolerance to commensal flora and acts as a negative feedback for hyperactive pro-inflammatory response hence keeping the immune response in balance[32-34].

Xiao et al discovered that a fusion protein using TIM-4 monoclonal antibody with the immunoglobulin region only could increase T cell proliferation but another fusion protein which has both the immunoglobulin and mucin domain in contrast inhibit T cell proliferation [35]. Whereas Park *et al*. discovered that without its cytoplasmic tail and the transmembrane region, TIM-4 is still capable of enhancing phagocyting activity in the APCs [36]. The immunoglobulin region of TIM-4 is responsible in recognizing apoptotic cells through PS receptor binding and this binding site is also the same site for anti-TIM-4 monoclonal antibodies binding [31].

Yamanishi *et al*. has discovered that the leucocyte mono-immunoglobulin-like receptor 5 (LMIR5) can bind to TIM-1 at the PS binding site and the binding does not interfere with the phagocyting ability of TIM-4 [37]. Interestingly, Wong *et al*. found that TIM-4 knock-out resident peritoneal macrophages are able to phagocytose necrotic and other opsonised targets but incompetent in phagocytosing apoptotic cells either in vitro or in vivo [38]. Regarding TIM-1 - TIM-4 binding site, it requires both TIMs intact glycosylated mucin stalk but mucin stalk alone is not yet sufficient for binding [39]. Miyanishi *et al*. found that TIM-1 - TIM-4 binding may be a kind of intercellular signalling via exosome that exposed PS [40]. However, TIM-4 may also bind with ligand other than TIM-1 and causing inhibition of naive T cells activation [30, 36, 38]. Several findings indicated that TIM-4 plays a significant role in intestinal allergic response and interaction with TIM-1 is related to T cell antigen-specific proliferation not only in the gut but also elsewhere, like the liver and kidney [29, 31, 41-43].

When an IEC encounters a commensal flora, it will release cytokines such as IL-10 and TGF-b to induce tolerance [44]. However in the case of inflammation, IECs in the mucosa layer are damaged and the continuity of the structure is broken hence giving pathogens more chances to break into the lamina propria [3, 8, 45]. In colitis, apoptotic IECs may probably relate to the pathogenesis of the disease leading to a TH1 immune response [46]. From our own unpublished data, we found that TIM-4 expression is significantly higher in colitis patients compared to healthy adults imposing that through PS receptor signalling pathway TIM-4 expressing APCs will direct proliferation toward TH1 response.

It is known that T helper type 2 (TH2) cells are responsible in the development of allergic response. In several in vivo and in vitro experiments, exposure to resident flora toxin markedly increases antigenic-specific response to allergen through increase of TH2 polarization and mast cells degranulation [28, 47, 48]. After administration of anti-TIM-4 and/or anti-TIM-1 antibodies, the allergic response decreases with a lesser level of TH2 polarization [49]. The antibody blocking works at the PS binding site at the immunoglobulin region, then apoptotic cells phagocytosing activity of TIM-4 expressing APCs should have been diminished [26]. If TIM-4 expressing APCs are still able to phagocytose necrotic cells and pathogens without PS signalling through other glycosylated ligands, then the inhibition of naive T cells proliferation seen by Mizui et al probably caused by a pathway other than TIM-1 binding [30, 36, 38]. Albacker *et al*. found that TIM-4 phagocyting activity of apoptotic cells markedly increase in the antigen-specific T cell population in inflammation but then help control the number of the remain antigen-specific T cells after the clearance [29]. Interestingly, a group of apoptosis resistant DCs have the ability to skew the immune response to TH2 polarization. This population can be isolated from antigen-primed mice then cultured with antigen-specific T cells; those that survived are able to induce TH2 differentiation from naive T cells either in vivo or in vitro[50].

Conclusion

TIM-4 ability to recognize apoptotic cells is dependent to the PS receptor on its immunoglobulin region and possibly with the help of TIM-1 that also has the same receptor. However without TIM-1 interaction, TIM-4 is able to bind with other glycosylated ligands. This versatile feature may be responsible for the bimodal character that somewhat contradicting each other. A future study is needed to see whether TIM-4 is present in mature APCs that are apoptotic resistant population and the phagocytosing activity in apoptotic T cell antigen-specific cells are aided by TIM-1 through PS receptor which favours the TH2 response. Regarding the induction of TH1 response such as that in colitis, TIM-4 may also play a role in the process either through other ligands or signalling pathways.

References

1. Rosenstiel P, Philipp EE, Schreiber S, Bosch TC. Evolution and function of innate immune receptors –insights from marine invertebrates. J Innate Immun 2009; 1:291-300.
2. Shanahan F, Bernstein CN. The evolving epidemiology of Inflammatory Bowel Disease. Current Opinion in Gastroenterology 2009; 25: 301–305.
3. Platt AM, Mowat AM. Mucosal macrophages and the regulation of immune response in the intestine. Immunol Lett 2008; 119:22-31.
4. Beutler BA. TLRs and innate immunity. Blood 2009; 113: 1399-1407.
5. Uematsu S, Fujimoto K. The innate immune system in the intestine. Microbiol Immunol 2010; 54: 645-657.
6. Cashman SB, Morgan JG. Transcriptional analysis of Toll-like receptors expression in M cells. Mol Immunol 2009; 47:365-372.
7. Wells JM, Loonen LM, Karczewski JM. The role of innate signalling in the homeostasis of tolerance and immunity in the intestine. Int J Med Microbiol 2010; 300: 41-48.
8. Gómez-Llorente C, Muñoz S, Gil A. Role of Toll-like receptors in the development of immunotolerance mediated by probiotics. Proc Nutr Soc 2010; 69: 381-389.
9. Bauernfiend F, Ablasser A, Kim S, Bartok E, Hornung V. An unexpected role for RNA in the recognition of DNA by the innate immune system. RNA Biol 2010; 7: 151-157.
10. Garside P, Millington O, Smith KM. The anatomy of mucosal immune response. Ann N Y Acad Sci 2004; 1029: 9-15.
11. Turley SJ, Fletcher AL, Elpek KG. The stromal and haematopoietic antigen-presenting cells that reside in secondary lymphoid organs. Nat Rev Immunol 2010; 10: 813-825.

12. Jeannin P, Jaillon S, Delneste Y. Pattern recognition receptors in the immune response against dying cells. Curr Opin Immunol 2008; 20:530-537.
13. Litvak ML, Palaniyar N. Review: Soluble innate immune pattern-recognition proteins for clearing dying cells and cellular components: implications on exacerbating or resolving inflammation. Innate Immun 2010; 16:191-200.
14. Barbosa T, Rescigno M. Host-bacteria interaction in the intestine: homeostasis to chronic inflammation. Wiley Interdiscip Rev Syst Biol Med 2010; 2:80-97.
15. Maldonado-Contreras AL, McCormick BA. Intestinal epithelial cells and their role in innate mucosal immunity. Cell Tissue Res 2011; 343:5-12.
16. Rakoff-Nahoum S, Bousvaros A. Innate and adaptive immune connections in inflammatory bowel disease. Curr Opin Gastroenterol 2010; 26:572-577.
17. Rescigno M. Intestinal dendritic cells. Adv Immunol 2010; 107:109-138.
18. Sicherer SH, Sampson HA. Food Allergy. J Allergy Clin Immunol 2010; 125:S116-125.
19. McIntire JJ, Umetsu SE, Akbari O, et al. Identification of Tapr (an airway hyperreactivity regulator locus) and the linked Tim gene family. Nat Immunol 2001; 2:1109-1116.
20. McIntire JJ, Umetsu DT, DeKruyff RH. TIM-1, a novel allergy and asthma susceptibility gene. Springer Semin Immunopathol 2004; 25:335-348.
21. Ohtani H, Nakajima T, Akari H, Ishida T, Kimura A. Molecular evolution in immunoglobulin superfamily genes in primates. Immunogenetics 2011; DOI 10.1007/s00251-011-0519-7
22. Rodriguez-Manzanet R, Meyers JH, Balasubramanian S, et al. TIM-4 expressed on APCs induces T cell expansion and survival. J Immunol 2008; 180:4706-4713.
23. Shakhov AN, Rybtsov S, Tumanov AV, et al. SMUCKLER/TIM4 is a distinct member of TIM family expressed by stromal cells of secondary lymphoid tissues and associated with lymphotoxin signalling. Eur J Immunol 2004; 34:494-503.
24. Meyers JH, Chakravarti S, Schlesinger D, et al. TIM-4 is the ligand for TIM-1, and the TIM-1-TIM-4 interaction regulates cell proliferation. Nat Immunol 2005; 6:455-464.
25. Nakae S, Iikura M, Suto H, et al. TIM-1 and TIM-3 enhancement of Th2 cytokine production by mast cells. Blood 2007; 110:2565-2568.
26. Rodriguez-Manzanet R, DeKruyff R, Kuchroo VK, Umetsu DT. The costimulatory role of TIM molecules. Immunol Rev 2009; 229:259-270.
27. Kuchroo VK, Umetsu DT, DeKruyff RH, Freeman GJ. The TIM gene family: emerging roles in immunity and disease. Nat Rev Immunol 2003; 3: 454-462.
28. Feng BS, Chen X, He SH, et al. Disruption of T-cell immunoglobulin and mucin domain molecule (TIM)-1/TIM4 interaction as a therapeutic strategy in a dendritic cell-induced peanut allergy model. J Allergy Clin Immunol 2008; 122:55-61.
29. Albacker LA, Karisola P, Chang YJ, et al. TIM-4, a receptor for phosphatidylserine, controls adaptive immunity by regulating the removal of antigen-specific T cells. J Immunolo 2010; 185: 6839-6849.
30. Mizui M, Shikina T, Arase H, et al. Bimodal regulation of T cell-mediated immune response by TIM-4. Int Immunol 2008; 20:695-708.
31. Kobayashi N, Karisola P, Peña-Cruz V, et al. TIM-1 and TIM-4 glycoprotein bind phosphatidylserine and mediate uptake of apoptotic cells. Immunity 2007; 27: 927-940.
32. Perruche S, Zhang P, Liu Y, Saas P, Bluestone JA, Chen W. CD3-specific antibody-induced immune tolerance involves transforming growth factor-beta from phagocytes digesting apoptotic T cells. Nat Med 2008; 14:528-535.
33. Proietto AI, van Dommelen S, Zhou P, et al. Dendritic cells in the thymus contribut to T-regulatory cell induction. Proc Natl Acad Sci USA 2008; 105:19869-19874.
34. Eastaff-Leung N, Mabarrack N, Barbour A, Cummins A, Barry S. Foxp3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. J Clin Immunol 2010; 30: 80-89.
35. Xiao S, Najafian N, Reddy J, et al. Differential engagement of Tim-1 during activation can positively or negatively costimulate T cell expansion and effector function. J Exp Med 2007; 204: 1691-1702.
36. Park D, Hochreiter-Hufford A, Ravichandran KS. The phosphatidylserine receptor TIM-4 does not mediate direct signalling. Curr Biol 2009; 19: 346-351.
37. Yamanishi Y, Kitaura J, Izawa K, et al. TIM1 is an endogenous ligand for LMIR5/CD300b: LMIR5 deficiency ameliorates mouse kidney ischemia/reperfusion injury. J Exp Med 2010; 207: 1501-1511.
38. Wong K, Valdez PA, Tan C, Yeh S, Hongo JA, Ouyang W. Phosphatidylserine receptor Tim-4 is essensial for the maintenance of the homeostatic state of resident peritoneal macrophages. Proc Natl Acad Sci USA 2010; 107:8712-8717.
39. Wilker PR, Sedy JR, Grigura V, Murphy TL, Murphy KM. Evidence for carbohydrate recognition and homotypic and heterotypic binding by the TIM family. Int Immunol 2007; 19:763-773.
40. Miyanishi M, Tada K, Koike M, Uchiyama Y, Kitamura T, Nagata S. Identification of TIM4 as a phosphatidylserine receptor. Nature 2007; 450: 435-439.
41. Rong S, Park JK, Kirsch T, et al. The TIM-1:TIM-4 pathway enhances renal ischemia-reperfusion injury. J Am Soc Nephrol 2011; 22:484-495.
42. Mariat C, Degauque N, Balasubramanian S, et al. Tim-1 signalling substitutes for conventional signal 1 and requires costimulation to induce T cell proliferation. J Immunol 2009; 182:1379-1385.

43. Uchida Y, Ke B, Freitas MC, et al. The emerging role of T cell immunoglobulin mucin-1 in the mechanism of liver ischemia and reperfusion injury in the mouse. Hepatology 2010; 51:1363-1372.
44. Frossard CP, Eigenmann PA. The role of IL-10 in preventing food-induced anaphylaxis. Expert Opin Biol Ther 2008; 8:1309-1317.
45. Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens. Nat Rev Immunol 2003; 3:331-341.
46. Qiu W, Wu B, Wang X, et al. PUMA-mediated intestinal epithelial apoptosis contributes to ulcerative colitis in humans and mice. J Clin Invest 2011; doi: 10.1172/JCI42917
47. Liu T, He SH, Zheng PY, Zhang TY, Wang BQ, Yang PC. Staphylococcal enterotoxin B increases TIM-4 expression in human dendric cells that drives naive CD4 T cells to differentiate into Th2 cells. Mol Immunol 2007; 44:3580-3587.
48. Yang PC, Xing Z, Berin CM, et al. TIM-4 expressed by mucosal dendritic cells plays a role in food antigen-specific Th2 differentiation and intestinal allergy. Gastroenterology 2007; 133: 1522-1533.
49. Zhao CQ, Li TL, He SH, et al. Specific immunotherapy suppresses Th2 responses via modulating TIM1/TIM4 interaction on dendritic cells. Allergy 2010; 65:986-995.
50. Arques JL, Regoli M, Bertelli E, Nicoletti C. Persistence of apoptosis-resistant T cell-activating dendritic cells promotes T helper type-2 response and IgE antibody production. Mol Immunol 2008; 45: 2177-2186.