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T Cell Ig and Mucin Domain Proteins and Immunity

Lawrence P. Kane

Proteins of the transmembrane (or T cell) Ig and mucin domain (TIM) family are expressed by multiple cell types within the immune systems of rodents and humans. Studies over the last several years have suggested that these proteins may be promising targets for therapeutic manipulation of immune responses. This review discusses the progress that has been made in understanding TIM protein function in the immune system, as well as some of the unresolved issues that remain on the road to eventually targeting TIM proteins for enhancing or inhibiting immunity. The Journal of Immunology, 2010, 184: 2743–2749.

The recent appreciation of the functions carried out by transmembrane (or T cell) Ig and mucin domain (TIM) family proteins in immunity has opened up the possibility of a new area for immune modulation. This review covers the most promising members of the TIM family in this regard: TIM-1 and -3. It also touches on the function of TIM-4, mainly in its context as a ligand for TIM-1. There have been a number of studies of the other Tim protein present in mouse: Tim-2. However, it seems that this member of the family is not present in the human genome, which has decreased overall interest in this protein. It remains to be seen whether the negative regulatory function ascribed to Tim-2 (1–3) has been assumed by another member of the human TIM family or even by an entirely different protein.

Domain structure and classification of TIM family proteins

The members of the TIM family are type I transmembrane proteins that possess an N-terminal Ig domain of the V type, followed by a mucin domain of variable length and containing from a few to dozens of potential sites of O-linked glycosylation (Fig. 1). There are also predicted sites of N-linked glycosylation in the Ig domain and the stalk domain that lies between the mucin and transmembrane domains (Fig. 1). Following the transmembrane domain is a cytoplasmic tail that ranges in length from ~38–65 residues. There are eight predicted im genes in the murine genome, four of which (tim1–tim4) encode functional proteins, whereas the human genome only contains three Tim genes (Tim1, Tim3, and Tim4). Based on their domain structure, TIM family proteins seem to be most closely related to mucosal addressin cellular adhesion molecule (7), which can bind to distinct ligands through its Ig domain (α4β7 integrin) and carbohydrate side chains (selectin). As discussed below, specific ligands have been described for the IgV domains of Tim-1 and Tim-3, although no ligands have been described for the respective mucin-like domains.

Discovery of the TIM family

The founding member of the TIM family was initially described as kidney injury molecule (Kim)-1, a putative adhesion molecule upregulated in a rat model of kidney ischemia (7). Production of a soluble form of Kim-1, generated by proteolytic cleavage, is now used clinically as a diagnostic marker for acute kidney injury (8). This protein is equivalent to Tim-1, as cloned in the mouse (see later discussion). Later, it was also shown in primates that Kim1/TIM1 is a receptor for hepatitis A virus (HAV) (9, 10); thus, the human and monkey forms are sometimes referred to as HAV cellular receptor 1.

The TIM family was largely ignored by immunologists until a landmark paper by DeKruyff and colleagues (11), who were studying the development of allergic asthma in a commonly used murine model. It is well known that BALB/c mice are much more susceptible to the development of type II immune responses compared with other strains, such as C57BL/6 and DBA/2 (12), and this includes the OVA-induced asthma model (13). This difference is thought to be due, at least in part, to polymorphisms in one or more genes contained in the so-called Th2 cytokine locus, which includes the genes for IL-4, -5, and -13 (14). DeKruyff and colleagues generated a series of congenic mouse strains to map loci responsible for the differential atopic sensitivity of BALB/c and DBA/2. One congenic strain (HBA) contained a segment of mouse chromosome 11 on an otherwise BALB/c background (11). In this strain, the Th2-prone phenotype was suppressed, such that production of Th2 cytokines and airway hyperresponsiveness were virtually identical to those seen with a pure DBA/2 mouse. When the locus in question was narrowed further, it was found to segregate independently of the Th2 cytokine locus, but it included the tim family genes, among others, and was also largely syntenic with human chromosome 5q33, which lies within a region previously linked to human atopic disease (11). Sequence analysis revealed the existence of
multiple polymorphisms in the genes encoding Tim-1 and -3 [known polymorphisms in human and mouse Tim-1 and -3 are discussed in more detail elsewhere (6)]. Although the investigators provided evidence to link T cells to the phenotypic differences between the mouse strains, they did not definitively prove that polymorphisms in Tim-1 or -3 (or both) were responsible. However, the case for Tim-1 seems to be stronger at this point, because a polymorphism in human Tim-1 (Fig. 1) is also associated with differential asthma risk (15). Intriguingly, this polymorphism is similar to one of the differences between Tim-1 from different mouse strains (i.e., an insertion/deletion in the mucin-like domain). Indeed, the presence of the insertion seems to confer a decreased risk for developing asthma but only in individuals who are seropositive for exposure to HAV (15). This finding suggests that polymorphisms in Tim-1 may contribute to asthma susceptibility because of direct or indirect effects on cellular interactions with HAV. Obviously, the connection to HAV cannot explain the results obtained with the congenic mouse strains that possess differential susceptibility to the OVA model of allergic asthma. Also, in mice, the longer mucin domain is found in the more atopic BALB/c strain, which is the opposite of the finding with human TIM-1. There is still a need for these issues to be addressed experimentally.

Around the same time that the DeKruyff group came upon the tim locus via a genetic approach, Kuchroo and colleagues (16) were on the hunt for more specific markers of Th1 T cells, using an Ab-generation approach. In 2002, they reported the generation of a mAb that could recognize all Th1 T cell clones and de novo-generated Th1 T cells but not naive T cells or Th2 T cell clones. When the Ag recognized by this Ab was identified, it was revealed to be murine Tim-3. Administration of Tim-3 Ab to mice exacerbated disease in the experimental autoimmune encephalomyelitis (EAE) model (16), the first indication that Tim-3 might negatively regulate Th1-dependent immune responses.

**Stimulatory and costimulatory functions of Tim-1 on T cells**

In 2005, several studies demonstrated that Tim-1 ligation can costimulate T cell proliferation and cytokine production (17–19). This was shown through the use of an agonistic Ab (19) and through transient overexpression (17). In addition, similar costimulatory function could be provided to T cells by interaction of Tim-1 with Tim-4, which is preferentially expressed by APCs (18, 20). The Tim-1–Tim-4 interaction seems to occur mainly through the Ig domains of the two proteins (Fig. 2), although it may be further regulated by the mucin domains (21). Recent studies suggested the existence of additional ligands for Tim-1, including the possibility that Tim-1 can homodimerize through a noncovalent interaction mediated by the Ig domain (discussed further below). The putative costimulatory function of Tim-1 seems to be more analogous to late-acting costimulatory molecules, such as OX-40, because Tim-1 is present at very low levels on naive T cells but is upregulated after activation (17–19). Also, Tim-4 itself may have one or more additional protein ligands. Thus, treatment of naive T cells (which do not express detectable Tim-1) with a soluble Tim-4 fusion protein inhibited T cell activation, whereas the same treatment of preactivated T cells enhanced activation (22). Although most studies have focused on the direct effects of TIM-1 ligation on effector T cells, agonistic TIM-1 Abs may also enhance immune responses through inhibition of regulatory T cell function or generation (23).

There has been some progress made in understanding the biochemical pathways downstream of Tim-1. The cytoplasmic tail of Tim-1 contains two tyrosines, one of which is contained within a sequence that makes it a likely site for phosphorylation. Thus, mutating tyrosine 276 within the cytoplasmic tail of murine Tim-1 impairs its ability to costimulate T cell activation in conjunction with TCR/CD28 ligation (17).
Phosphorylation of Y276 functions in part by recruiting the p85 adaptor protein through one or more of its SH2 domains (24). This leads to downstream activation of the serine/threonine kinase Akt (20, 24), which likely augments NFAT activity through inhibition of the NFAT inhibitory kinase glycogen synthase kinase 3. Another downstream target for Tim-1 is ERK MAPK, the phosphorylation of which is augmented by Tim-1 ligation (20). In addition, Tim-1 signaling may intersect at a more proximal point with TCR signaling pathways. Thus, Tim-1 costimulation can increase tyrosine phosphorylation of the transmembrane adaptor protein linker for activation of T cells (20) and the TCR-proximal tyrosine kinases ZAP70 and Itk (25). At least in the case of human T cells, these observations are consistent with a report that Tim-1 may be in close association with the TCR/CD3 complex (25).

The ability of Tim-1 ligation by itself to initiate T cell activation has been observed with a single Tim-1 Ab (the mAb 3B3; Table I) (28, 30), whereas other Tim-1 Abs and the ligand Tim-4 seem to only act as costimulatory agents (18–20). Intriguingly, at least two studies have demonstrated differential effects of Tim-1 ligation, depending upon the Ab used. First, in a work by Rennert and colleagues (26), two Tim-1 Abs (1H8.2 and 5D1.1; Table I) were shown to significantly enhance responses to model Ags, as determined by ex vivo restimulation or in vivo inflammation, whereas two other Abs (3A2.5 and 4A2.2) attenuated inflammation. The mechanistic basis for the different effects seen with the activating versus inhibitory Tim-1 Abs is unclear, although it is intriguing that the activating Abs in this case recognized parts of the mucin domain, whereas the inhibitory Abs recognized the stalk or IgV domain (Table I). However, a different Ab to the Tim-1 IgV domain (1H9.9) had no obvious effects on inflammation (26). Similar observations were reported by Kuchroo and colleagues (19), who compared the 3B3 Ab with another mAb (RMT1-10). These two Abs recognize the IgV domain and may compete with each other. However, although 3B3 enhanced proliferation and Th1 cytokine production of Ag-primed T cells, RMT1-10 suppressed proliferation and Th1 cytokine production (27). In this same study, 3B3 exacerbated, whereas RMT1-10 ameliorated, proteolipid protein-induced EAE. Although both Abs were found to bind to the IgV domain, the 3B3 Ab had a significantly higher affinity for Tim-1 (27). It is not known how possible differences in signaling by these Abs might translate into the different responses to them in vivo or in vitro.

Thus, although a substantial amount of data are consistent with a costimulatory function for Tim-1, the findings with different Tim-1 Abs discussed above suggest that, under some circumstances, Tim-1 may also be capable of inhibiting T cell activation. Such activity could be mediated by Tim-1 binding to a distinct (non–Tim-4) ligand or possibly by binding to the known ligand Tim-4, under different conditions of cellular activation or differentiation.

Table I. Selected Abs to mouse and human TIM-1 that have been functionally characterized in the literature

<table>
<thead>
<tr>
<th>Tim-1 Abs</th>
<th>Epitope</th>
<th>Functional Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3B3</td>
<td>IgV</td>
<td>Activation; costimulation</td>
<td>19</td>
</tr>
<tr>
<td>1H8.2</td>
<td>Mucin/stalk (BALB/c only)</td>
<td>Increased Th2</td>
<td>26</td>
</tr>
<tr>
<td>5D1.1</td>
<td>Mucin/stalk (BALB/c only)</td>
<td>Increased Th2</td>
<td>26</td>
</tr>
<tr>
<td>3A2.5</td>
<td>Stalk</td>
<td>Decreased Th2</td>
<td>26</td>
</tr>
<tr>
<td>4A2.2</td>
<td>IgV</td>
<td>Decreased Th2</td>
<td>26</td>
</tr>
<tr>
<td>1H9.9</td>
<td>IgV</td>
<td>No apparent effects</td>
<td>26</td>
</tr>
<tr>
<td>RMT1-10*</td>
<td>IgV</td>
<td>Inhibition of T cell responses</td>
<td>27–29</td>
</tr>
<tr>
<td>3D1 (human)</td>
<td>IgV</td>
<td>Blocks HAV and PS binding</td>
<td>30</td>
</tr>
</tbody>
</table>

*This Tim-1 Ab should not be confused with a commercially available Ab with the same name.

Inhibition of T cell responses by Tim-3

As stated above, initial studies of Tim-3 in murine EAE suggested that it is a negative regulator of Th1 immune responses (16). This interpretation was consistent with subsequent studies in which a soluble Tim-3–Ig fusion protein enhanced proliferation and cytokine production by primed T cells and prevented the induction of tolerance by soluble Ags (31). A genetic deficiency for Tim-3 expression also impaired the induction of tolerance (31). Similar conclusions were reached with a transfer model of autoimmune diabetes; treatment with an Ab to Tim-3 (Table II) or a Tim-3–Ig fusion protein could exacerbate disease (32).
In this same study, it was also shown that blocking Tim-3 interaction with its putative ligands could prevent the induction of tolerance by the combined treatment of donor-specific transfusion and anti-CD40L Ab. Thus, putative blocking of Tim-3–Tim-3 ligand interactions enhanced the development of autoimmune disease and inhibited the induction of tolerance. Consistent with this model, the upregulation of Th1 immune responses by blocking Tim-3 may result in an accompanying decrease in Th2 responses (33).

The findings of the above blocking studies are consistent with the discovery by Kuchroo and colleagues (39) of the first ligand for Tim-3: β-galactoside binding protein galectin-9 (Fig. 2). Thus, the addition of galectin-9 to Th1 T cells caused a rapid and atypical cell death. Similarly, in vivo administration of galectin-9 caused downregulation of Th1-dependent immune responses. In addition to causing effector T cell death, galectin-9 treatment may also lead to an increase in regulatory T cells, as recently demonstrated in a model of viral immunopathology (34). One challenge to interpreting these experiments is the fact that galectin-9 (and indeed all galectins) can have pleiotropic effects, through binding to multiple proteins with β-galactoside modifications (40). In the case of galectin-9, this includes known binding to CD44 (40).

As with TIM-1, the in vivo function of TIM-3 seems to be more complex than initial reports suggested. Thus, two studies have now demonstrated that treatment of mice with galectin-9 also promotes the generation and/or survival of regulatory T cells, at the expense of proinflammatory Th17 T cells (34, 41). In addition, both of these studies provided direct evidence for the suppression of Th17 development by galectin-9, whereas one also showed that de novo generation of regulatory T cells was enhanced by galectin-9 (34). TIM-3 also seems to negatively regulate the development and/or survival of human Th17 T cells, because an antagonist TIM-3 Ab can enhance the production of IL-17 by human T cells (35).

Perhaps the most exciting recent development regarding TIM protein function is the association of TIM-3 with the phenomenon of immune exhaustion. Thus, in addition to the previously described subset of programmed death 1-expressing nonresponsive T cells in individuals with chronic HIV infection, there is a largely nonoverlapping population of CD8+ T cells that express TIM-3 (36). Expression of TIM-3 correlates with disease progression and is associated with a lack of activation potential. Most strikingly, soluble TIM-3–Ig or a putative blocking Ab (Table II) for human TIM-3 can partially reverse the activation defect of these cells, and blocking both TIM-3 and PD-1 leads to a cooperative or synergistic rescue of T cell activation (36). Upregulation of TIM-3 on CD4+ and CD8+ exhausted T cells was also recently reported in patients with chronic hepatitis C virus infection (38). As in the case of HIV infection, blocking the interaction of TIM-3 with its ligands partially rescued the functionality of such cells. It remains to be seen whether a similar role exists for TIM-3 in other settings of infection or cancer where chronic stimulation may result in T cell exhaustion.

### Table II. Selected Abs to mouse and human TIM-3 that have been functionally characterized in the literature

<table>
<thead>
<tr>
<th>Tim-3 Abs</th>
<th>Epitope</th>
<th>Functional Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8B.2C12</td>
<td>(BALB/c &gt; &gt; BL/6)</td>
<td>Increased Th1</td>
<td>16</td>
</tr>
<tr>
<td>5D12</td>
<td>IgV</td>
<td>Increased Th1</td>
<td>37</td>
</tr>
<tr>
<td>8H7</td>
<td>?</td>
<td>Increased Th1/decreased Th2</td>
<td>32, 33</td>
</tr>
<tr>
<td>RMT3-23</td>
<td>?</td>
<td>Increased Th1</td>
<td>34</td>
</tr>
<tr>
<td>2E2 (human)</td>
<td>?</td>
<td>Reversal of CD8+ exhaustion (HIV)</td>
<td>35, 36</td>
</tr>
<tr>
<td>1G5 (human)</td>
<td>?</td>
<td>Reversal of T cell nonresponsiveness (HCV)</td>
<td>38</td>
</tr>
</tbody>
</table>

Unless otherwise stated, the Abs recognize murine Tim-3. ?, epitope not yet mapped; HCV, hepatitis C virus.

### Positive regulation of T cell responses by Tim-3

Although it is clear that Tim-3 can negatively regulate Th1 immune responses, Tim-3 also seems to act as a positive regulator of T cell responses, at least under some circumstances. Such effects may be indirect in part, (i.e., through effects on APCs). Tim-3 is constitutively expressed by some monocytic cells, including dendritic cells (DCs) and microglia, and ligation of Tim-3 on these cells can increase their expression of costimulatory receptors and cytokines (37). Several studies have also provided evidence for positive effects of Tim-3 on T cells themselves, particularly in response to tumors. Injection of Tim-3+ Th1 T cells into SJL mice inhibited the growth of spontaneous or transplanted B cell lymphomas (42). Additionally, expression of a naturally occurring soluble form of Tim-3 inhibited the responses of mice to B16 melanoma cells. This inhibitory effect was even observed when purified T cells were stimulated in vitro with Abs to CD3 and CD28, arguing against an indirect effect on APCs (43). The in vivo administration of galectin-9 increased the number of Tim-3+ CD8+ T cells and enhanced the killing of Meth-A sarcoma cells in syngeneic mice, although, in this case, at least part of the effect of galectin-9 was due to enhanced APC function (44).

It is still not clear precisely how the positive and negative effects of Tim-3 might balance out one another in vivo. Given the constitutive expression of Tim-3 on APCs and late upregulation on effector T cells, it is possible that Tim-3 enhances T cell activation and/or differentiation during the early phase of an immune response, while acting to help terminate a response at a later time. However, it cannot be ruled out that ligation of Tim-3 on T cells by different ligands or under certain activation conditions may lead to direct augmentation of T cell activation.

### Signaling by TIM-3

At this point, relatively little is known about how TIM-3 might transmit signals that inhibit T cell activation, cause cell death, or even augment T cell activation or effector function, all functions discussed above. The cytoplasmic tail of TIM-3 is considerably more complex than that of TIM-1. Although TIM-1 contains one tyrosine that is a good candidate for phosphorylation, TIM-3 possesses five such tyrosines. At least one of these tyrosines (Y265 in human TIM-3, corresponding to Y256 in mouse Tim-3) can be phosphorylated, at least in...
HEK 293 cells (45), which may be mediated by the Tec family tyrosine kinase Itk. It is not known how tyrosine phosphorylation of TIM-3 might regulate its function in T cells or other cell types in which it is active. However, it has been reported that Ab-mediated cross-linking of Tim-3 elicits different patterns of tyrosine phosphorylation in murine Th1 T cells and DCs (37). Identification of these substrates may lead to a greater understanding of Tim-3 function. Finally, Tim-3 ligation can enhance activation of MAPK and NF-κB pathways (37), although the role of these pathways in mediating TIM-3 function has yet to be determined.

Structural insights into TIM protein function

The IgV domains of all four TIM proteins have been subjected to structural analysis. The structures of the murine Tim-1 and -2 Ig domains were the first to be reported (4). Perhaps the most interesting revelations about Tim-1 and -2 revealed by these structures were the findings regarding dimerization of the proteins. Thus, the Ig domain of Tim-1 crystallized in anti-parallel dimers, suggestive of trans homodimerization of Tim-1 molecules expressed on different cells (Fig. 2A) (4). Biochemical experiments confirmed that Tim-1 can homodimerize and that high-affinity binding requires the Ig and mucin domains (4). Although Tim-2 Ig domain crystals also contained dimers, these were very different from those observed with Tim-1. Specifically, the parallel dimers of Tim-2 that formed in the crystals were suggestive of cis homodimerization that would occur between molecules expressed on the same cell (4).

Detailed study of the Tim-3 Ig domain (Fig. 2B) also revealed some surprises about this member of the TIM family. Thus, bacterially derived tetramers of Tim-3 could stain the surface of numerous leukocytes, including T cells, B cells, macrophages, and DCs (5). Because such rTim-3 would not be glycosylated, there must be one or more non-galectin-9 ligands(s) for Tim-3 on the surface of leukocytes. The identity of such a ligand or ligands is not known. Although phosphatidylerine (PS) can be transiently expressed on the surface of activated immune cells, the fact that Tim-3 uniformly stains freshly isolated murine leukocytes seems to rule out PS as the ligand in this case.

TIMs as ligands for PS

One of the hallmark events associated with apoptosis is the translocation of PS to the outside of the plasma membrane, exposing it to phagocytic cells that have specific receptors for PS (46). This results in the recognition and phagocytosis of the apoptotic cell. Several articles that appeared in the last few years demonstrated a role for TIM family proteins in the recognition of PS and phagocytosis of apoptotic cells. Initially, it was shown that Tim-1 and -4 can bind to PS and, if expressed by a phagocytic cell, could mediate phagocytosis (47, 48). These findings were confirmed by a structural study, in which the Tim-4 Ig domain was co-crystallized with PS (49). Binding of PS to Tim-4 occurred mainly in a pocket between the CC′ and FG loops (Fig. 2A); intriguingly, the FG loop, which contains aromatic residues, seems to coordinate with the fatty acid chains of the PS and the plasma membrane of the target cell on which the PS is present (49). Similar activity is also possessed by Tim-3 (Fig. 2B), and phagocytosis of apoptotic cells mediated by Tim-3 can result in cross-presentation of Ags to CD8+ T cells (50). Tim-2 seems to be the only member of the family that does not mediate binding of PS (48). Because Tim-1 and -3 can be expressed by T cells, it remains to be seen what the effects are of PS binding to these Tims on T cells, which are not phagocytic. In addition, the role of TIM proteins in the normal clearance of apoptotic cells during development, tissue injury, and inflammation is not clear.

**TIM protein effects on other immune cell types**

Although TIMs have been most extensively studied for their effects on T cell function, they can also regulate myeloid cell function. As discussed above, the function of APCs, such as DCs and microglia, can be enhanced by Tim-3 ligation. The mast cell is another myeloid cell type in which TIM function has been characterized; mouse bone marrow-derived mast cells express Tim-1 and -3 (51). Treatment of mouse mast cells with rTim-4, presumably through Tim-1 ligation, increased the production of several cytokines in response to IgE and Ags (51). A polyclonal Ab to Tim-3 also enhanced mast cell production of type 2 cytokines in conjunction with IgE/Ag. However, neither treatment had any effect on mast cell degranulation (51). Given the central role of mast cells in atopy, these findings warrant further study, because they might shed additional light on how Tim-1 and -3 polymorphisms contribute to Th1/Th2 skewing. Finally, Tim-1 is expressed at low levels on murine B cells (18, 19), whereas Tim-3 is not detectable (16). The potential function of Tim-1 on B cells has not been reported.

Conclusions

The expression of TIM proteins by activated T cells in various pathogenic settings has opened up the possibility that targeting these proteins may inhibit or augment immune responses, depending upon the clinical situation. Clearly, in vitro and murine in vivo studies revealed that targeting TIM protein function can modulate immune responses. There are still limited in vitro studies with human cells, but these showed promise, particularly in the case of TIM-3, as discussed above. Modulating the function of TIM proteins through traditional protein drug approaches (i.e., use of blocking Abs or soluble receptors) may be complicated by the fact that TIM–ligand interactions are somewhat promiscuous (Fig. 2). Also, the ability of different TIM Abs or even concentrations of ligand to differentially affect activation of different subsets of T cells (and possibly other cell types) is a potential concern for future use in patients. A cautionary tale in this regard is the recent clinical experience with a superagonist mAb specific for CD28. Although such Abs functioned in preclinical models to preferentially expand regulatory T cells at the expense of effector T cells, they were actually quite effective at activating memory/effector T cells in humans, resulting in a potentially fatal cytokine storm (52).

With regard to the normal functions of TIM-1 and -3 in immunity, it will be necessary to more clearly define the requirements for binding of each putative and confirmed ligand, as well as to determine the identity of specific ligands (if any) for the mucin domains of these proteins. It will also be important to obtain a better understanding of the effects of TIM-1 and -3 ligation on downstream signaling pathways that enhance or inhibit leukocyte activation.

**Disclosures**

The author has no financial conflicts of interest.
References


Corrections


Footnote a in Table I of this Brief Review should state that the anti–Tim-1 Ab RMT1-10, used in several publications, is the same as the commercial Ab with the same name. I regret any confusion this error may have caused.

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