Analysis of therapeutic potential of preclinical models based on DR3/TL1A pathway modulation (Review)

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Abstract. Death receptor 3 (DR3) and its corresponding ligand, tumor necrosis factor-like ligand 1A (TL1A), belong to the tumor necrosis factor superfamily. Signaling via this receptor-ligand pair results in pro-inflammatory and anti-inflammatory effects. Effector lymphocytes can be activated to exert pro-inflammatory activity by triggering the DR3/TL1A pathway. By contrast, DR3/TL1A signaling also induces expansion of the suppressive function of regulatory T cells, which serve an important role in exerting anti-inflammatory functions and maintaining immune homeostasis. Preclinical evidence indicates that neutralizing and agonistic antibodies, as well as ligand-based approaches targeting the DR3/TL1A pathway, may be used to treat diseases, including inflammatory and immune-mediated diseases. Accumulating evidence has suggested that modulating the DR3/TL1A pathway is a promising therapeutic approach for patients with these diseases. This review discusses preclinical models to gauge the progress of therapeutic strategies for diseases involving the DR3/TL1A pathway to aid in drug development.

Contents

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1. Introduction

The tumor necrosis factor superfamily (TNFSF) consists of 19 ligands and 29 receptors (1,2). Death receptor 3 (DR3) and tumor necrosis factor-like ligand 1A (TL1A) are a TNFSF receptor-ligand pair that serve an essential role in regulating immunity, inflammation, cell proliferation and death, angiogenesis, and tumor metastasis (2,3). The expression of DR3 and TL1A has been demonstrated in mice and humans, and preclinical and clinical studies have shown that the DR3/TL1A pathway serves a dual role in the development of inflammatory and immune-mediated diseases (4). On one hand, interaction between DR3 and TL1A may trigger the proliferation of T effector cells and cytokine production by these cells, which accelerate disease progression (5-7). On the other hand, activation of the DR3/TLA pathway serves an anti-inflammatory role through the expansion of regulatory T cells (Tregs) and alleviates diseases (8-10).

Based on the role of the DR3/TL1A pathway in pro-inflammatory and anti-inflammatory processes, this review summarizes DR3-associated signals and reviews therapeutic strategies targeting the DR3/TL1A pathway in preclinical models, intending to facilitate the development of attractive drug candidates.

2. Expression and composition of TL1A and DR3

DR3. In the late 1990s, a clone was found to exhibit identity to the death domains (DDs) of cluster of differentiation 95 (CD95; 23% identity) and tumor necrosis factor receptor-1 (TNFR-1; 47% identity), which are both members of the TNFSF (11). Additionally, the homologies of the cysteine-rich repeats between the clone and CD95 and TNFR-1 were 22 and 26%, respectively (11). Therefore, the clone was classified as a member of the TNFSF and was designated as DR3 (TNFRSF25, APO-3, TRAMP, WSL-1, TR3 or LARD) (11,12). DR3 is encoded by the *Tnfrsf25* gene located in the 4E1 region of the mouse chromosome (13) and 1p36.3 of the human chromosome (4). As a type I transmembrane protein with a calculated molecular weight of 45 kDa and 417-amino acid (aa) sequence, full-length DR3 is composed of an N-terminal signal sequence (aa 1-24), a repeat sequence consisting of four cysteine residues, two potential *N*-linked glycosylation sites (aa 25-198), a transmembrane domain

(aa 199-244), and an intracellular domain with a DD (aa 255-417) (14,15). Notably, DR3 is exclusively expressed in lymphocyte-rich tissues, including the thymus, spleen, colon and intestine (11); however, low levels of expression are detected in the fetal lung (16), kidney (17), hippocampus (18) and peritoneal tissue (12). At the cellular level, DR3 is mainly expressed in immune cells, including naïve or resting $CD4^+$ T cells, $CD8^+$ T cells, natural killer T cells, innate lymphoid cells (ILCs), B cells and mononuclear cells (10,19). Notably, sustained expression of DR3 is found in Tregs. However, DR3 also exists in non-immune cells, including bone cells (20) and endothelial cell colony-forming cells (21). Expression of DR3 is highly regulated in multiple pathologies. The levels of DR3 are significantly increased in inflammatory bowel disease (IBD) (22), pulmonary sarcoidosis (23) and psoriasis vulgaris (24). By contrast, DR3 expression in mononuclear cells is downregulated in diseases, including sickle cell anemia (25) and colon cancer (26).

TL1A. TL1A, also known as vascular endothelial growth inhibitor (VEGI)-251 or TNFSF15, is the only proven ligand for DR3 to date (5). TL1A is a single-pass type II transmembrane protein encoded by the *Tnfsf15* gene on chromosome 4 in mice and 9q32 in humans (4). Similar to other TNFSF cytokines, membrane-bound TL1A can be cleaved by alternative splicing or through TNF-α-converting enzyme, and is shed from the extracellular domain to form soluble TL1A (sTL1A) (4,5,27). Notably, sTL1A may continue to efficiently activate DR3. Endothelial cells, dendritic cells (DCs), monocytes/macrophages, activated T cells and human umbilical vein endothelial cells have been identified as major sources of TL1A (5,28-30). Additionally, the expression of TL1A on DCs and macrophages is increased upon activation via the receptor for the Fc region of IgG (FcγR) and Toll-like receptors (TLRs), including TLR2 and TLR4, while expression of TL1A on endothelial cells may be enhanced by interleukin-1 beta (IL-1β) and TNF-α stimulation (15). Nevertheless, chondrocytes, synovial fibroblasts, tissue macrophages and lamina propria lymphocytes also express TL1A at low levels under conditions of inflammation or upon stimulation (5,6). Therefore, the binding of TL1A to DR3 triggers signal transduction and exerts pro- and anti-inflammatory functions.

3. DR3/TL1A signal transduction

Upon binding to DR3 on immune cells, TL1A triggers an interaction between the DD of DR3 and the adaptor protein, TNFR-associated death domain (TRADD). Subsequently, TNFR-associated factor 2 and receptor-interacting protein 1 bind to the DR3-TRADD complex, leading to activation of mitogen-activated protein kinase (MAPK), nuclear factor (NF)-κB, and phosphoinositide 3-kinase (PI3K) signaling. Consequently, three distinct signaling cascades induce immune cell activation, proliferation and cytokine secretion (Fig. 1). The activation of DR3 on immune cells by TL1A is an important prerequisite for its pro-inflammatory and anti-inflammatory effects. Accumulating evidence has revealed that pharmacological blockade or agonistic activation of DR3/TL1A signaling is a novel and promising target for inflammatory or immune-mediated diseases (6,8,10).

4. Co-stimulation of effector immune cells

Co-stimulatory molecules expressed by antigen-presenting cells and T cells appear to be indispensable for the activation of T cells. The absence of co-stimulatory signals leads to T cell incompetence (31). The TNFSF is considered as one such group of co-stimulatory molecules that activates T cells. Several studies have demonstrated that, as a lymphocyte co-stimulatory signaling pathway, DR3/TL1A amplifies effector $CD4^+$ T cells in a non-specific manner to aggravate the pathology of inflammatory diseases by triggering the release of inflammatory cytokines. Furthermore, abundant evidence also indicates that DR3 on ILCs affects the progression of inflammatory diseases (32-34).

Co-stimulation of effector $CD4^+$ T cells. A subset of $CD4^+$ T cells activated by the DR3/TL1A signaling serves a pro-inflammatory role under established conditions. Decreased lung inflammation in $DR3^{-/-}$ mice is attributed to fewer $CD4^+$ T cells in the alveolar passage following an ovalbumin (OVA) challenge (35). TL1A, alone or in combination with IL-12 and IL-18, has been found to boost the secretion of interferon-γ (IFN-γ) and TNF-α, which are characteristic cytokines produced by Th1 cells (19,36,37). Activation of the DR3/TL1A pathway may aggravate disease progression by boosting Th1 immune responses in SAMP1/YitFc (SAMP) mice with ileitis (28). Furthermore, Th2-induced immunopathology is exacerbated by the non-specific stimulation of lymphocytes by DR3 signaling. Th2-mediated immune responses result in high levels of IL-5 and IL-13 produced in the intestinal mucosa, as well as aggravated inflammation in SAMP mice with ileitis via DR3/TL1A signaling (4,28,38). Additionally, Th2 cells, activated by the DR3 axis and accompanied by high IL-13 production, have been implicated in allergic inflammation in mouse models (39,40). Th17 cells show higher expression of DR3 compared with Th1 and Th2 cells (41). However, the role of DR3 signaling in Th17 differentiation is controversial. Inhibition of Th17 cell generation by DR3 signaling has been demonstrated in $CD4^+$ T cells and spleen cells from humans and wild-type mice, respectively (42). By contrast, other studies have demonstrated that TL1A promoted Th17 cell differentiation and participates in the development of inflammation, such as rheumatoid arthritis (RA) (43) and experimental autoimmune encephalomyelitis (EAE) (44). Notably, the proliferation of Th17 cells was augmented upon DR3 activation. Pappu *et al* (44) verified that the decreased proliferation of Th17 cells in TL1A-deficient mice ameliorated the pathology of EAE. This evidence indicates that the DR3/TL1A axis aggravates inflammatory reactions triggered by activated Th17 cells. A recent study demonstrated that the DR3/TL1A pathway drives the differentiation of naïve T cells to Th9 cells, aggravating inflammatory pathology in an allergic lung inflammation model (7). Similarly, preclinical and clinical studies in chronic colitis have demonstrated that TL1A facilitates the differentiation of Th9 cells and increases IL-9 secretion, aggravating intestinal inflammation (45). Additionally, Tsuda *et al* (46) reported that TL1A induced the expression of basic leucine zipper ATF-like transcription factor 3 to promote Th9 cell differentiation and IL-9 production to drive intestinal inflammation.

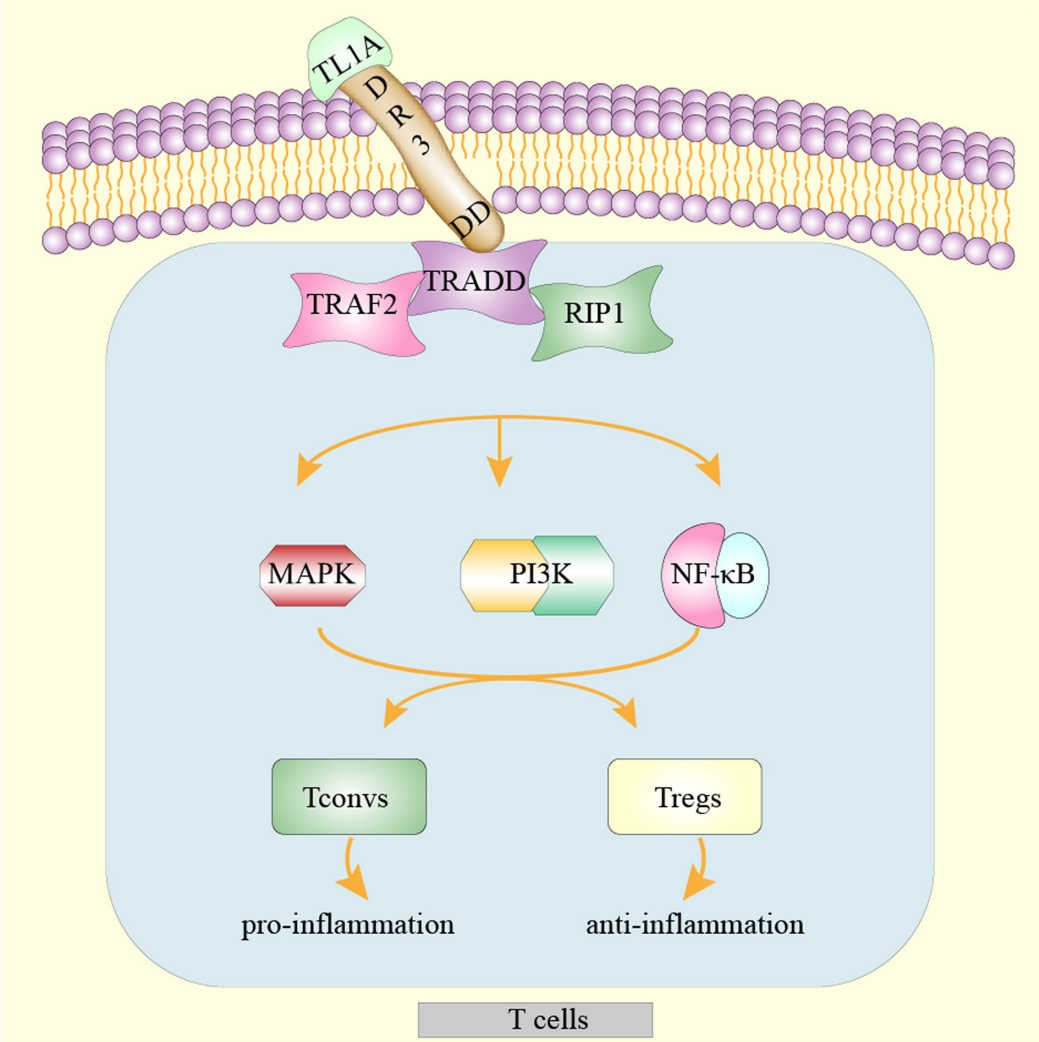

Figure 1. DR3/TL1A pathway in T cells. Upon binding to TL1A, the DD of DR3 signals via the TRADD, which in turn, recruits RIP1 and TRAF2 to form a signaling complex in T cells, accompanied by the downstream activation of MAPK, NF-κB and PI3K. The signaling ultimately triggers pro-inflammatory responses from Tconvs and anti-inflammatory signals from Tregs. DR3, death receptor 3; TL1A, tumor necrosis factor-like ligand 1A; DD, death domain; TRADD, TNFR-associated death domain; RIP1, receptor-interacting protein 1; TRAF2, TNFR-associated death domain; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinase; Tconvs, conventional T cells; Tregs, regulatory T cells.

Co-stimulation of ILCs. In addition to T cells, the DR3/TL1A pathway co-stimulates ILCs. ILC2s and ILC3s are subsets of ILCs. DR3 signaling can expand ILC2s and ILC3s, driving IL-5 and IL-13 secretion from these cells. *In vivo* experimental evidence has demonstrated that ILC2s cause deterioration in allergic lung inflammation (34,35,47). By contrast, ILC3s exert positive effects by increasing IL-22 production. Loss of DR3 signaling with decreased IL-22 production has been associated with a higher histopathological score in a DR3-deficient, dextran sulfate sodium (DSS)-induced colitis model (33,48). Furthermore, an anti-DR3 antibody triggered the loss of ILC3s from the intestine, ultimately aggravating the colitis condition (32).

Therapeutic application. The DR3/TL1A pathway has been clearly implicated in several diseases, including allergic lung inflammation (35), psoriasis (5), IBD (4) and rheumatoid arthritis (43). The aforementioned diseases share a common molecular mechanism in which DR3 signaling exerts pleiotropic effects on the activation, differentiation, proliferation and cytokine release of ILC2s and T helper cells (including Th1, Th2, Th9 and Th17 cells). Therefore, these findings suggested that pharmacological blockade of the DR3/TL1A axis may have therapeutic value for human inflammatory and immune-mediated diseases. An anti-TL1A monoclonal antibody (anti-TL1A mAb) targeting the DR3/TL1A pathway has emerged as a promising anti-inflammatory therapeutic agent in preclinical studies (5,6,31,49). Furthermore, unlike anti-TNF, anti-TL1A mAb may be relatively safe and effective because it does not induce immunodeficiency (50).

It is evident that TL1A/DR3 signaling dampens gut immune homeostasis and accelerates disease progression (4). Thus, blocking the TL1A/DR3 pathway may be a useful strategy for relieving IBD. Studies in animal models have demonstrated that anti-TL1A mAb exerts a protective function in DSS-induced chronic colitis by suppressing Th1 and Th17 cell activation (51). Additionally, in acute 2,4,6-trinitrobenzene-sulfonic acid (TNBS)-induced colitis involving increased production of Th1 cells and IFN-γ, blocking the DR3/TL1A axis with anti-TL1A mAb almost completely prevented weight loss and

alleviated the histological score of inflammation (52). However, administration of anti-TL1A mAb, a neutralizing agent, mitigated the early phase, but not the late stage of TNFΔARE/$^{+}$ ileitis, thereby suggesting the existence of other DR3 ligands aside from TL1A (31). Of note, the aforementioned studies have only demonstrated a decreased in inflammation caused by anti-TL1A mAb rather than alleviation of intestinal fibrosis, a hallmark of IBD. In DSS, as well as in the adoptive T cell transfer chronic colitis models, treatment with anti-TL1A mAb resulted in a decrease in the number of myofibroblasts and fibroblasts, leading to a reversal of colonic fibrosis (53). Furthermore, Li *et al* (54) discovered that intestinal inflammation and fibrosis were attenuated in T cell transfer chronic colitis models. Clarke *et al* (6) also confirmed that anti-TL1A mAb significantly alleviated the clinical pathology of IBD by decreasing inflammatory cell filtration and colonic fibrosis. In general, therapeutic blockade of the DR3/TL1A pathway by anti-TL1A mAb has numerous advantages, including amelioration of intestinal inflammation and reversal of colonic fibrosis, compared with traditional treatment for IBD, which only controls intestinal inflammation.

In addition to IBD, blocking the DR3/TL1A pathway with anti-TL1A mAb relieves collagen-induced arthritis (49), strongly reduces inflammatory cell infiltration in OVA-induced asthma (6), and effectively alleviates the histopathological changes in a psoriasis-like mouse model (5). Taken together, these results suggested that anti-TL1A mAb has therapeutic potential for treating inflammatory and immune-mediated diseases (Table I).

5. Co-stimulation of CD4^{+} CD25^{+} Foxp3^{+} Tregs

Basic characteristics of Tregs. Tregs are a subset of CD4^{+} T cells that function primarily to maintain the homeostasis of immune function by negatively regulating effector lymphocyte activation and proliferation (55). Tregs are mainly characterized by CD4, CD25 and Foxp3. Williams and Rudensky (56) reported that, rather than acquiring the ability to produce IL-2 and Th1 cytokines, the immunosuppressive function was eliminated in mature Tregs following the deletion of the *FOXP3* gene. Therefore, Foxp3 is essential for maintaining the immunoregulatory function of Tregs. In addition to CD4 and Foxp3, Tregs express a high-affinity IL-2 receptor (IL-2R) that may bind IL-2Rα (CD25), IL-2Rβ (CD122) and IL-2Rδ (CD132) (57). As expected, IL-2 is a critical signal for Treg differentiation.

Therapeutic application. Activation of DR3 using an anti-DR3 agonistic antibody or sTL1A has been shown to mediate Treg cell activation and expansion because of the constitutive expression of DR3 on Treg cells. DR3-mediated activation of Tregs mainly triggers the activation of MAPK, NF-κB and PI3K signaling via DR3/TL1A signal transduction (15,58,59), thereby exerting anti-inflammatory effects and preventing inflammatory and immune-mediated diseases in mice.

Due to the strong immunosuppressive function of Tregs, adoptive transfer of exogenously expanded Tregs or IL-2/IL-2 complexes expanded Tregs *in vivo* can alleviate a variety of immune-mediated diseases such as experimental autoimmune neuritis (60), headache disorders (61), systemic lupus erythematosus (62), IBD (63) and allograft tolerance (64-66), as well as inflammatory diseases such as transfusion-related acute lung injury (67,68) in preclinical models. Moreover, adoptive Treg transfer and low-dose IL-2 therapy have been associated with disease improvement and unconspicuous adverse effects in patients (66). However, the ability to obtain an adequate number of Tregs through adoptive transfer limits their clinical use, while the cytotoxicity, off-target effects and short half-life of IL-2 therapy *in vivo* necessitate the use of approaches employing expanded Tregs (64).

Anti-DR3 agonist. Clone 4C12 is an anti-DR3 agonistic antibody that activates and expands Tregs and thus has been useful for preventing or treating diseases in preclinical models (8,10,69). To begin with, the stimulation of DR3 using 4C12 leads to rapid and selective expansion of Tregs without influencing Tconvs (8,9,70,71). Furthermore, 4C12 retains its capacity to expand Tregs *ex vivo* (8). Additionally, the half-life of 4C12 is 5 days (9), ensuring prolonged contraction of expanded Tregs following 4C12 treatment compared with treatment with IL-2 or IL-2 complexes (8). Prolonged contraction of expanded Tregs is important for ameliorating inflammatory and immune-mediated diseases.

Preclinical models have demonstrated that Tregs expanded by 4C12 may alleviate disease. Schreiber *et al* (8) first discovered that lung inflammation was alleviated following treatment with 4C12 compared with the control group in OVA-induced acute allergic pneumonia. Madierddi *et al* (69) also demonstrated that the administration of 4C12 relieved allergic pneumonia and suppressed EAE through the expansion of Tregs. At present, 4C12 is widely applied in the field of transplants, including organ transplant, tissue transplant and cell transplant, aiming to alleviate graft-versus-host disease (GVHD). For example, Tregs expanded *in vivo* by 4C12 may provide tolerance to cardiac allografts (71). Recipients transplanted with donor-expanded Treg by 4C12 exhibited enhanced skin allograft survival (72). Furthermore, the infusion of 4C12 in recipient mice enhances skin graft survival associated with boosted graft-infiltrating Tregs (73). Administration of 4C12 also efficiently ameliorated GVHD in hematopoietic stem cell transplantation (HSCT) mismatch mouse models. Several studies have suggested that donor-derived Tregs are more effective than recipient-derived Tregs for GVHD treatment (74,75). Transfer of donor-derived Tregs expanded by 4C12 markedly protected mice from GVHD (10,72,76). Notably, Nishikii *et al* (29) demonstrated that treatment of recipients with 4C12-induced Treg activation and proliferation was sufficient to dampen GVHD lethality prior to exposure to HSCT. By contrast, mice transplanted with Tregs that were expanded by 4C12 following HSCT exposure led to donor T cell proliferation and ultimately fueled GVHD (29). These findings demonstrated that activation of DR3 mitigated the lethality of GVHD, depending on the timing of triggering DR3. Due to the significance of IL-2 signals in DR3-mediated Tregs expansion (8), low-dose IL-2 combined with 4C12 for donors resulted in decreased GVHD morbidity and prolonged survival (10). Additionally, the absolute number of Tregs induced by that combination was larger than that observed following the treatment with 4C12 alone (10). Therefore, this therapeutic strategy may be an improvement for delaying allogeneic rejection.

Table I. Effects of anti-TL1A mAb on preclinical disease models.

Disease model	Mechanisms	Effects	Authors/Refs.
DSS-induced chronic colitis	Downregulation of Th1 and Th17 activation	Dampened weight loss; weakened colon shortening	Takedatsu *et al* (51), 2008
TNBS-induced colitis	Amelioration of local inflammation	Deceleration of weight loss; reduced morbidity and mortality	Meylan *et al* (52), 2011
$TNF^{\Delta ARE/+}$ ileitis	Blockade of secretion of inflammatory cytokines	Relieved early stage of intestinal inflammation	Buttó *et al* (31), 2019
Adoptive transfer T cell and DSS induced colitis	Decreased number of intestinal fibroblasts and myofibroblasts	Reversal of colonic fibrosis	Shih *et al* (53), 2014
Adoptive transfer T cell-induced colitis	Reduced inflammatory cell filtration, collagen deposition and fibroblast activation	Reversal of intestinal structure; alleviated intestinal fibrosis	Li *et al* (54), 2018
TNBS-induced colitis	Reduced inflammatory cell filtration	Ameliorated colon length reduction; improved histopathology	Clarke *et al* (6), 2018
Collagen-induced arthritis	Reduced leukocyte filtration in synovial tissue	Decreased inflammatory score of arthritis	Bull *et al* (49), 2008
OVA-induced asthma	Decreased number of inflammatory cells in alveolar lavage fluid	Mitigated lung inflammation	Clarke *et al* (6), 2018
Imiquimod-induced psoriasis	Reduced release of IFN-γ and IL-17 and infiltration of inflammatory cells	Relieved histopathology of psoriasis; improved disease progression	Li *et al* (5), 2020

Anti-TL1A mAb, anti- tumor necrosis factor-like ligand 1A monoclonal antibody; DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzene-sulfonic acid; TNF, tumor necrosis factor; OVA, ovalbumin; IFN-γ, interferon- γ; IL-17, interleukin-17.

Table II. Therapeutic approach of Tregs via DR3/TL1A pathway modulation in a preclinical model.

Therapy type	Disease model	Time of intervention	Intervention target	Effects	Authors/Refs.
4C12	OVA/alum-induced acute allergic pneumonia	Before	Model	Improvement in allergic pneumonia	Schreiber *et al* (8), 2010; Madireddi *et al* (69), 2017
	EAE	Before	Model	Median clinical score decreased	Madireddi *et al* (69), 2017
	Allogeneic heart transplantation	Before	Recipient	Delayed heart transplant rejection	Wolf *et al* (71), 2012
	Allogeneic skin transplantation	After	Recipient	Reduced proliferation of cytotoxic T cells and mixed lymph; enhance graft survival	Gorczynski *et al* (73), 2017
		Before	Donor	No skin fibrosis or thickening of the skin in recipient mice	Wolf *et al* (72), 2018
	MHC-mismatch HSCT	Before	Donor	Reduced GVHD-related morbidity and mortality	Kim *et al* (76), 2015
		Before	Donor	Reduced weight loss in recipient mice; decreased clinical pathology score	Wolf *et al* (72), 2018
		Before	Donor	Reduced GVHD-related morbidity and mortality	Mavers *et al* (10), 2019
		Before	Recipient	GVHD score dropped	Nishikii *et al* (29), 2016
sTL1A	OVA-induced acute asthma	Before	Model	Decreased lung pathology score	Khan *et al* (9), 2013
	MHC-mismatch HSCT	Before	Donor	Reduced GVHD-related morbidity and mortality	Mavers *et al* (10), 2019
4C12+IL-2	MHC-mismatch HSCT	Before	Donor	Reduced GVHD-related morbidity and mortality	Mavers *et al* (10), 2019
sTL1A+IL-2	MHC-mismatch HSCT	Before	Donor	Facilitated transplant tolerance without GVHD	Wolf *et al* (77), 2017
		Before	Donor	Effectively relieved GVHD; promoted survival	Copsel *et al* (78), 2018
		Before	Donor	Reduced GVHD-related morbidity and mortality	Mavers *et al* (10), 2019

Before, before disease model establishment; after, after disease model establishment; DR3, death receptor 3; TL1A, tumor necrosis factor-like ligand 1A; Tregs, regulatory T cells; OVA, ovalbumin; EAE, experimental autoimmune encephalomyelitis; MHC, major histocompatibility complex; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host-disease; sTL1A, soluble TL1A; IL-2, interleukin-2.

sTL1A. In addition to the anti-DR3 agonistic antibody, which may induce rapid and selective expansion of Tregs, sTL1A is sufficient as a soluble ligand for DR3 to trigger its signaling and to expand Tregs *in vivo* (9). Due to the shorter half-life of sTL1A (13.5 h), daily injection is required to maintain the desired serum levels. Khan *et al* (9) reported that sTL1A-meditated Treg expansion alleviated allergic lung inflammation through repeated administration, by blocking eosinophil infiltration into the alveolar fluid and reversing the ratio of Tconvs to Tregs in the lung without inducing any inflammatory changes in the liver, kidney and myocardium. Additionally, sTL1A, alone or combined with IL-2-expanded and IL-2-activated Tregs in donor mice, led to decreased GVHD morbidity and mortality in HSCT models (10). Consistent with this observation, low-dose IL-2 combined with sTL1A improved the clinical score, dampened weight loss and increased survival prior to HSCT exposure in animal models (77,78). Low-dose IL-2 combined with sTL1A expanded a higher proportion of Tregs in the peripheral blood, lymph nodes and spleen, compared with sTL1A alone (10). Whether the activation of Tregs through sTL1A/IL-2 may prevent GVHD manifestations more effectively than the treatment regimen of sTL1A requires further investigation.

6. Conclusions and perspectives

In conclusion, activation of the DR3/TL1A pathway has been reported to alleviate allergic lung inflammation, improve EAE symptoms and abrogate GVHD (Table II). Physiologically, DR3 triggers pro-inflammatory and anti-inflammatory effects. Blockade of DR3 signaling through anti-TL1A mAb exerts anti-inflammatory effects by suppressing effector immune cell activation. As anti-TL1A mAb is a neutralizing antibody, the receptor-binding epitope and binding avidity may affect antibody activity. As DR3 and Decoy receptor 3 (DcR3) are receptors for TL1A, whether an antibody preferentially inhibits TL1A binding to DR3 or to DcR3 should be determined during antibody discovery campaigns. Additionally, activation of the DR3/TL1A axis via 4C12, sTL1A or in combination with IL-2 shows distinct immunosuppressive functions and controls aberrant immune reactions. Due to the dose-dependent, DR3-mediated expansion of Tregs, it is necessary to determine the optimal dose for Treg-based therapies. During the development of an anti-DR3 agonistic antibody, attention should be paid to FcγR-induced cellular cytotoxicity so as to realize the full agonistic potential, while limiting binding to FcγR. Therapeutically, interfering with the DR3/TL1A pathway in preclinical models has shown great promise. Neutralizing antibodies and agonists activating the DR3/TL1A pathway are required to target inflammatory and immune-mediated diseases.

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Authors' contributions

YY and PJ designed the review. PS and NS analyzed the relevant literature. YY drafted the manuscript and constructed the figure. PJ edited the manuscript and constructed the tables. FL provided financial resources and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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