Review article

TL1A, a novel alarmin in airway, intestinal, and autoimmune disorders

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The term *alarmin* denotes a broad class of molecules rapidly released to alert the immune system through the engagement of specific receptors on immune cells. Three alarmin cytokines—thymic stromal lymphopoietin, IL-33, and IL-25—are released from epithelial and certain stromal cells. TNF-like cytokine 1A (TL1A) is a member of the TNF cytokine superfamily, first identified in human endothelial cells. TL1A is now considered a novel alarmin expressed by human and mouse bronchial and intestinal epithelial cells. TL1A exerts its biological activities by binding to a trimeric receptor DR3 (death receptor 3), expressed on a wide spectrum of immune and structural cells, including lung fibroblasts, endothelial cells, and bronchial epithelial cells. TL1A has been implicated in experimental and human inflammatory bowel diseases as well as in airway inflammation and remodeling in severe asthma. A monoclonal antibody anti-TL1A (tulisokibart) is effective in inducing clinical remission in ulcerative colitis patients. Increasing evidence suggests that TL1A is also involved in certain autoimmune disorders, such as rheumatoid arthritis and psoriasis. These emerging findings broaden the role of TL1A in various human inflammatory conditions. Several clinical trials are currently evaluating the safety and efficacy of monoclonal antibodies targeting TL1A in asthma or inflammatory bowel disease patients. (J Allergy Clin Immunol 2025;155:1420-34.)

Key words: *Airway inflammation, alarmins, asthma, autoimmune disorders, inflammation, inflammatory bowel disease, remodelling*

Abbreviations used

AT1/2:	Alveolar type 1/2
CD:	Crohn disease
cIAP1/2:	Cellular inhibitor of apoptosis proteins 1 and 2
DC:	Dendritic cell
DD:	Death domain
DR3:	Death receptor 3
FADD:	Fas-associated DD
IBD:	Inflammatory bowel disease
ILC:	Innate lymphoid cell
ILC1/2/3:	Type 1/2/3 ILC
iNKT:	Invariant natural killer T
mAb:	Monoclonal antibody
MAIT:	Mucosal-associated invariant T
NF-κB:	Nuclear factor kappa–light-chain enhancer of activated B cells
NK:	Natural killer
RA:	Rheumatoid arthritis
RIPK1:	Receptor-interacting protein kinase 1/3
T1/2:	Type 1/2
TL1A:	TNF-like cytokine 1A
TNFR1:	TNF receptor 1
TNFRSF:	TNF receptor superfamily
TNFSF15:	TNF superfamily member 15
TRADD:	TNF receptor–associated DD
TRAF2:	TNF receptor–associated factor 2
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin
UC:	Ulcerative colitis
VEGI:	Vascular endothelial growth inhibitor

The term *alarmin* was coined long ago by Joshua Farber and then popularized by Joost J. Oppenheim at the National Institutes of Health[1] to denote a broad class of molecules that are rapidly released to alert the immune system through the engagement of specific receptors expressed on a wide range of cells of both the innate and adaptive immune system.[2-5] Recent literature has mainly focused on 3 cytokines—thymic stromal lymphopoietin (TSLP), IL-33, and IL-25—which are rapidly released from epithelial cells[6,7] and are critical for the initiation and activation of immune responses.[8-10] Although these alarmins share certain similar biochemical and immunologic characteristics—such as production by epithelial cells and activation of type 2 innate lymphoid cells (ILC2s)—they also exhibit striking differences. For instance, TSLP is a member of the IL-2 cytokine family and is a distant paralog of the IL-7 family. TSLP activates the heterodimeric TSLPR-IL-7Rα receptor expressed on a wide spectrum of cells of innate and adaptive immune system.[3] In addition, TSLP is released from diverse types of bronchial epithelial

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cells[11-13] and keratinocytes.[14] Moreover, TSLP is selectively localized in the cytoplasm of human lung macrophages.[15] In contrast, IL-33 is a nuclear cytokine[16-20] and a member of the IL-1 superfamily of cytokines.[21] This alarmin selectively activates the ST2 and the coreceptor IL-1 receptor accessory protein (IL-1RAcP).[22] While the reduced form of IL-33 signals through the ST2 receptor, an oxidized form binds to the receptor for advanced glycation end products and signals by complexing with the epidermal growth factor receptor on airway epithelium.[23] Finally, IL-33 is mainly localized in and released from bronchial basal cells.[24,25] IL-25, also called IL-17E, belongs to the IL-17 cytokine family and binds as a dimer to the heterodimeric receptor composed of IL-17RA and IL-17RB.[26] This receptor is more restricted than TSLPR and ST2.[3,27] Finally, IL-25 is mainly released by a small subset of bronchial epithelial cells named tuft or brush cells.[28] Table I summarizes some of the similarities and differences among the 3 canonical alarmins.[29-66]

Recently, the role has been emerging of a novel alarmin, named TNF-like cytokine 1A (TL1A), which binds with high affinity to death receptor 3 (DR3). Increasing evidences indicate that the TL1A/DR3 axis plays a role in different experimental and human inflammatory disorders.[29,30] In this review, we focus on the immunologic features of TL1A, and we summarize the clinical relevance of this novel alarmin in airway, intestinal, and autoimmune disorders, as well as the possibility of targeting TL1A in these disorders.

TL1A IS A NOVEL ALARMIN

TL1A, also referred to as TNF superfamily member 15 (TNFSF15) or vascular endothelial growth inhibitor (VEGI), belongs to the TNF cytokine superfamily first identified in human endothelial cells in 2002.[67] The *Tnfs15* gene encoding TL1A is located at chromosome 9q32 in human and chromosome 4 in mouse. The gene location of TL1A in human is on 5q22.1, while the gene location of IL-33 in human is on 9p24.1. TL1A is a trimeric protein,[42] and human and mouse TL1A, despite sharing only approximately 64% sequence homology, have similar biological functions.[67] Like other TNF family members, TL1A is a type 2 transmembrane protein that self-assembles into stable homotrimers.[42] Besides its membrane-bound form, TL1A also exists as a soluble protein, produced either through alternative mRNA splicing or via proteolytic cleavage of its extracellular domain mediated by matrix metalloproteinases.[42] Recent studies emphasize the different effects of soluble TL1A versus membrane-bound TL1A.[68] For instance, the membrane-bound form of TL1A facilitates the release of cytokines in mouse lung, whereas the soluble form does not.[68] Additional studies appear necessary to better understand the mechanisms underlying DR3 signaling associated with these two TL1A forms in human. Three TL1A mRNA splice isoforms, namely VEGI-251, VEGI-192, and VEGI-174, have been reported in humans.[35] However, it remains uncertain whether they also differ in their functional roles.

TL1A has recently been recognized as an alarmin exhibiting a wide range of pleiotropic effects, driven by the activation of the DR3 receptor on various immune and nonimmune cells.[29,30,69]

TL1A RECEPTOR DR3

TL1A binds with high affinity to the cytokine receptor DR3, also referred to as TNFRSF25, TRAMP, LARD, and WSL-1.[56,57] The *Tnfrsf25* gene encoding DR3 is located at chromosome 1p36.3 in human.[70] This receptor is a trimer on the cell membrane and belongs to the TNF receptor superfamily (TNFRSF).[56] DR3 possesses the intracellular motif death domain (DD), which can initiate programmed cell death on signaling.[71] In particular, DR3-mediated activation via the DD recruits the TNF receptor 1 (TNFR1)-associated DD (TRADD) adaptor protein, which promotes apoptosis by recruiting the Fas-associated DD (FADD).[72] Notably, DR3, in addition to promoting apoptosis, can induce cell activation and proliferation.[73] TL1A also exhibits a higher binding affinity for the soluble decoy receptor DcR3 (TNFRSF6B) compared to DR3,[67] thus inhibiting TL1A from activating T cells.[74]

An interesting feature of DR3 is the existence of splice variants (13 in humans and 10 in mice). The functional implications of these variants are presently unknown, although there is some evidence that encoded proteins may have distinct functions.[75] The DR3 receptor is expressed on endothelial cells,[76] intestinal epithelial cells,[77] bronchial epithelial cells,[78] and lung fibroblasts.[78] While DR3 shares the greatest homology with TNFR1 among TNFRSF receptors, it differs in both its expression and function.[79]

SIGNALING PATHWAYS OF DR3

The engagement of DR3 by TL1A can promote two different biochemical pathways inducing either proinflammatory and proliferative or proapoptotic activities in T cells. Fig 1 shows that the proinflammatory signaling via DR3 is initiated by the activation of the DD motif in the cytoplasmic tail of DR3, which subsequently recruits TRADD. TRADD, which also contains a DD, binds to DR3 through a DD-DD interaction.[80] This interaction creates a platform for the recruitment of downstream signaling molecules, including TNF receptor–associated factor 2 (TRAF2), cellular inhibitor of apoptosis proteins 1 and 2 (cIAP1/2) and receptor-interacting protein kinase 1 (RIPK1). Polyubiquitination of RIPK1 by cIAP1/2 activates downstream molecules, such as mitogen-activated protein kinase 1 (aka MAPK1), NF-κB, and phosphoinositide 3-kinase (aka PI3K). These 3 pathways induce gene expression causing inflammation. Soluble TL1A binding to DR3 predominantly stimulates the proinflammatory pathway.[81]

An alternative DR3 signaling pathway can trigger programmed cell death via the caspase 8 cascade (Fig 1).[82-85] In this event, TRADD interacts with FADD and receptor-interacting kinase 3 (RIPK3), leading to the activation of the caspase 8 pathway and subsequent apoptotic cell death.[82] It is unknown what factors determine whether DR3 signaling leads to activation or apoptosis, or why DR3 may trigger different outcomes depending on the cell type. It is also uncertain whether both pathways can occur simultaneously within the same cell.

CELLULAR TARGETS AND BIOLOGICAL PROPERTIES OF TL1A

TL1A binds to DR3 on several immune cells and some structural cells (Fig 2).[86-116] Differently from TNFR1, DR3 expression is more limited in its localization, being predominantly present on T cells among lymphocytes.[58] DR3 expression is higher on $CD4^+$ compared to $CD8^+$ T cells.[86] $Foxp3^+$ regulatory T (Treg) cells constitutively express more DR3 compared to

TABLE I. Similarities and differences among alarmins

Characteristic	TSLP	IL-33	IL-25/IL-17E	TL1A
Cytokine family	IL-2	IL-1	IL-17	TNF-α
Cytokine gene name in humans	*TSLP*	*IL33*	*IL25*	*TNFSF15*
Gene location in humans	5q22.1	9p24.1	14q11.2	9q32
Genetic variants or isoforms	lfTSLP and sfTSLP[3,31,32]	rs928413, rs16924159, rs7037276[33]	Subtype 1, subtype 2[34]	VEGI-174, VEGI-192, VEGI-251[35]
Cleavage products	Several cleavage products are generated by tryptase and chymase[10,15,36]	Full length (flIL-33), mature (mIL-33), oxidized (ox–IL-33)[24,37-41]	—	Soluble TL1A cleaved from membrane-bound TL1A[42]
Cellular localization	Cytoplasm[15]	Nucleus[16-20]	Cytoplasm[43]	Cytoplasm and nucleus[44]
Prominent cellular source	Bronchial epithelial cells,[45] intestinal epithelial cells,[46] macrophages,[8,15] keratinocytes[47]	Bronchial basal epithelial cells,[24,25,48] endothelial cells,[17,19] airway epithelial cells,[18] keratinocytes[20]	Tuft/brush cells[28,49-51]	AT1, AT2, bronchial basal cells,[29,52] DCs[53,54]
Receptor	TSLPR:IL-7Rα, heterodimeric[55]	ST2: IL-1RAcP, heterodimeric, RAGE[22]	IL-17RA: IL-17RB, heterodimeric[26]	DR3, trimeric[56,57]
Receptor gene name in humans	*TSLPR*	*IL1RL1: IL1RAP*	*IL17RA: IL17RB*	*TNFRSF25*
Expression of receptor	Widely expressed on immune and structural cells	Widely expressed on immune and structural cells	More restricted than that of TSLPR and ST2[27]	More restricted than that of TSLPR and ST2[58]
Signaling	JAKs, STAT5	NF-κB, AP1	NF-κB, AP1	TRADD, TRAF2, cIAP1/2, RIPKI
Activation of ILCs	ILC2[59]	ILC2[60,61]	ILC2[62]	ILC2,[63,64] ILC3[65,66]

conventional $CD4^+$ T cells.[73] DR3 mRNA and protein levels are low in resting T cells,[67] but activated T cells overexpress DR3.[87] For instance, CD3 ligation on $CD4^+$ T cells increases the expression of DR3; similarly, activation of naive $CD8^+$ T cells increase DR3 expression.[42] Although TL1A alone does not induce proliferation of T cells,[67] pretreatment with TL1A substantially increases anti-CD3/CD28–induced T-cell proliferation in response to IL-2. Similarly, TL1A costimulation leads to a marked increase in cytokine production by T cells.[67]

DR3 is expressed on T_H17 cells and TL1A is required for optimal differentiation of naive $CD4^+$ T cells.[88] TL1A also promotes the differentiation and cytokine release from human T_H17 cells.[89] The TL1A/DR3 axis promotes the differentiation of naive $CD4^+$ T cells into T_H1/T_H17 subsets that are impaired in *Tnfsf15*$^{-/-}$ mice.[44]

Innate lymphoid cells (ILCs), although comprising only a small percentage of lymphocytes, secrete copious amounts of cytokines.[90] There are 3 subtypes of ILCs classified by their transcription factors and cytokine profiles. Group 1 ILCs express T-bet and secrete IFN-γ. Group 2 ILCs (ILC2) are $ROR\alpha^+$ and $GATA3^+$ and release IL-13 and IL-5. Group 3 ILCs (ILC3) express RORγt and produce IL-17 and IL-22.[90] ILC2 and ILC3 display the highest levels of DR3. TL1A costimulated ILC2s[63] and ILC3s[66] and increased the release of IL-13 and IL-22, respectively.[63,65,66] DR3 activation can enhance the number and function of ILC2s in models of allergic disorders that are either T-cell dependent and independent.[63]

Treg cells express the cytokine receptor DR3,[91] and the TL1A/DR3 axis modulates the proliferation and suppressive functions of these cells.[30] In particular, TL1A enhances TCR/IL-2–induced Treg cell activation in mice.[91,92] The proliferative effects of TL1A on Treg cells has been recently confirmed in human *ex vivo* studies.[79] Intriguingly, Treg cell expansion in mice by TL1A prevents experimental airway inflammation.[91] Given the functional heterogeneity of human Treg cells,[93,94] further studies are needed to evaluate the TL1A/DR3 axis in the context of airway inflammation.

The TL1A/DR3 axis promotes the differentiation of murine T cells into T_H9 subset producing IL-9.[95] Moreover, TL1A priming induces a T_H9 cell phenotype in a mouse model and in humans.[96] Recently, it has been demonstrated that TL1A cooperates with IL-33 for the induction of $IL\text{-}9^{high}$ ILC2s in a model of airway inflammation.[29]

Mucosal-associated invariant T (MAIT) cells are an unconventional T-cell population activated through both TCR-dependent and -independent mechanisms.[97] MAIT cells recognize vitamin B_2-related metabolites produced by microbes presented by nonpolymorphic major histocompatibility complex class I–related protein 1, or MR1.[97] TL1A triggers human MAIT cell activation (ie, expression of IFN-γ, TNF-α, and granzyme B) in combination with suboptimal concentrations of IL-12 and IL-18.[98,99] IL-2, IL-15, and IL-18 significantly boost the expression of DR3 on MAIT cells.[99] Severe asthma is associated with deficiency of MAIT cells in both circulation and lung.[100] The TL1A/DR3 axis can contribute to their recruitment.[101] DR3 is also expressed on invariant natural killer T (iNKT) cells in the spleen, lymph nodes, and lung.[73] DR3 is a costimulatory molecule in a subset of iNKT cells.[73] DR3 expression has been also found in some γδ T cells.[101]

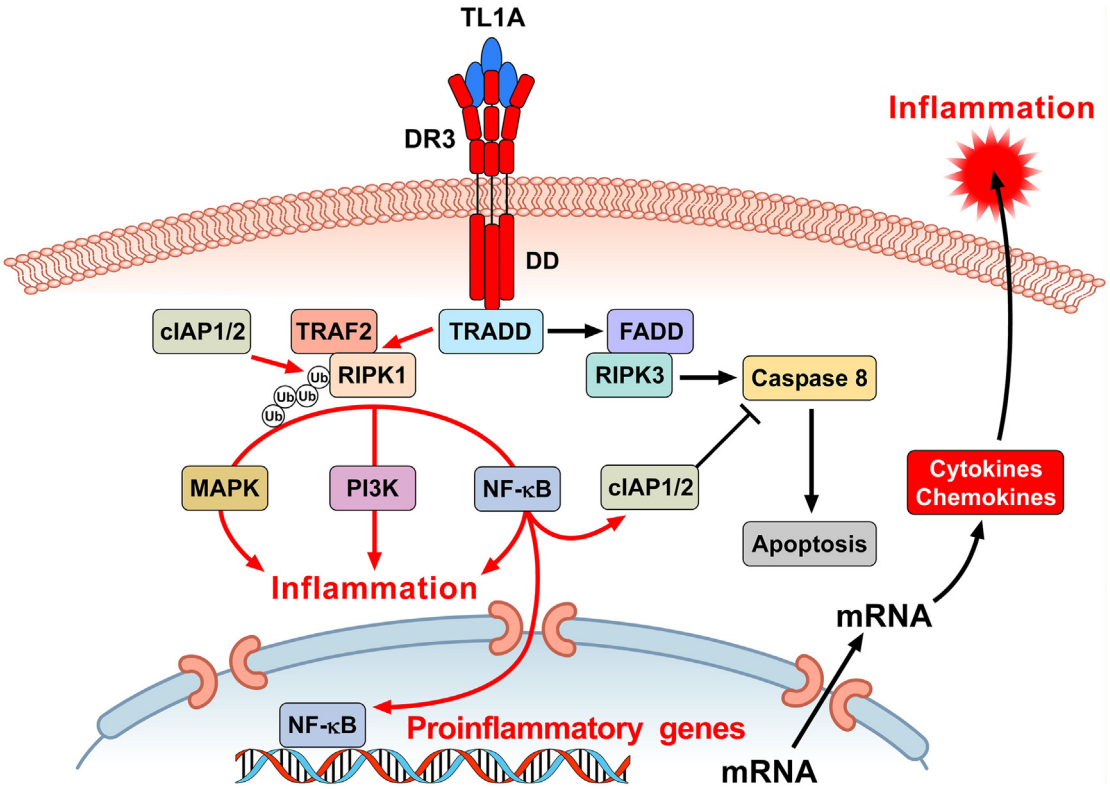

FIG 1. Activation of DR3 by TL1A can induce both proinflammatory and proapoptotic pathways. Two pathways can operate downstream of DR3 activation by TL1A. One pathway promotes proinflammatory effects through activation of DD motif in cytoplasmic tail of DR3, which recruits adaptor protein TRADD[83] that allows recruitment of TRAF2, cIAP1/2, and RIPK1.[84] Polyubiquitination of RIPK1 by cIAP1/2 activates mitogen-activated protein kinase (MAPKs), NF-κB, and phosphoinositide 3-kinase (PI3K) signaling pathways.[84] These 3 pathways induce cytokine gene expression leading to proinflammatory activities. Nuclear translocation of transcription factor NF-κB can activate transcription of various proinflammatory genes inducing production of cytokines and chemokines and promoting cell inflammation and cell proliferation.[85] In alternative pathway, TL1A can induce programmed cell death through recruitment of TRADD, which binds to FADD and RIPK3, activating caspase 8 and leading to apoptosis.[79] Modified with permission from Liman et al.[69]

There is evidence that human monocyte–derived macrophages[102] and mouse alveolar macrophages[78] express DR3. TL1A promotes macrophage foam cell formation in a macrophage cell line[103] and reactive oxygen species production from monocyte-derived macrophages.[102]

EXPRESSION AND RELEASE OF TL1A

Migone et al first identified TL1A mRNA in human endothelial cells.[67] They also demonstrated that TL1A was inducible by TNF-α and IL-1 and that DR3 was the receptor for the cytokine. In the same groundbreaking article, they demonstrated that TL1A induces cytokine release both *in vitro* and *in vivo*.[67] Immune complex–mediated activation of FcγR induces TL1A mRNA and protein release from human monocytes and monocyte-derived dendritic cells (DCs).[107-109] Lipopolysaccharide rapidly induces TL1A mRNA in mouse DCs.[53] Inflammatory bowel disease (IBD)-associated microbiota induces TL1A from mouse mononuclear cells.[66]

Using data from the LungMAP single-cell human lung atlas,[117] Schmitt et al have recently reported that TL1A is constitutively expressed in both type 1 (AT1) and type 2 (AT2) alveolar epithelial cells, as well as in basal cells of healthy human lungs.[29] These findings have been confirmed by analyzing the Human Cell Atlas single-cell RNA sequencing datasets of healthy and asthmatic lung epithelium.[52] Fig 3 supports the notion that TL1A could also be constitutively expressed by human lung monocytes and macrophages. Schmitt et al confirmed TL1A protein expression in the mouse lung and concluded that TL1A should be considered an alarmin cytokine, one expressed in alveolar epithelium and airway basal cells of both healthy and asthmatic human lungs.[29]

SYNERGISTIC EFFECTS OF TL1A ON IMMUNE CELL ACTIVATION

One of the most important characteristics of TL1A is the ability to synergize with different stimuli or immune cell activation (Table II).[117-124]

This fundamental property of TL1A was identified for the first time by Migone et al, demonstrating both *in vitro* and *in vivo* that this alarmin enhances the production of IFN-γ and granulocyte-macrophage colony-stimulating factor from human T cells activated by anti-CD3 plus anti-CD28.[67] The cooperation between

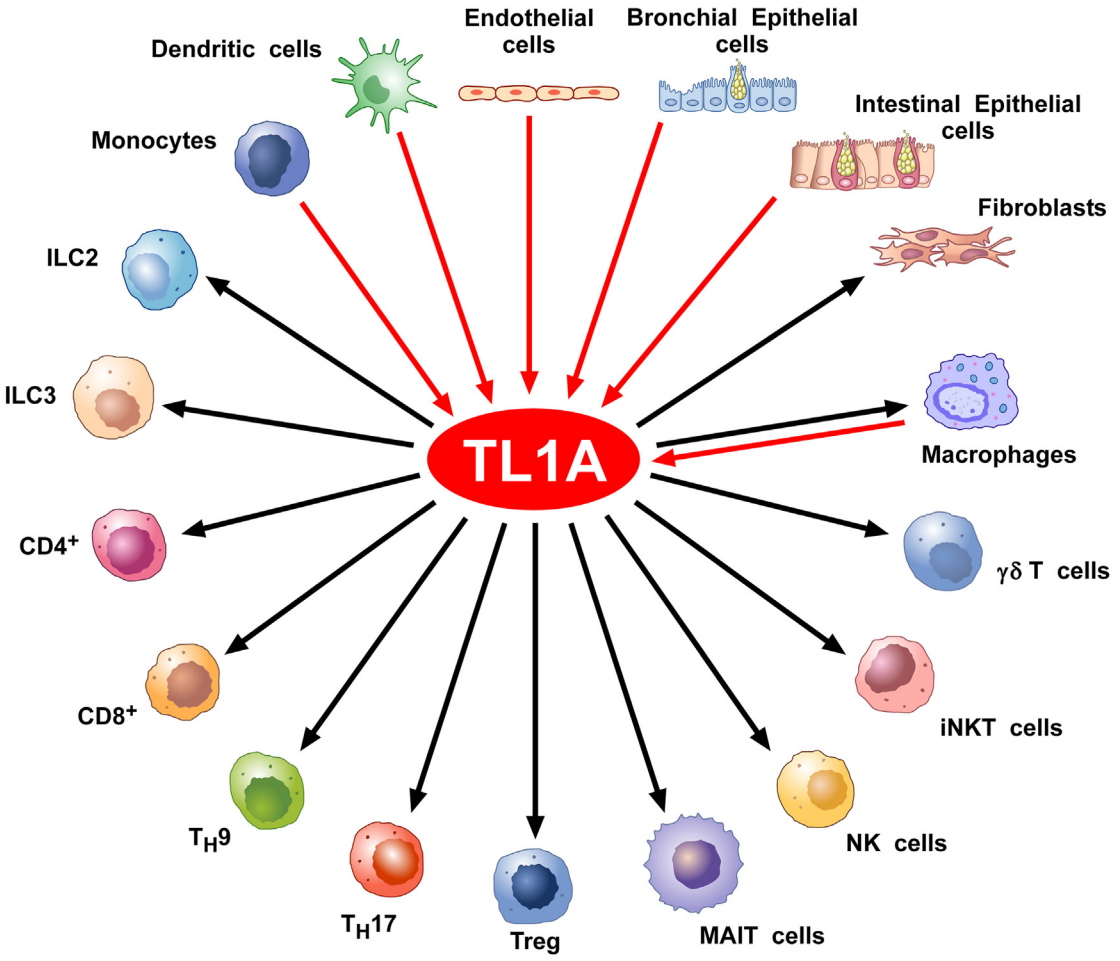

FIG 2. Schematic representation of cellular sources and targets of TL1A. Several triggers can activate lung,[29,104,105] gut epithelial cells,[106] and endothelial cells[67,76] to release TL1A. This alarmin can also be produced by activated human[104,107-109] and mouse monocytes[66] and DCs.[44,53,78] TL1A activates human[110] and mouse CD4$^+$[42,111] and CD8$^+$ T cells,[42] human[104] and mouse ILC2,[29,63] human[65] and mouse ILC3,[66,112] human[96] and mouse T_H9 cells,[29,96,113] human[88,111,112] and mouse T_H17 cells,[88] Treg cells,[79,92] human MAIT cells,[98,99] NK cells,[114] iNKT cells,[73] mouse iNKT cells,[73] mouse γδ T cells,[101] human monocyte-derived macrophages[102] and intestinal macrophages,[115] and human[116] and mouse lung fibroblasts.[78]

TL1A and different stimuli on immune cell activation has been extended by several studies in mice[29,53,111,124,125] and in humans.[89,119,120,122,123] Moreover, the synergism between TL1A and various stimuli has been documented *in vitro*[67,89,119,121-124] and *in vivo*.[29,67,125] In particular, TL1A potentiates the release of several cytokines released from CD4$^+$ T cells[53,67,110,119] and NK T cells.[86] TL1A potentiates the differentiation of mouse and human T_H17 cells[123] and synergizes with IL-17 on the expression of ADAMS in macrophages.[120] TL1A also enhances IL-22 secretion from human T_H17 cells.[89] TL1A synergizes with IL-23 and IL-1β to induce IL-22 from intestinal ILC3s.[121] TL1A also synergizes with IL-15 to induce several cytokines from CD4$^+$ T cells and proliferation of IL-18Rα$^+$CD4$^+$ T cells.[124]

Recently, Schmitt et al elegantly demonstrated that TL1A, expressed by human and mouse alveolar epithelium, synergizes with IL-33 for early induction of IL-9^{high} ILC2s during allergic airway inflammation.[29] This original observation is of great translational relevance for several reasons. First, it is the first demonstration of synergism between TL1A and IL-33 on the activation of ILC2s. Second, IL-33 and TL1A genes are located on the same chromosome (9p24.1 and 9q32, respectively). Finally, IL-33 has been implicated as a possible therapeutic target in several pathologic conditions, such as asthma,[6] chronic obstructive pulmonary disease,[126] and cancer.[127] The discovery of the synergism between IL-33 and TL1A in the pathobiology of airway inflammation suggests that the simultaneous targeting of these two alarmins could have a therapeutic advantage compared to the blockade of IL-33 alone.

TL1A AND AIRWAY INFLAMMATION

Asthma is a chronic airway inflammatory disease affecting approximately 10% of adults.[128] The heterogeneity of this immunologic disorder is evident through its various phenotypes, which vary in etiology, pathogenic mechanisms, clinical presentation, and severity.[129] Asthma can be divided into type 2–high (T2-high) and type 2–low (T2-low)[129,130] and can also be categorized into eosinophilic and noneosinophilic endotypes.[131]

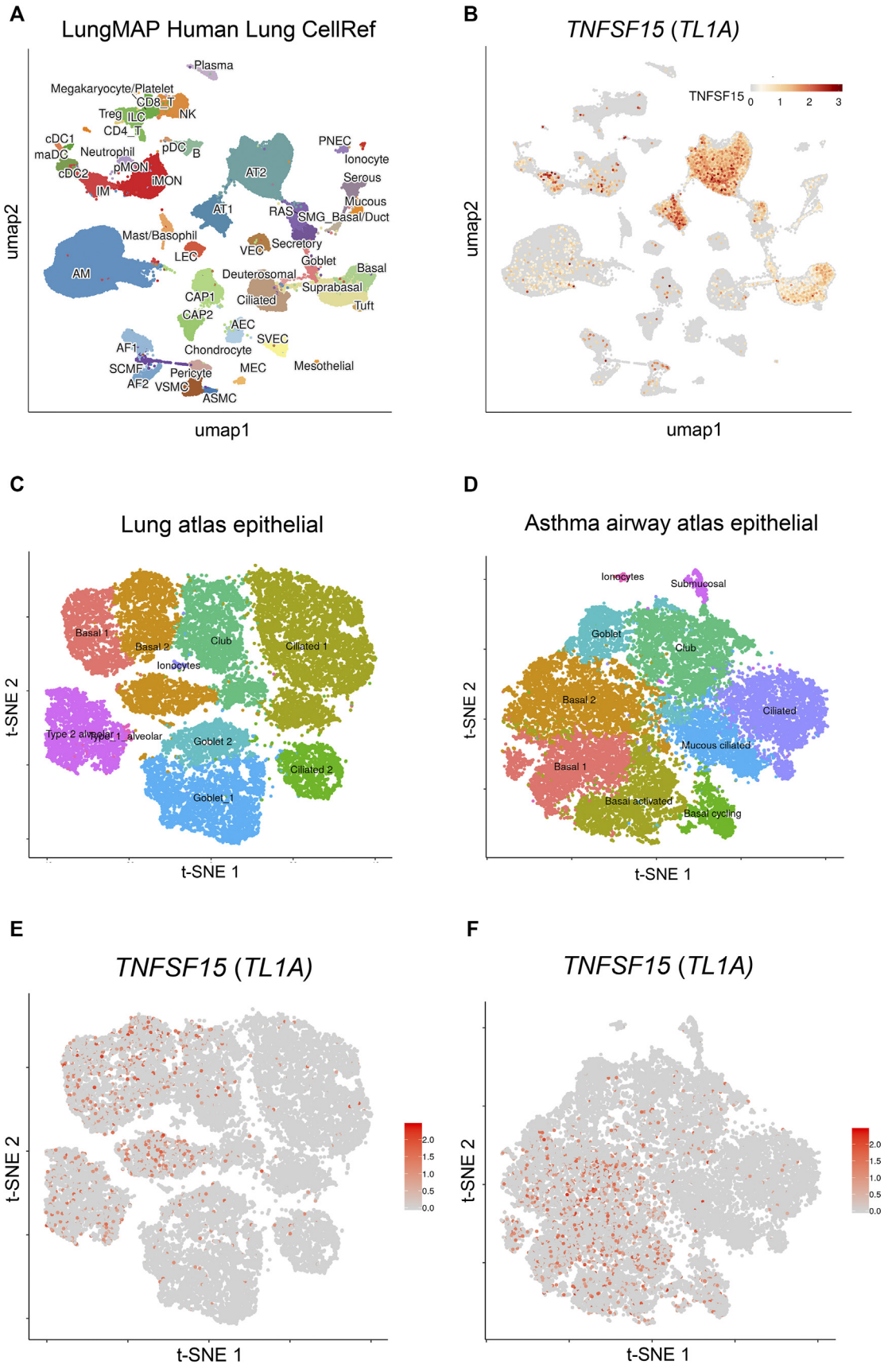

FIG 3. (**A** and **B**) Single-cell RNA sequencing (scRNA-Seq) analysis of TNFSF15 (TL1A) expression in LungMAP single-cell human lung atlas.[29] TL1 is expressed in human alveolar epithelial cells (AT1 and AT2) and airway basal cells. Results are based on data generated by LungMAP Consortium.[117] **(C-F)** scRNA-Seq analysis of TNFSF15 (TL1A) expression in epithelial cells from human healthy (*C* and *E*) and asthmatic (*D* and *F*) lungs. t-SNE plots were extracted from data obtained by human lung single-cell atlas[52] and downloaded from asthma.cellgeni.sanger.ac.uk. *t-SNE, t*-Distributed stochastic neighbor embedding.

TABLE II. Synergism between TL1A and different stimuli on activation of immune cells

Human	Mouse	*In vitro*	*In vivo*	Target cell type	Effects and references
+		+	+	Human T cells	TL1A synergizes with anti-CD3/anti-CD28 to induce release on IFN-γ and GM-CSF release from human T cells both *in vitro* and *in vivo*.[66]
+		+		Human $CD4^+$ T cells	TL1A synergizes with anti-CD3/anti-CD28 on production of IFN-γ from human $CD4^+$ cells.[107]
	+	+		Mouse NK T cells	TL1A synergizes with anti-CD3 on production of IL-13 from mouse NK T cells.[85]
	+	+		Mouse $CD4^+$ T cells, mouse T_H17 cells	TL1A potentiates production of IL-2 from mouse $CD4^+$ cells activated by anti-CD3/anti-CD28; TL1A potentiates mouse T_H17 differentiation.[87]
	+	+		Mouse $CD4^+$ T cells	TL1A potentiates proliferation and cytokine (IL-2, IFN-γ, IL-4) production from mouse $CD4^+$ cells.[52]
	+		+	Mouse $CD8^+$ T cells	TL1A promotes proliferation of antigen-specific mouse $CD8^+$ T cells *in vivo*.[115]
+		+		Human $CD4^+$ T cells	TL1A synergizes with anti-CD3 on cytokine (IFN-γ, TNF-α, IL-2) from human $CD4^+$ T cells *in vitro*.[116]
+				Human macrophages	TL1A synergizes with IL-17 on expression of ADAMTS-1, -4, and -5 in human macrophages.[117]
	+	+		Mouse ILC3	TL1A synergizes with IL-23 and IL-1β to induce IL-22 from mouse intestinal ILC3.[118]
+		+		Human peripheral blood mononuclear cells	TL1A synergizes with IL-12, IL-15, and IL-18 to induce TNF-α and IL-6 from human peripheral blood mononuclear cells.[119]
+		+		Human $CD4^+$ T cells	TL1A enhances T_H17 differentiation of naive $CD4^+$ T cells isolated from RA patients induced by TGF-β and IL-6 and IL-17A release.[120]
+		+		Human $CD4^+$ T cells	TL1A synergizes with IL-15 to induce cytokines (INF-γ, IL-6, TNF-α, GM-CSF, IL-5, IL-13) from human $CD4^+$ T cells. TL1A and IL-15 synergize to induce proliferation of IL-$18R\alpha^+$ of human $CD4^+$ T cells.[121]
+		+		Human T_H17 cells	TL1A enhances secretion of IL-22 from human T_H17 cells.[88]
+		+	+	Human T cells	TL1A synergizes with anti-CD3 to induce IFN-γ release from human T cells *in vitro* and *in vivo*.[108]
	+		+	Mouse granulopoiesis	TL1A synergizes with IL-18 to promote GM-CSF–dependent thymic granulopoiesis in mice.[122]
	+		+	Mouse ILC2	TL1A synergizes with IL-33 to promote IL-9^{high} ILC2s during allergic airway inflammation in mice.[29]

GM-CSF, Granulocyte-macrophage colony-stimulating factor.

Approximately 6% of asthma patients have severe asthma, which is associated with a higher risk of exacerbations, hospitalizations, and mortality.[132]

In T2-high asthma, immunologic stimuli (eg, allergens in sensitized subjects, viral and bacterial superantigens, and pollutants) activate key effector cells in allergic responses (ie, mast cells and basophils) via the interaction with specific IgE, leading to the production of several cytokines (eg, IL-3, IL-4, IL-5, and IL-13). Eosinophils play a role in IgE-mediated asthma, particularly in eosinophilic asthma. T2-low asthma is less common than T2-high disease;[133,134] it is heterogeneous and presumably comprises multiple phenotypes involving mast cells, macrophages, neutrophils, and/or a combination of these immune cells.[129,130] Alarmins derived from bronchial epithelial cells (eg, TSLP, IL-33, and IL-25) act as upstream cytokines that trigger immunologic processes ultimately leading to airway remodeling.[3,135] The latter is a complex process characterized by goblet cell metaplasia, fibroblast and myofibroblast activation,[136] and overexpression of angiogenic factors[137,138] that result in structural changes of the blood vessels and bronchial walls. These alterations contribute to a narrowing of the airways and increased stiffness, ultimately causing severe respiratory symptoms.

An early study in a mouse model of airway inflammation reported that TL1A/DR3 axis is critical for T_H2 polarization and IL-13 production.[86] Interestingly, antibody blockade of TL1A before antigen exposure inhibits lung inflammation and IL-13 production. Meylan et al have elegantly demonstrated that TL1A promotes experimental airway inflammation through the activation of DR3 on ILC2s.[63] The same group of investigators have demonstrated in a mouse model of allergic immunopathology that TL1A enhances T_H9 differentiation and pathogenicity.[95] Interestingly, a recent study in subjects with eosinophilic asthma has reported that the TL1A/DR3 axis is a costimulator of ILC2s.[104] This is particularly relevant in severe asthma patients where IgG against eosinophil peroxidase or immunoglobulin heterocomplexes induced by an IgG_1 anti–IL-

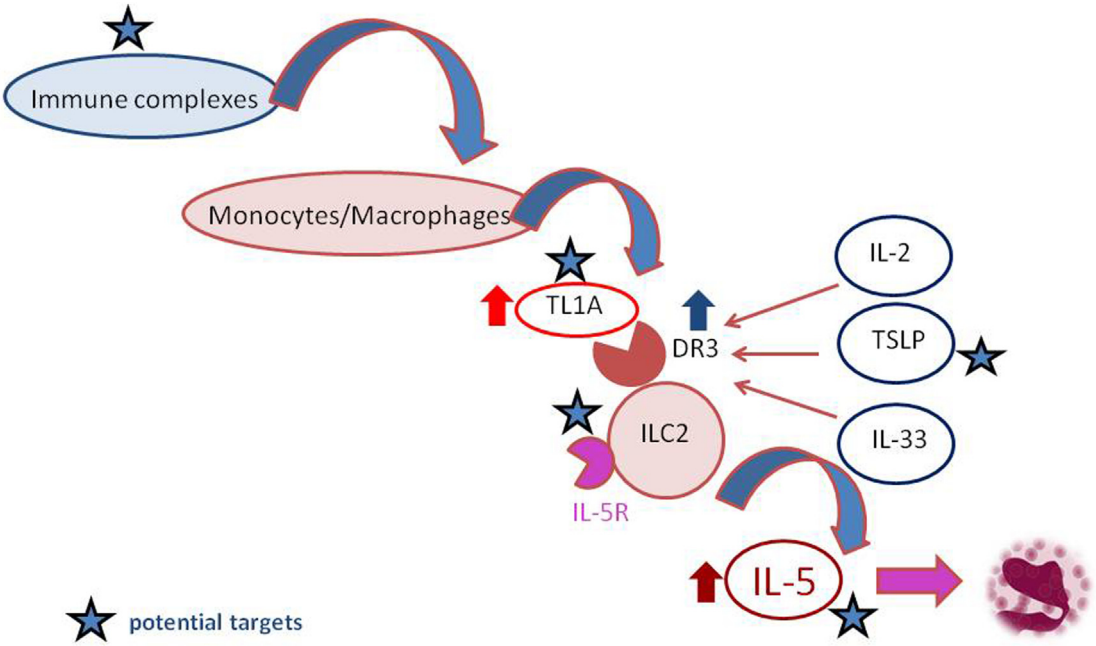

FIG 4. Immune complexes activate ILC2 cells. Antieosinophil peroxidase (EPX) IgG and immunoprecipitated immunoglobulins in airway of patients with severe asthma can activate human monocyte-derived macrophages to release TL1A. IL-2, TSLP, and IL-33 can upregulate DR3 expression on ILC2. TL1A engages DR3 receptor on ILC2 to release IL-5, which activates human eosinophils.[104]

5 monoclonal antibody (mAb) (ie, mepolizumab)[139] could stimulate the release of TL1A from airway macrophages.[104] TL1A can stimulate ILC2 cells through DR3, resulting in the release of IL-5 and IL-13.[104] The latter mechanism and/or an inadequate neutralization of IL-5 in the airways (eg, underdosing or sequestration of anti–IL-5 due to immune complexes) might contribute to explain the paradoxical persistence or increase of eosinophils in the airways of patients with suboptimal response to mepolizumab (Fig 4).[139]

Recently, Zhang et al demonstrated that the TL1A/DR3 axis is upregulated in bronchial biopsy samples of asthmatic patients and in a mouse model of airway inflammation.[105] The deletion of the TL1A/DR3 axis by knocking out the *TL1A* gene improves airway inflammation and epithelial–mesenchymal transformation of epithelial cells.[105] Finally, ovalbumin-challenged mice exhibit increased airway inflammation, tissue remodeling, and airway hyperreactivity after intratracheal administration of TL1A. The same group reports that TGF-β1 increases the expression of TL1A mRNA in the bronchial epithelial cell line BEAS-2B.[140] The levels of TL1A in both induced sputum and bronchoalveolar lavage fluid are increased in asthmatic patients compared to healthy subjects.[140] Moreover, sputum TL1A levels are increased after allergen challenge compared to preallergen levels in subjects with mild asthma.[104] These studies provide evidence of TL1A expression in the airways of asthmatic subjects.

Vieira Braga et al have made the groundbreaking demonstration that TL1A is constitutively expressed mainly by AT2 and AT1 cells in human lung.[52] They have found that interstitial macrophages and inflammatory monocytes also express TL1A. Importantly, TL1A is overexpressed in epithelial cells of asthmatic lung compared to healthy donor.[52,105] Recently, Schmitt et al have also demonstrated that TL1A, constitutively expressed in alveolar epithelium in both mice and humans, cooperates with IL-33 for early induction of IL-9^{high} ILC2s in the initiation of allergic airway inflammation.[29] This elegant study has highlighted the synergistic activation by TL1A and IL-33 of ILC2s to promote IL-5–dependent airway inflammation. Collectively, these innovative results demonstrate that TL1A is a novel alarmin and an important cofactor of IL-33–induced airway inflammation.[29]

ILC3s express DR3 and TL1A promotes the activation of these cells.[65,66] Moreover, DR3 is expressed on human T_H17 cells and TL1A induces their differentiation and cytokine release via IL-9 induction.[89] Finally, the TL1A/DR3 axis promotes T-cell differentiation into T_H9 subset producing IL-9 and IL-13 in mouse models of allergic immunopathology[29,95,96] and in humans.[96] Finally, Niese et al have demonstrated that anti-TL1A treatment decreases T_H9 cells and airway hyperreactivity in a mouse model of airway inflammation.[96] Collectively, these findings suggest that TL1A/DR3 axis might be relevant to different endotypes of asthma (eg, T_H17, T_H9) or even T2-low asthma.

A genome-wide association study has recently identified TNFSF15 variants associated with a cohort of Korean asthmatic children. It will be interesting to know how risk variants of *TNFSF15* may affect TL1A concentrations in the bronchoalveolar lavage fluid of asthmatic subjects.[141]

TL1A AND AIRWAY REMODELING

Airway remodeling in asthma is marked by structural changes, such as subepithelial matrix protein deposition and fibrosis, goblet cell metaplasia, hyperplasia/hypertrophy of airway smooth muscle (ASM) cells, and inflammatory angiogenesis.[136,137,142]

Accumulation of extracellular matrix proteins in the reticular basement membrane, lamina propria, and submucosa contributes to the airway wall thickening and airflow obstruction in asthma.[143] ASM hypertrophy/hyperplasia contributes to airway remodeling.[144] The damage of the airway epithelium is a key element of the innate immune response and serves as the trigger for airway remodeling in asthma.[142,145] A plethora of environmental insults (eg, allergens, cytokines, microbial proteins, smoke extracts, and pollutants) activate epithelial cells to release TSLP,[3,146] IL-33,[145] and IL-25/IL-17E,[135] which activate a wide spectrum of immune cells involved in the pathogenesis of airway remodeling.[7,9,10,15,147]

TL1A injection into the mouse lungs promotes airway remodeling and fibrosis mediated by the activation of DR3.[78] TL1A is expressed after house dust mite challenge in macrophages, the most prevalent immune cells in the lung.[52] DR3 is constitutively expressed on alveolar macrophages and after house dust mite challenge. Mouse and human lung fibroblasts express DR3- and TL1A-induced fibroblast proliferation and promote the production of collagen and periostin,[78] two cardinal features of lung fibrosis.[138,147] Importantly, in mice lacking DR3, house dust mite administration attenuates collagen accumulation and lung smooth muscle mass compared to wild-type mice.[78] In another study, TGF-β increases TL1A mRNA in human bronchial epithelial cells (BEAS-2B).[140] TL1A is overexpressed in bronchial biopsy samples of asthmatic patients compared to controls and TL1A levels in sputum, and levels in bronchoalveolar lavage fluid in asthmatic subjects are higher compared to controls.[140] In the same study, the authors report that intratracheal instillation of TL1A promotes collagen accumulation and airway remodeling. Similarly, ovalbumin-challenged mice exhibit increased airway inflammation and remodeling associated with hyperresponsiveness to methacholine.[140] Importantly, DR3 knockdown alleviates ovalbumin-induced airway inflammation and remodeling. Collectively, these studies emphasize the crucial role of the TL1A/DR3 axis in cardinal features of airway remodeling, such as activation of lung fibroblasts and macrophages and involvement of TL1A in bronchial epithelial cells.

The exact source of TL1A that might be crucial to airway remodeling is presently largely unclear, but prior studies have demonstrated that this alarmin can be made by epithelial cells,[29,52] endothelial cells,[67] macrophages,[52,78] monocytes,[104,107] and DCs.[44] The normal human lung contains at least 48 immune and structural cell types.[117] Future studies should determine whether other normal immune and structural cells in the lung or those from asthmatic patients can produce TL1A.

Mucus overproduction and mucus plugging, critical features of severe asthma and chronic obstructive pulmonary disease,[148] can be associated with increased morbidity and mortality.[149] IL-13 plays a central role for mucus overproduction via direct effects on goblet cells.[150] Intratracheal administration of TL1A in mice induces mucus production from goblet cells.[151] This effect is mediated, at least in part, by the release of IL-13 from ILC2s activated by TL1A. Importantly, genetic deletion or blocking DR3 inhibits IL-13 and mucus production by goblet cells in allergen-induced asthma.[151]

Collectively, these studies suggest that aside its proinflammatory role in airway inflammation, TL1A can promote several cardinal features of airway remodeling. Fig 5 schematically illustrates the potential mechanisms of TL1A involvement in human and experimental models of airway remodeling. These findings have translational relevance implying that targeting TL1A appears a novel approach to treat airway inflammation and remodeling associated with asthma and chronic obstructive pulmonary disease.

TL1A AND INTESTINAL INFLAMMATION

The IBDs are chronic intestinal disorders, including Crohn disease (CD) and ulcerative colitis (UC).[152] Mucosal inflammation in UC initiates in the rectum and extends proximally in the colon in a continuous fashion.[153] Mucosal inflammation in UC is characterized by transmural inflammation, which can lead to ulcerations, fibrotic strictures, fistulas, and abscesses. In contrast, inflammation in CD shows patchy lesions scattered anywhere in the gastrointestinal tract. Despite some common immunologic features, there are important differences between UC and CD pathobiology[154] and genetic aspects. A comprehensive understanding of the underlying pathobiological mechanisms resulting in these divergent IBDs is still lacking.

Certain polymorphisms in the *Tnfsf15* gene have been linked to CD in Japanese and European cohorts.[155-157] In two animal models of CD, DR3 expression and TL1A production are increased in the intestinal mucosa,[87] and DR3 expression in lymphocytes is also induced via an alternative mRNA splice mechanism.[158] Furthermore, DR3 signaling causes the proliferation of effector memory T cells, indicating that DR3 activation could potentially exacerbate intestinal inflammation.[77]

Genome-wide association studies have linked TL1A single nucleotide polymorphisms with severe UC[159] and CD.[160] (A complete list of studies is provided by Valatas et al.[30]) Moreover, TL1A is upregulated in IBD tissue and expression level correlated to disease severity.[161] In two murine models of chronic colitis, TL1A appears to be an important cytokine that not only modulates mucosal inflammation but also induces intestinal fibrosis[162] through the activation of intestinal fibroblasts.[163] In a mouse model, TL1A-mediated intestinal inflammation and fibrosis is dependent on the gut microbiome.[164] The same group of investigators have demonstrated that the administration of anti-TL1A antibody reduces intestinal inflammation and fibrosis in mouse models of chronic colitis.[165] Moreover, preclinical studies in colitis models have shown that anti-TL1A antibodies can reduce fibroblast-mediated fibrosis and clinical disease score.[166] A recent phase 2 trial has demonstrated that a humanized IgG_1 kappa mAb (tulisokibart), which binds to the membrane-bound and soluble forms of TL1A, induces clinical remission in patients with active moderate-to-severe UC.[167] Tulisokibart administration over a period of 3 months is associated with endoscopic and histologic improvements, mucosal healing and progressive decrease of inflammatory biomarkers (ie, fecal calprotectin and serum C-reactive protein) in UC patients.

TL1A AND AUTOIMMUNE DISORDERS

Rheumatoid arthritis (RA) is a systemic autoimmune condition associated with dysregulated expression of DR3 and/or TL1A. In patients with RA, serum and synovial fluid concentrations of TL1A positively correlate with disease severity.[107] TL1A is involved in collagen-induced arthritis, a canonical model for RA.[168] Moreover, DR3-knockout mice develop less bone

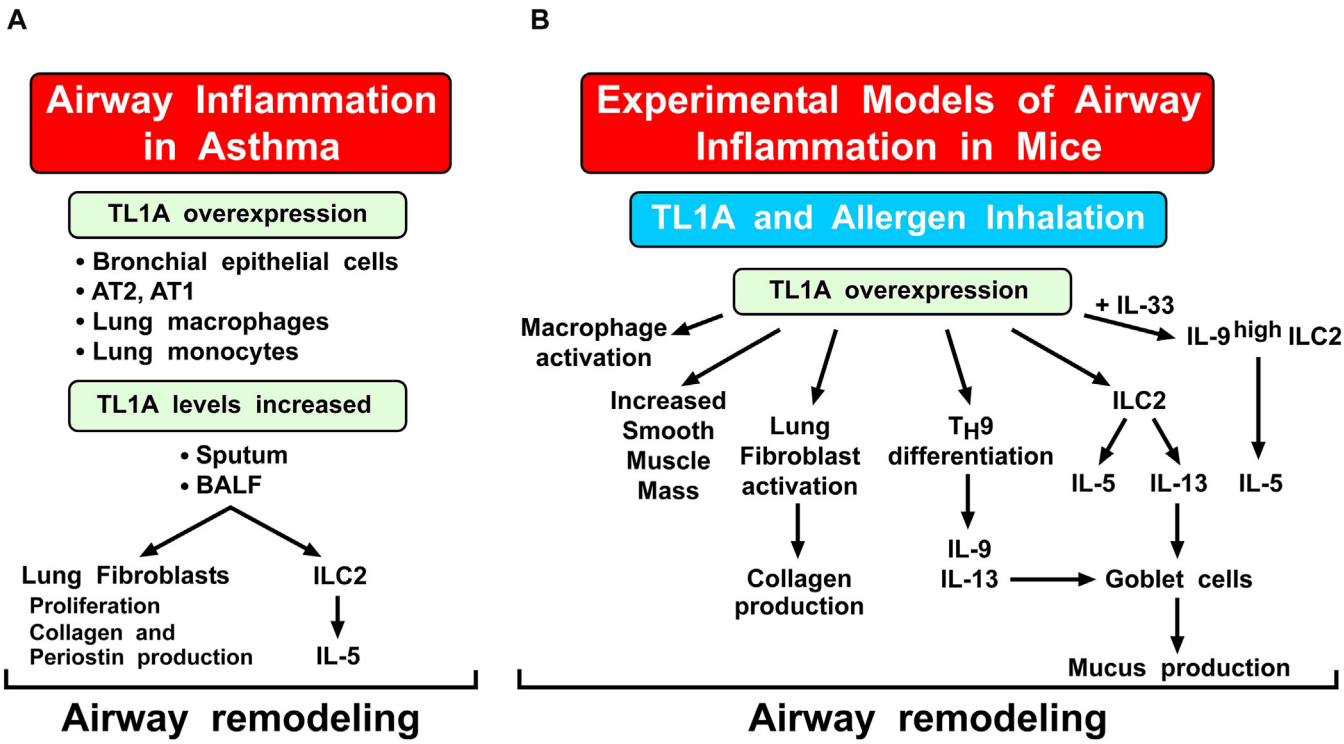

FIG 5. Potential mechanisms of TL1A involvement in human and experimental models of airway remodeling. TL1A is overexpressed in bronchial biopsy samples of asthmatic patients and experimental airway inflammation.[105] **(A)** TL1A is overexpressed by human lung AT2 and AT1 cells and by macrophages and monocytes in asthmatic patients compared to healthy donors.[52] TL1A levels in sputum supernatant and bronchoalveolar lavage fluid (BALF) samples is increased in asthmatic patients compared to controls.[104,140] TL1A activates human IL-5$^+$ ILC2.[104] TL1A induces proliferation of human lung fibroblasts and production of collagen and periostin through engagement of DR3.[78] **(B)** In experimental mouse models, TL1A inhalation and allergen challenge induce activation and proliferation of lung fibroblasts, collagen accumulation, increased smooth muscle mass, and activation of alveolar macrophages.[78,140] TL1A promotes differentiation of T cells into T_H9 subset producing IL-9 and IL-13.[29,113] Intratracheal administration of TL1A induces activation of ILC2 to release IL-13, which activates goblet cells to promote mucus production.[151] Allergen inhalation in mice rapidly releases TL1A from bronchial epithelial cells cooperating with IL-33 to promote IL-9–producing ILC2s and IL-5–dependent eosinophilic airway inflammation.[29] Collectively, these findings suggest that TL1A might play crucial role in airway remodeling in asthma and in experimental models of airway inflammation.

pathology in antigen-induced arthritis.[169] These findings suggest that the TL1A/DR3 axis plays a role in the cytokine network contributing to the pathobiology of RA. Further experimental and clinical studies are warranted to explore the therapeutic potential of blocking the TL1A/DR3 axis in RA.

Psoriasis is a chronic inflammatory disease primarily affecting the skin. Although traditionally classified as an organ-specific autoimmune disease, increasing evidence supports that psoriasis is a systemic inflammatory disorder extending beyond the skin.[170] In the imiquimod-induced psoriasis model, TL1A has been implicated in psoriasis development through the stimulation of T_H17 immunity.[171] Exogenous TL1A exacerbates the psoriatic phenotype, while treatment with anti-TL1A blocking mAb reduces the disease burden.[171] TL1A expression is upregulated in infiltrating inflammatory cells, keratinocytes, and endothelial cells from psoriatic patients.[172] Collectively, these findings suggest that the TL1A-DR3 axis plays a pathogenic role in psoriasis as well. Blockade of TL1A/DR3 axis needs further studies in psoriasis.

CONCLUSIONS AND PERSPECTIVES

TL1A, a cytokine identified in human endothelial cells, was originally characterized by its ability to activate CD4$^+$ T cells in humans and mice.[67] There is compelling evidence that TL1A can directly and/or indirectly activate a wide range of immune and nonimmune cells involved in various allergic[29,104] and chronic inflammatory disorders.[77,173]

During the last decades, significant progress has been made in understanding the biology of TL1A/DR3 pathway in both healthy and pathologic contexts. Genetically modified animal models have been instrumental in elucidating the role of TL1A and its receptor in disease models, such as asthma, colitis, arthritis, and psoriasis.[44,77] Furthermore, genetic associations between the TL1A/DR3 axis and human diseases have shed light on the distinct functions mediated by this pathway.[159,160] Finally, genetically modified animals have provided useful information into various diseases that could benefit from therapies targeting the TL1A/DR3 axis. Several experimental and human studies have demonstrated that TL1A activates and/or

TABLE III. Biologics targeting TL1A currently under investigation in clinical trials

Biologic	Clinical trial/ study	Results
RVT-3101 (previously PF-06480605)	NCT01989143	Phase 1 in healthy subjects. PF-06480605 is generally well tolerated; binding of soluble TL1A is maintained throughout dose interval.
	NCT05107492	Phase 1 in Chinese healthy subjects.
	NCT04269538	Phase 1 in Japanese healthy subjects.
	NCT05471492	Phase 2 in adults with moderate-to-severe CD.
	NCT02840721[176]	Phase 2 in subjects with moderate-to-severe UC. PF-06480605 demonstrates acceptable safety profile and significant endoscopic improvement.
	NCT04090411	Phase 2b in subjects with moderate-to-severe UC.
	NCT05910528	Phase 2 in subjects with moderate-to-severe CD.
Tulisokibart (previously MK-7240/PRA023)	NCT05354349	Phase 1.
	NCT04676178	Phase 1.
	NCT05013905[178]	Phase 2a in subjects with moderate-to severe active CD (APOLLO-CD). Tulisokibart has acceptable safety profile and significant reductions from baseline in CRP and fecal calprotectin.
	NCT05270668	Phase 2 in subjects with systemic sclerosis associated with interstitial lung disease (ATHENA-SSC-ILD).
	NCT04996797[165]	Phase 2 in subjects with moderate-to-severe UC (ARTEMIS-UC). Tulisokibart induces clinical remission in patients with UC.
	NCT06430801	Phase 3 in subjects with moderate-to-severe CD.
	NCT06052059	Phase 3 in subjects with moderate-to-severe UC.
TEV-48574	NCT04545385	Phase 2 in subjects with asthma.
	NCT05499130	Phase 2 in subjects with moderate-to-severe UC or CD (RELIEVE UCCD).
	NCT05668013	Phase 2 in subjects with moderate-to-severe UC or CD.
SPY002	Hassan-Zahraee[175]	Preclinical study.

CRP, C-reactive protein.

cooperates with other stimuli to activate a wide spectrum of immune cells.

Most of the studies conducted so far have focused on the expression of DR3 and the immunologic effects of TL1A on several subpopulations of T lymphocytes and other immune cells (ie, ILCs, $CD4^+$ and $CD8^+$ T cells, T_H9, T_H17, Treg cells, MAIT cells, NK cells, and iNKT cells). Further research should investigate whether TL1A, alone or in combination with other immunologic stimuli, can activate relevant peripheral blood (eg, eosinophils, basophils, and neutrophils) and tissue-resident immune cells (eg, macrophages and mast cells) that play a key role in the pathobiology of several immune disorders, such as allergic and intestinal diseases.

TL1A is well known as an amplifier of cytokine production[66] and signaling.[30] Although in several cases TL1A alone is not a particularly potent stimulus, the synergism between this alarmin and a wide spectrum of stimuli confers this property a clinical relevance in different pathologic disorders.

TL1A exists as a membrane-bound or soluble protein. The latter can be produced either via alternative mRNA splicing or through proteolytic cleavage mediated by extracellular matrix metalloproteinases.[42] The canonical alarmins—TSLP[10,36] and IL-33[39]—can be cleaved by several extracellular proteases. There is emerging evidence that cleavage products of both TSLP[10] and IL-33 exert different effects compared to the native proteins.[39] Recent studies have already revealed different effects of soluble versus1 membrane-bound TL1A.[68] Additional studies are needed to evaluate the functions of the two forms of TL1A in the pathobiology of several inflammatory disorders.

The expression of DR3 on human lung fibroblasts and the ability of TL1A to promote fibroblast proliferation and collagen accumulation highlights the relevance of TL1A/DR3 pathway in several chronic inflammatory diseases characterized by tissue remodeling,[78] such as severe asthma[138,142] and IBD.[174] The recent demonstration that tulisokibart, a mAb anti-TL1A, induced clinical remission in patients with active UC opens the possibility that targeting the TL1A/DR3 pathway might arrest, or even reverse, intestinal and perhaps lung fibrosis. Further studies appear necessary to better understand the role of TL1A/DR3 axis in various forms of fibrosis. Moreover, studies are urgently needed to evaluate the efficacy and safety of tulisokibart in patients with inflammatory airway disorders characterized by tissue remodeling.

A recent groundbreaking article has demonstrated that TL1A is a novel alarmin preferentially expressed by human AT1 and AT2 cells.[29] The study's authors have proposed that allergens rapidly release TL1A from bronchial epithelial cells that cooperate with IL-33 to promote IL-9–producing ILC2s and IL-5–dependent eosinophilic asthma. Interestingly, in a phase 2 study evaluating anti-TL1A in patients with UC, there is a reduction of serum IL-5,[175] a key cytokine in allergic and eosinophilic asthma.[176] Given the role of TL1A in different experimental models of asthma,[29,96,104] this cytokine appears an attractive therapeutic target. A phase 2 trial is evaluating the safety and efficacy of a mAb anti-TL1A (TEV-48574) in subjects with asthma (NCT04545385) (Table III). Further research is required to investigate the role of TL1A/DR3 pathway in driving eosinophilic and noneosinophilic asthma in humans.

Currently, 4 anti-TL1A mAbs are under investigation in preclinical (SPY002)[177] or clinical trials: RVT-3101 (previously PF-06480605),[166,178] tulisokibart (previously MK-7240 and PRA023),[167] and TEV-48574.[179] Table III summarizes the results from several clinical trials assessing the efficacy and safety of these mAbs targeting TL1A in patients with UC, CD, and asthma.[180] The recent demonstration that tulisokibart induced clinical remission in UC[167] suggests that the range of the disease targets for these biologics will expand in the near future to other inflammatory disorders, such as bronchial asthma, RA, and psoriasis.

Given the complexity of the interactions between TL1A and DR3 on a plethora of immune cells involved in different diseases, further research may uncover new insights into this intriguing signaling pathway. The coming years are expected to yield significant insights into the efficacy of biologics targeting TL1A or its DR3 receptor in clinical settings.

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