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Interleukin-17-producing γδ T (γδ17) cells in inflammatory diseases

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Summary

Interleukin-17 (IL-17) is a pro-inflammatory cytokine and is involved in the development of many diseases. Recent studies have revealed that IL-17-producing γδ T cells (γδ17 cells) in addition to IL-17-producing CD4$^+$ T cells [T helper type 17 (Th17) cells] are often the main producers of IL-17 in mouse models of inflammatory diseases. γδ T cells are functionally committed during intra-thymic differentiation. γδ thymocytes capable of producing IL-17, which express the transcription factor retinoic-acid-receptor-related orphan receptor γt and the signature cytokine receptor IL-23R, leave the thymus, and produce IL-17 rapidly by *the* stimulation with IL-1β and IL-23 in the periphery. Therefore, γδ17 cells play important roles in the early phase of host defence against pathogens and in inflammatory diseases. γδ T cells that can produce IL-17 are also increased in the skin of patients with psoriasis and in peripheral blood of patients with ankylosing sclerosis. Indeed, the therapy targeting IL-17 has been approved or is in clinical trials, and proved to be very efficient to treat psoriasis, psoriatic arthritis and ankylosing sclerosis. In this review, we discuss recent knowledge about the pathophysiological function of γδ17 cells in infection and inflammatory diseases and therapeutic advances targeting IL-17.

Keywords: cytokines; inflammatory disease; pathogen clearance.

Introduction

Interleukin-17A (IL-17A, called 'IL-17' hereafter) is a member of the IL-17 family.[1] The binding of IL-17 to the heterodimeric receptor consisting of IL-17RA and IL-17RC subunits transduces signals to activate a group of cytokines and chemokines such as tumour necrosis factor, IL-1, IL-6, granulocyte colony-stimulating factor, CXCL1 and CXCL2 through activation of the actin related gene 1-TNF receptor associated factor 6–nuclear factor-κB axis in the downstream.[1] The function of IL-17 is pleiotropic. It plays a crucial role in the host defence against bacterial and fungal infection by inducing pro-inflammatory cytokines and chemokines, recruiting neutrophils, and activating T cells and B cells.[1,2] Mice deficient for IL-17RA are highly susceptible to *Klebsiella pneumoniae*[3] and IL-17-deficient mice are susceptible to bacterial and fungal infection.[4,5] Interleukin-17 is also implicated in various inflammatory/autoimmune disease models such as experimental autoimmune encephalomyelitis (EAE), arthritis in IL-1 receptor antagonist-deficient (*Il1rn*$^{-/-}$) mice and imiquimod-induced psoriatic dermatitis in mice.[6–10] Anti-IL-17 and anti-IL-17RA antibodies are effective to treat patients with psoriasis and psoriatic arthritis.[11–13] Interleukin-17 is also important for the maintenance of intestinal barrier integrity and its functional deficiency causes the development of inflammatory bowel diseases.[14–16] In contrast, suppression of IL-17F, another highly homologous member of IL-17 family, is suggested to be beneficial for the treatment of inflammatory bowel diseases.[17]

Interleukin-17 was initially found to be produced by helper CD4$^+$ T [T helper type 17 (Th17)] cells, but subsequent studies showed that innate immune cells and innate-like immune cells are also important sources of IL-17 in inflamed tissues.[18,19] γδ T cells are the principal source of IL-17 in some mouse inflammatory disease models and thereby exert considerable impact on disease development and progression.[20–24] The IL-17-producing γδ T cells (γδ17 cells) share many features with Th17 cells, such as cell surface expression of IL-23R and CCR6 and the expression of transcriptional factor retinoic-acid-receptor-related orphan receptor γt (RORγt). To induce IL-17, naive T cells have to differentiate into Th17 cells in the periphery by the stimulation with T-cell receptor

(TCR) and cytokines such as IL-6 and transforming growth factor-β. In contrast, the functional potential to produce IL-17 in γδ17 cells is already established during intra-thymic development[25–27] and IL-17 is directly induced by IL-23 and IL-1 without TCR stimulation in the periphery. This pre-programming contributes to rapid IL-17 production in peripheral tissues in the early phase of pathogen infection. In this review, we would like to introduce the roles of γδ17 cells in inflammatory diseases and recent therapeutic advances targeting IL-17.

γδ T-cell subsets and their development

γδ T cells and αβ T cells are generated in thymus from common progenitor cells. Unlike αβ T cells, γδ T cells are functionally committed during intra-thymic differentiation.[28,29] In mice, the TCR-γ locus consists of seven Vγ (Vγ1–Vγ7) genes (Heilig & Tonegawa's nomenclature[30]) that are closely correlated with the effector function, although Vγ3 is a pseudogene in most mouse strains.[31] Production of IL-17 is mostly limited to Vγ4$^+$ and Vγ6$^+$ γδ T cells,[32] although Vγ1$^+$ γδ T cells also produce IL-17 in some cases.[33] On the other hand, interferon-γ (IFN-γ) production is associated with Vγ1$^+$, Vγ5$^+$ and Vγ7$^+$ γδ T cells. Although overall gene expression patterns are similar between Vγ4$^+$ and Vγ6$^+$ subsets,[34] each subset has distinct features (Fig. 1). Vγ6$^+$ γδ T cells express the invariant Vγ6/Vδ1 TCR, develop only in the late embryonic thymus and preferentially localize to the uterus, vagina, lung, dermis and peritoneal cavity.[35,36] On the other hand, Vγ4$^+$ γδ T cells develop in both fetal and adult thymus, have more diverse TCR repertoire and reside in the dermis, lung, liver and secondary lymphoid organs.[37,38] In addition to RORγt, transcription factors such as Blk,[39] Hes-1,[40] nuclear factor-κB,[41] Sox4 and Sox13[42] are also important for γδ17 cell development. Transforming growth factor-β and IL-7 are required for γδ17 thymocyte development and expansion, respectively.[43–45] Epigenetic and transcriptional regulation during γδ17 cell differentiation has been reviewed elsewhere.[46] γδ thymocytes capable of producing IL-17, which express the transcription factor RORγt and the signature cytokine receptor IL-23R,[34] leave the thymus as functionally committed cells,[47] and produce IL-17 directly by the stimulation with IL-1β and IL-23 in the periphery. Although IL-23R is constitutively expressed on γδ17 cells, the expression of IL-1R in peripheral γδ17 cells is tissue-dependent.[48] In addition to IL-1R and IL-23R, the expression of scavenger receptor 2 (Scart 2)[49] and CCR6,[27] and the lack of CD122[25] and CD27 expression[26] are often used as markers for γδ17 cells, with the exception for IL-17-producing Vγ1$^+$ γδ T cells.[33] These phenotypes, established during thymic development, distinguish γδ17 cells from IFN-γ-producing γδ T (γδIFN-γ) cells (Fig. 2). γδ17 cells that develop before birth persist in adult mice as self-renewing, long-lived cells.[50]

The requirement of TCR signalling for γδ17 cell development is not fully understood.[51] Early T-cell precursors can produce IL-17 before TCR recombination[50] and Sox4 and Sox13 are expressed before activation with TCR

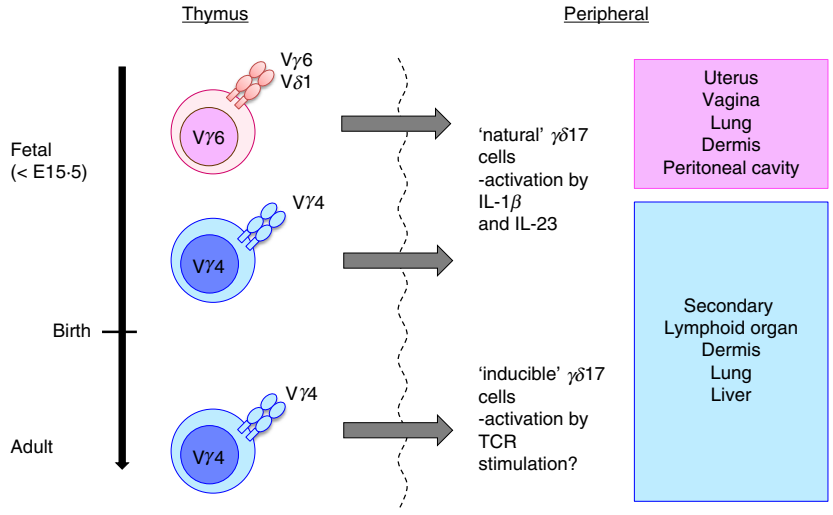

Figure 1. Distinct features of γδ17 cell subset and suggested model of 'natural' γδ17 cells versus 'inducible' γδ17 cells. Vγ6$^+$ γδ T cells express the invariant Vγ6/Vδ1 T-cell receptor (TCR), develop only in the late embryonic thymus, and preferentially localize to the uterus, vagina, lung, dermis and peritoneal cavity. On the other hand, Vγ4$^+$ γδ T cells develop in both fetal and adult thymus and have a more diverse TCR repertoire. These cells circulate in blood and reside in the dermis, lung, liver and secondary lymphoid organs. In according to Haas *et al.*[50] 'natural' γδ17 cells (Vγ6$^+$ and part of Vγ4$^+$) developed before birth acquire interleukin-17 (IL-17) -producing ability in thymus and produce IL-17 stimulated by IL-1β and IL-23 in the periphery. Conversely, IL-17 production induced by TCR signalling was also reported.[56] Naive γδ T cells developed after birth may egress the thymus as 'inducible' γδ17 cells (mostly Vγ4$^+$) and differentiate to produce IL-17 after encounter with antigen.

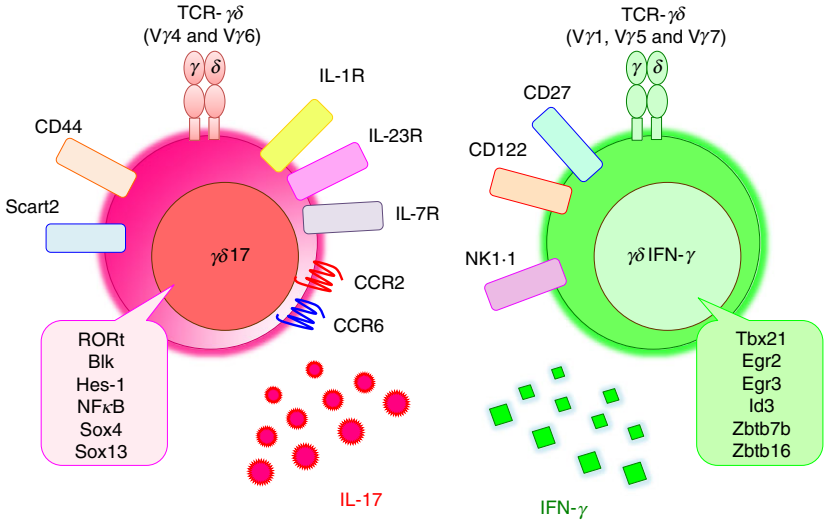

Figure 2. Characterization of γδ17cells. γδ17 cells have some distinct phenotypes and are distinguished from interferon-γ (IFN-γ)-producing γδ T cells ; γδ17 cells express interleukin-1 receptor (IL-1R), IL-23R, IL-7R, CCR2, CCR6, CD44 and Scart2 on the cell surface. The transcriptional factors of RORγt, Blk, Hes-1, NF-κB, Sox4 and Sox13 are important for γδ17 development. On the other hand, IFN-γ-producing γδ T cells express CD27, CD122 and NK1.1. These phenotypes are established during thymic development.

signalling.[42] Antigen-naive γδ T cells in the thymus differentiate into IL-17 producers, whereas antigen-experienced cells make IFN-γ.[28] Furthermore, $V\gamma5^{+}V\delta1^{+}$ thymocytes induce Egr3 upon recognition of Skint-1 expressed on thymic epithelial cells, resulting in the induction of IFN-γ expression and suppression of RORγt and Sox13 expression.[52] Thus, TCR signalling seems to direct γδ thymocytes to differentiate into IFN-γ-producing γδ T cells by suppressing the 'default' IL-17 programme.

The mechanism of IL-17 production in γδ17 cells

γδ17 cells are functionally committed in the thymus, producing IL-17 in the periphery after stimulation with IL-1β and IL-23 without additional TCR stimulation.[21,24] The 'ready-to-go' phenotype of γδ17 cells is especially efficient for early-stage pathogen clearance. A combination of IL-1β and IL-23, but not IL-1β or IL-23 alone, is required to induce IL-17 by γδ17 cells.[20] Further study revealed that IL-23 is required for the induction of IL-1R, and IL-1β is essential for the induction of IL-17.[20] However, because IL-1β alone does not induce IL-17 production in *Il1rn*$^{-/-}$ mouse-derived splenic γδ T cells[20] and in normal peritoneum- and lung-derived γδ T cells, in which high levels of IL-1R are expressed,[48] IL-23 may play other roles than up-regulating IL-1R in the induction of IL-17 expression in γδ T cells. In this context, RORγt expression is up-regulated by IL-1β and IL-23 in a synergistic manner.[20] The inflammatory cytokine IL-18,[53] complement C5a,[54] the ligand of Toll-like receptors 1 and 2, and dectin-1[55] also induce IL-17 in collaboration with IL-23. Although γδ17 cells typically behave as innate-like immune cells, IL-17 induction by TCR signalling is also reported. Mouse and human γδ T cells recognize an algal protein, phycoerythrin, and differentiate to IL-17-producing cells after immunization by this antigen.[56] These studies, in combination with cell reconstitution studies,[50] suggest that 'natural' γδ17 cells ($V\gamma6^{+}$ and part of $V\gamma4^{+}$) acquire IL-17-producing ability in the fetal thymus and do not require TCR stimulation in the periphery, whereas 'inducible' γδ17 cells (mostly $V\gamma4^{+}$) that develop after birth produce IL-17 upon encounter with antigens[57] (Fig. 1). Notably, phycoerythrin antigen stimulation induces IL-1R expression on γδ T cells.[56] Therefore, γδ TCR activation may make 'inducible' γδ17 cells respond to IL-1β and IL-23 to induce IL-17. A similar activation mechanism is also suggested in Th17 cell differentiation; IL-1R expression is increased upon Th17 differentiation from naive $CD4^{+}$ T cells,[58] and the polarized Th17 cells can produce IL-17 by IL-1 and IL-23 in the absence of TCR stimulation.[59] However, the molecular basis for the 'inducible' state and the difference between 'naive' and 'inducible' γδ17 cells remain to be elucidated.

The pathogenic roles of γδ17 cells in mouse inflammatory disease models

Il17$^{-/-}$ mice show significantly reduced severity in various inflammatory and autoimmune disease models, such as collagen-induced arthritis,[6] *Il1rn*$^{-/-}$ mouse arthritis,[7] EAE[8] and imiquimod (IMQ)-induced skin inflammation,[9,10] suggesting critical roles of IL-17 in inflammatory/autoimmune diseases. γδ17 cells are detected in inflamed tissues of these disease models. However, the roles of γδ T cells in the development of diseases and the responsible γδ subset are different in different models (Table 1). As

no conditional *Il17*$^{-/-}$ mice in which the *Il17* gene is deleted specifically in γδ17 cells are available, the pathogenicity of γδ17 cells has been analyzed using γδ T-cell-deficient mice (*Tcrd*$^{-/-}$ mice) or the γδ17 cell subset from these disease models.

In the collagen-induced arthritis model, both γδ17 cells and Th17 cells are found in joints and draining lymph nodes and the majority of the γδ17 cells are Vγ4$^+$/Vδ4$^+$.[22,24] Vγ4$^+$ cell depletion reduces Th17 cell number[60] as well as arthritis severity,[22] suggesting that the Vγ4$^+$/Vδ4$^+$subset aggravates disease by promoting a Th17 cell response. Some components of heat-killed *Mycobacterium tuberculosis* in complete Freund's adjuvant or inflammatory cytokines induced by the adjuvant are suggested to induce Vγ4$^+$/Vδ4$^+$ cell expansion.[24,60] *Il1rn*$^{-/-}$ mice develop arthritis spontaneously in an IL-17-dependent manner.[7] In these mice, however, only γδ17 cells are the IL-17 producer in the joints, although both γδ17 cells and Th17 cells are detected in the draining lymph nodes.[20] IL-17-GFP reporter mice reveal that the Vγ6$^+$/Vδ1$^+$ cells predominantly produce IL-17 in affected joints. Adoptive transfer of *Il1rn*$^{-/-}$ T cells into *scid/scid* mice shows that only a mixture of γδ T and CD4$^+$ T cells, but not γδ T cells or CD4 T cells alone, can induce arthritis. Moreover, γδ17 cells localize in joints only when γδ T cells are transferred together with CD4$^+$ T cells. These observations suggest that CD4$^+$ T cells are required for γδ17 cells to localize in joints, and IL-17 from γδ17 cells drives the development of arthritis. Interestingly, Vγ6$^+$ γδ17 cells in *Il1rn*$^{-/-}$ mice intrinsically express IL-1R at high levels, indicating that these cells are ready for IL-17 production. Hence, IL-17 derived from different γδ17 cell subsets is suggested to play a crucial role in the development of arthritis in mouse models.

The mouse model of multiple sclerosis (MS), EAE is another model in which IL-17 plays a crucial role in the pathogenesis. After induction of EAE, γδ17 cells as well as Th17 cells are found in the brain, with Vγ4$^+$ cells as the major component.[21] *Tcrd*$^{-/-}$ mice delay the onset of disease and reduce the clinical scores. γδ T cells activated

Table 1. γδ17 induction and function in inflammatory disease

Disease	Disease model	Dominant subset	Induction of γδ17 cells	γδ17 function	References
Rheumatoid arthritis (RA)	collagen-induced arthritis	Vγ4$^+$ Vδ4$^+$	*Mycobacterium tuberculosis* components in complete Freund's adjuvant (CFA) or subsequent cytokine induction	Promote Th17 cells	22,24,60
	Il1rn$^{-/-}$ mice	Vγ6$^+$ Vδ1$^+$	Up-regulation of interleuki -1 receptor (IL-1R)	IL-17-induced hyperinflammation	20
Spondyloarthritides (SpA)	IL-23 overexpression	Vγ6$^+$	Hyper IL-23 induction	IL-17-induced hyperinflammation	65
Multiple sclerosis (MS)	EAE	Vγ4$^+$	IL-1β and IL-23 from dendritic cells (DC) induced by *Mycobacterium tuberculosis* components in CFA	Promote Th17 cells, and suppress regulatory T cells	21,61
Uveitis	EAU	Vγ4$^+$ Vδ4$^+$	Components in CFA or subsequent cytokine induction	Promote Th17 cells	104
Psoriasis	IMQ	Vγ4$^+$ and Vγ6$^+$	Imiquimod (IMQ)-induced IL-23 from DC	IL-17 production and subsequent neutrophil inflammation	9,10,23,35,42,64
	IL-23		Hyper IL-23 induction	IL-17 production and subsequent neutrophil inflammation	23
Uveoretinitis in autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APCED)	*Aire*$^{-/-}$ mice	Vγ6$^+$ Vδ1$^+$	Up-regulation of IL-7 in the thymus	IL-17-induced hyperinflammation	44
Skin graft rejection	Male to female skin transplantation	Vγ4$^+$	Accumulation CCR6$^+$ γδ17 cells in skin graft	IL-17 promotes the accumulation of DC in draining lymph nodes to subsequently activate Th17 cells	66

with IL-1β and IL-23 promote IL-17 production by CD4$^+$ T cells *in vitro* and co-transfer of CD4$^+$ and $\gamma\delta$ T cells promote development of EAE, suggesting that $\gamma\delta$17 cells act in an amplification loop for IL-17 production by Th17 cells.[21] Interleukin-23-activated $\gamma\delta$ T cells also prevent regulatory T-cell function, resulting in the enhancement of $\alpha\beta$ T-cell responses and EAE development.[61]

A pathogenic role for $\gamma\delta$17 cells is implicated in psoriasis. Vγ5$^+$/Vδ1$^+$ $\gamma\delta$ T cells, also called dendritic epidermal T cells, uniquely residing in epidermis produce IFN-γ and participate in immunosurveillance.[62] On the other hand, dermis contains Vγ4$^+$ and Vγ6$^+$ subsets responsible for IL-17 production. The pathogenicity of $\gamma\delta$17 cells in psoriasis is well studied in a mouse model of psoriasis, IMQ-induced dermatitis.[9,23] Imiquimod is a Toll-like receptor-7/8 agonist and induces IL-17-dependent psoriasiform dermatitis by inducing IL-23.[63] The IMQ-induced epidermal thickening is significantly decreased in *Tcrd*$^{-/-}$ mice, but not in *Tcrb*$^{-/-}$ mice.[9] Development of dermatitis is also suppressed by the deficiency of innate lymphoid cells (ILCs), suggesting that $\gamma\delta$17 cells and IL-17-producing group 3 ILCs (ILC3s) are responsible for the development of psoriasiform dermatitis in mice.[9,23] Both Vγ4$^+$ and Vγ6$^+$ subsets produce IL-17 after IMQ treatment of the skin.[35] Skin inflammation after IMQ treatment is significantly attenuated in *Sox4*$^{-/-}$ mice, in which dermal Vγ4$^+$ but not dermal Vγ6$^+$ $\gamma\delta$ T cells are greatly reduced.[42] Congenic CD45.1$^+$ (B6.SJL) mice with naturally occurring *Sox13* mutation, in which dermal Vγ4$^+$ $\gamma\delta$17 cell development is defective, develop attenuated ear skin inflammation with less acanthosis and fewer epidermal neutrophil pustules upon treatment with IMQ.[64] However, both wild-type bone marrow cell-reconstituted mice and neonatal thymocytes plus CD45.1$^+$(B6.SJL) bone marrow cell-reconstituted mice (in which Vγ4$^+$ and Vγ6$^+$ cells are predominant, respectively) similarly develop epidermal thickening with increased dermal $\gamma\delta$17 cells and neutrophil infiltration, suggesting that both $\gamma\delta$17 subsets induce IMQ-induced dermatitis.[35] Interleukin-17F and IL-22 from $\gamma\delta$ T cells are also pathogenic in IMQ-induced dermatitis.[9] Interleukin-23-induced skin inflammation is another model of psoriasis. The IL-17-producing dermal cells are significantly reduced in *Tcrd*$^{-/-}$ mice accompanied with less skin inflammation and acanthosis, whereas *Tcra*$^{-/-}$ mice normally develop dermatitis,[23] suggesting that $\gamma\delta$17 cells play major roles in the pathogenesis of psoriatic dermatitis in this model. The involvement of $\gamma\delta$17 cells in the development of psoriasiform dermatitis suggests that innate immune responses rather than an autoimmune reaction are important for the development of psoriatic dermatitis.

The involvement of Vγ6$^+$ $\gamma\delta$17 cells in the pathogenesis of uveoretinitis in *Aire*-deficient mice, a model of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APCED), is suggested, because Vγ6$^+$ $\gamma\delta$17 thymocytes are expanded due to high levels of IL-7 expression in *Aire*$^{-/-}$ medullary thymic epithelial cells.[44] Importantly, expansion of IL-17-producing Vγ9$^+$/Vδ2$^+$ $\gamma\delta$ T cells is observed in APCED patients, suggesting the involvement of $\gamma\delta$17 cells in these patients. $\gamma\delta$17 cells are also implicated in the pathogenesis of spondyloarthritis; the CD27$^-$ $\gamma\delta$ T-cell population is increased in the Achilles tendon after over-expression of IL-23, which induces spondyloarthritis-like enthesitis in mice.[65] The Vγ4$^+$ subset produces IL-17 in the skin grafts and in the host epidermis around grafts, suggesting the involvement in skin graft rejection.[66] Vγ4$^+$cell-derived IL-17 promotes the accumulation of mature dendritic cells in the draining lymph nodes to subsequently increase Th17 cells after skin graft transplantation.[66]

Migration of $\gamma\delta$17 cells to inflammatory sites

Trafficking of $\gamma\delta$17 cells to the inflammatory sites is important for the development of inflammation. Naive $\alpha\beta$ T cells express a chemokine receptor CCR7, which is important for homeostatic circulation; its expression is down-regulated during differentiation and the inflammatory chemokine receptor CCR6 is induced on Th17 cells instead. CCR6$^+$ Th17 cells are recruited by CCL20 to cause inflammation, as shown in SKG mice[67] and the EAE model.[68,69] On the other hand, a gene array analysis shows that the expression of chemokine receptors such as CCR6, CCR2 and CXCR6 is already up-regulated in $\gamma\delta$17 cells during thymic development.[34] Recent studies have indicated that the CCL20–CCR6 axis is mainly required for $\gamma\delta$17 cell recruitment into homeostatic sites such as dermis,[70] whereas the CCL2–CCR2 axis recruits $\gamma\delta$17 cells into inflammatory sites, including psoriatic skin,[71] arthritic joints,[20] central nervous system in EAE, infected mucosal tissues and tumours.[70] Interestingly, $\gamma\delta$17 cells constitutively express both CCR2 and CCR6, but down-regulate CCR6 expression after inflammation.[70] This is consistent with the 'ready-to-go' nature of $\gamma\delta$17 cells and suggests a $\gamma\delta$17 cell-recruiting mechanism in which $\gamma\delta$17 cells are released from the tissue-specific harness to migrate into inflammatory sites by reducing the tissue-specific homing receptor.

$\gamma\delta$17 cells in tumours

Pro-tumour function of $\gamma\delta$17 cells has been demonstrated in several cancer models, including a breast cancer metastasis model[72] and an ovarian cancer model,[73] and the roles of $\gamma\delta$17 cells in the development of tumours have been reviewed elsewhere.[74] Abundant $\gamma\delta$17 cell infiltration accompanied by immunosuppressive myeloid-derived suppressor cells is found in human colorectal cancer with positive correlation with advanced

tumour clinicopathological features, suggesting that γδ17 cells induce myeloid-derived suppressor cell-mediated immunosuppression.[75] On the other hand, anti-tumour function of γδ17 cells after therapeutic treatment has also been reported. γδ17 cells infiltration is observed when bladder cancer is treated by intravesical injection of *Mycobacterium* bovis bacillus Calmette–Guérin, (BCG) and these cells are protective against tumour development by recruiting neutrophils.[76] Moreover, γδ17 cell infiltration in epithelial tumours is observed after chemotherapy and γδ17 cells enhance the recruitment of IFN-γ-producing $CD8^+$ T cells that mediate the anti-tumour function.[77]

γδ17 cells in pathogen clearance

Interleukin-17 plays protective roles against bacterial and fungal infection by recruiting neutrophils, activating T cells and inducing antimicrobial peptides and inflammatory cytokines.[1,4,5] γδ17 cells produce much more IL-17 than Th17 cells after *Mycobacterium tuberculosis*[78] or *Mycobacterium bovis* BCG infection.[79] Expression of IL-17 is detected in lungs from the first day after infection with BCG and induces not only neutrophil-mediated inflammation but also granuloma formation.[79] Dermal γδ T cells also produce IL-17 at the first day after intradermal BCG infection and induce neutrophil recruitment and antigen-specific $CD4^+$ T-cell expansion.[80] Rapid IL-17 production by $V\delta1^+$ T cells is also observed in the peritoneum after intraperitoneal infection with *Escherichia coli*, followed by neutrophil recruitment.[81] γδ17 cells are also found in the liver after *Listeria monocytogenes* infection[82] and in lungs after *Klebsiella pneumoniae* infection.[83]

γδ17 cells produce IL-17 rapidly after infection with fungi, such as *Candida albicans*. γδ17 cells are observed in lungs after systemic *C. albicans* infection, and both $Il17^{-/-}$ and $Tcrd^{-/-}$ mice are defective in neutrophil recruitment and fungal clearance.[84] Interleukin-17 is produced in tongue-resident γδ T cells as well as $CD3^+$ $CD4^+$ $CD44^{hi}$ TCR-β^+ $CCR6^+$ natural Th17 cells within 1–2 days after oral *C. albicans* infection.[85] As IL-17 production in γδ T cells is found at the early stage after infection, γδ17 cells are suggested to play an important role in early host defence before establishment of acquired immunity. In humans, patients carrying mutations in either STAT3, IL-17RA, or IL-17F or producing anti-IL-17F autoantibodies are also highly susceptible to skin infection with *Staphylococcus aureus* and *C. albicans*.[86,87] However, the involvement of γδ17 cells in host defence in humans against these pathogens remains to be elucidated.

Recently, pathogen-specific memory γδ T cells have been implicated in several infection models. Memory γδ T cells are elicited in mesenteric lymph nodes after oral *L. monocytogenes* infection and contribute to clearance of the bacteria by promptly producing IL-17 after secondary infection.[88,89] Interestingly, both $V\gamma4^+$ and $V\gamma1^-$ $V\gamma4^-$ γδ (potentially $V\gamma6^+$) T cells produce IL-17 in the lungs as early as 2 hr after *Bordetella pertussis* infection, whereas the exclusively $V\gamma4^+$ subset expands in lungs 14 days after infection. Moreover, lung $V\gamma4^+$ γδ T cells produce IL-17 in response to heat-killed *B. pertussis* in the presence of antigen-presenting cells.[90] These studies suggest that $V\gamma4^+$ T cells, but not $V\gamma6^+$ T cells, behave like adaptive immunological memory cells in a pathogen-specific manner.

γδ17 cells in human inflammatory diseases

Although it has been thought that psoriasis is caused by an autoimmune mechanism,[91] recent studies using mouse models suggest the involvement of innate immunity.[92] High frequency of γδ T cells is detected in psoriasiform dermal lesions in mice induced by IMQ, and these cells produce IL-17 through stimulation with IL-23,[23] indicating the innate immune nature of the disease. γδ T cells, especially $V\gamma9^+V\delta2^+$ cells which can produce IL-17, are also accumulated in the skin of patients with psoriasis.[93] In this report, however, $V\gamma9^+V\delta2^+$ cells were activated to produce cytokines from keratinocytes by the specific antigen, suggesting that recognition of specific antigens may be important for the development of psoriasis. Because Th17 cells[94] and ILC3s[95] as well as γδ17 cells[91] are also detected in the psoriatic skin, the involvement of autoimmunity and the main source of IL-17 during the development of psoriasis still remain obscure in humans.

Recently, several antibodies targeting IL-17 and its receptor have been approved or are in clinical trials for the treatment of psoriasis and psoriatic arthritis.[96] Secukinumab, an anti-IL-17 antibody, has been approved in Japan in 2014 and by the US Food and Drug Administration in 2015 for the treatment of psoriasis and psoriatic arthritis. Treatment with secukinumab for psoriasis patients in a phase III trial shows that more than half of the patients accomplish almost complete remission after 12 weeks of treatment, as determined by the Psoriasis Area and Severity Index (PASI 90), and show better efficacy than a tumour necrosis factor inhibitor (etanercept).[11] Ixekizumab, another monoclonal antibody against IL-17, and Brodalumab, a monoclonal antibody against IL-17RA, are also effective for the treatment of psoriasis in phase III trials[12,13] and approved for the treatment of psoriasis. Secukinumab has also been approved for the treatment of ankylosing spondylitis.[97]

As described, the importance of IL-17 in the development of rheumatoid arthritis (RA) is suggested in mouse models and γδ17 cells are accumulated in arthritic joints,[7,20,22,24] but the importance of γδ17 cells in patients

with RA is controversial. A recent report shows that Vδ2$^+$ $\gamma\delta$ T cells accumulate in the synovium of patients with RA and produce high levels of IL-17 as well as IFN-γ.[98] However, the predominance of IFN-γ-producing $\gamma\delta$ T cells instead of $\gamma\delta$17 cells in affected joints is reported elsewhere.[24] This discrepancy may result from the differences of medical treatment and/or stages of RA. Because the efficacy of anti-IL-17 treatment of RA is moderate except for some patients with specific HLA types,[99,100] $\gamma\delta$17 cells may not play crucial roles in the development of RA in humans. Further studies in patients with RA are necessary.

Elevated IL-17 expression in $\gamma\delta$ T cells, but not CD4$^+$ T cells, was found in patients with systemic juvenile idiopathic arthritis,[101] and IL-17 production was detected in CD161^{hi} CCR6$^+$ $\gamma\delta$ T cells in cerebrospinal fluid of patients with MS.[102] Treatment of patients with MS with secukinumab non-significantly reduced the number of combined unique active lesions and significantly reduced the number of cumulative new gadolinium-enhancing T1 lesions by 67%.[103] Further studies are necessary to elucidate the role of $\gamma\delta$17 cells in the development of these diseases.

Concluding remarks

In this review, we discussed the development and the function of $\gamma\delta$17 cells and the roles of $\gamma\delta$17 cells in inflammatory/autoimmune diseases and host defence against pathogens. However, several important questions still remain to be elucidated. The function of TCR signalling in the thymic development of $\gamma\delta$17 and the functional roles of TCR signalling in the periphery upon infection and inflammation are not completely elucidated. Elucidation of epigenetic modifications of genes in 'natural' and 'inducible' $\gamma\delta$17 cells may provide important information. Discovery of $\gamma\delta$17 cell-specific markers may provide a more efficient approach to induce $\gamma\delta$17 cell-specific dysfunction in inflammatory diseases without affecting systemic Th17 cells. Most importantly, it is not clear how well mouse disease models represent the pathogenesis of human diseases, especially those of psoriasis, MS and RA. In the case of psoriasis, inhibition of IL-17 signalling efficiently cures the symptoms both in psoriasis patients and IMQ-induced psoriasis models, suggesting that $\gamma\delta$17 cells play important roles in both humans and mice. However, in MS and RA, in which the involvement of $\gamma\delta$17 is suggested by mouse models, the therapeutic effects of anti-IL-17 are not so drastic as indicated by these models, suggesting that the pathogenic mechanisms may be different in some parts between diseases in humans and mice. Clearly, further analysis of pathogenic mechanisms in patients is necessary to explain this discrepancy.

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Disclosures

The authors declare no conflict of interest.

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