Functions of IL-17-Producing γδ T Cells

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Abstract: IL-17 producers in γδ T cell subsets have been recently identified to play protective roles against bacterial infection by inducing neutrophil infiltrations, organizing granulomas and acquired immunity. During ontogeny, γδ T cells develop, maturate and localize at different tissues depending on Vγ repertoires. Vγ1+, Vγ4+ and Vγ6+ cells are reportedly able to produce IL-17. Vγ6+ cells, which develop in the thymus at a very early stage of ontogeny, migrate into the uterus and reproductive organs, whereas Vγ1+ and Vγ4+ cells, which develop at a later stage in the fetal thymus, migrate into the spleen, lung and liver. Vγ6+ cells functionally differentiate into IL-17 producers within the thymus and can consequently rapidly exert an ability to produce IL-17 in response to various stimuli. Thus, by finding IL-17-producing γδ T cells will open a new paradigm to reveal the unique ontogeny and novel molecular mechanisms of γδ T cells.

INTRODUCTION

Interleukin(IL)-17 (IL-17A) was originally cloned by Rouvier *et al*. in 1993 and named CTLA8 which was shown to have 57% homology with the open reading frame of T lymphotropic herpesvirus samirii [1]. Since CTLA8 bound a novel cytokine receptor called IL-17 receptor (IL-17R), CTLA8 was renamed as IL-17. IL-17 is a proinflammatory cytokine mainly produced by T cells. Recently, it has been revealed that IL-17 produced by helper CD4+ T cells contributes to the induction and development of autoimmune diseases such as encephalomyelitis, inflammatory bowel disease and arthritis in mice [2-5]. Due to the clinical relevance of IL-17 in autoimmune diseases, studies have focused on these fields and consequently Th17 cells as novel lineages of helper CD4+ T cells were established [6]. In addition to Th17 cells, other IL-17 producers such as CD8+ αβ T cells, γδ T cells and NKT cells have also been reported [7-9]. Among these populations, protective roles of γδ T cells by orchestrating innate immunity have been reported [10-14]. Indeed, IL-17-producing γδ T cells are often localized in mucosal tissues such as lung, intestine, peritoneal cavity and reproductive organs exposed to exogenous stimuli, including pathogens, where rapid responses are required as a first line of host defense. Therefore, IL-17-producing γδ T cells can respond to various stimuli faster than Th17 cells, which are generated in the periphery under specific conditions such as autoimmune diseases. This unique feature of γδ T cells is generated within the thymus under normal condition [15]. In this review, roles and molecular mechanisms of IL-17-producing γδ T cells will be discussed.

BIOLOGICAL ACTIVITY OF IL-17

IL-17 is a disulfide-linked homodimeric glycoprotein consisting of 155 amino acids [16]. Homology-based cloning has recently revealed five additional IL-17 family members, IL-17B to IL-17F [17-21]. IL-17 family members form homodimers and have a conserved C-terminal domain. Particularly, IL-17 and IL-17F share five unique, spatially conserved cysteine residues accounting for the characteristic cysteine-knot formation [22].

IL-17 receptor A (also known as IL-17RA) was originally found as a novel receptor for IL-17. IL-17RA is a type 1 transmembrane protein consisting of a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain and a 521 amino acid cytoplasmic tail. A homology-based study showed that four additional IL-17 receptor family members, IL-17RB, RC, RD and RE, have been identified so far [23]. Monoclonal antibody (mAb) treatment against IL-17RA inhibited IL-17 signaling [24]. A recent study also showed that IL-17 might bind to and signal through a IL-17RA and IL-17RC complex [25]. These results suggest that IL-17RA is indispensable for IL-17 function. IL-17RA mRNA expression was detected in the spleen, lung, liver and kidney and various cell lines such as fibroblasts, epithelial cells, endothelial cells, myeloid cells and T cells [16]. NF-κB and the mitogen-activated protein kinase (MAPK) pathway were directly activated by the IL-17-mediated signal through tumor necrosis factor receptor-associated factors (TRAF6) [26]. More recently, Act1 was identified as a molecule directly binding to IL-17RA [27]. Act1 deficiency could not mount IL-17-induced inflammation *in vivo* and *in vitro* [27, 28].

IL-17 has various but different functions depending on the cell type. The most well-documented role of IL-17 is to induce local tissue inflammation *via* induction of CSFs (colony-stimulating factors) and neutrophil-mobilizing cytokines. CSFs such as G-CSF and GM-CSF induce granulopoiesis by acting on myeloid cells, whereas neutrophil-mobilizing cytokines are locally produced in the inflammatory site to recruit inflammatory cells such as neutrophils and monocytes [29]. IL-17 also induces generation of osteoclasts through receptor activator of NF-κB ligand (RANKL) induction [30]. IL-17 in synergy with IL-22 enhances the expression of anti-bacterial peptides [31].

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Multiple actions of IL-17 could be explained not only by the expression of IL-17RA on various cell types but also by different signaling pathways used in each cell type. Precise studies on molecular mechanisms of IL-17-mediated signaling will help us to understand overall IL-17 actions.

IDENTIFICATION OF IL-17-PRODUCING γδ T CELLS

IL-17-producing γδ T cells were first reported by Stark *et al*. using adhesion molecule-deficient mice having neutrophilia [10]. In this model, IL-17-producing γδ T cells contributed to homeostasis by controlling neutrophil numbers in the periphery. γδ T cells were reported as a dominant producer of IL-17 at the site of infection at the early phase of pulmonary *Mycobacterium tuberculosis* infection [11]. Similarly, in pulmonary *Mycobacterium bovis Bacille Calmette-Guerin* (BCG) infection, IL-17-producing γδ T cells were found in the lung at an early phase. IL-17KO mice decreased the Th1 response and impaired granuloma formation following BCG infection [12].

IL-17-producing γδ T cells were also identified in the liver and spleen at an early phase after an intraperitoneal infection with *Listeria monocytogenes* [14, 32]. The IL-17-producing γδ T cells which were distinct lineages from IFN-γ producing γδ T cells were Vγ4+ and Vγ6+ cells. Again, infiltration of inflammatory cells and organization of granulomatous lesions were severely blocked in IL-17KO mice infected with *L. monocytogenes.* These results suggest that IL-17-producing γδ T cells were directly or indirectly involved in granuloma formation following infection with intracellular bacteria. We have found that resident Vδ1+ γδ T cells rapidly produced IL-17 in response to exogenous IL-23 after intraperitoneal infection with *E. coli*, an extracellular bacterium [13]. Antibody-mediated depletion of γδ T cells decreased IL-17 production and neutrophil infiltration to the site of *Escherichia coli* infection, hampering the resolution of the infection. This result indicated that IL-17-producing γδ T cells played an important role in protection against *E. coli* infection as an innate immunity (Fig. **1**). We also found that the peritoneal Vγ6+ γδ T cells capable of producing IL-17 were a CD25-positive CD122-negative phenotype, while CD25-positive CD122-negative peritoneal Vγ6+ γδ T cells produced IFN-γ [15]. Thus, IL-17-producing γδ T cells were a distinct lineage from IFN-γ producing γδ T cells.

IL-17-producing γδ T cells have another role to induce or accelerate autoimmune diseases. In the collagen-induced arthritis (CIA) mouse model, Vγ4+ IL-17-producing γδ T cells appeared during the development of CIA [33]. Treatment with Anti-Vγ4 mAb significantly reduced symptoms of CIA and collagen-specific IgG2a, suggesting that IL-17 produced by Vγ4+ γδ T cells could be a crucial mediator for CIA development. The experimental autoimmune encephalomyelitis (EAE) mouse model has been used to study Th17 cells. It has recently been shown that IL-17-producing γδ T cells were detected in lymph nodes at an earlier phase than Th17 cells appearing in the EAE model [34]. IL-17 production by γδ T cells was enhanced by myelin oligodendrocyte glycoprotein (MOG) 35-55 peptide. CδKO mice immunized with MOG peptide exhibited reduced clinical scores. These results suggest that Ag-specific IL-17-producing γδ T cells contribute to EAE induction. In the chronic granulomatous disease (CHD) mouse model, the number of Vγ1+ IL-17-producing γδ T cells gradually increased in the inflammatory site and contributed to the infiltration of neutrophils [35].

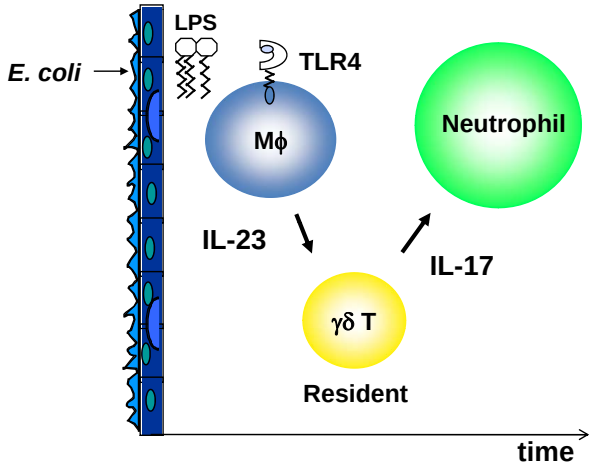

Fig. (1). Host defense mechanism after intraperitoneal infection with *Escherichia coli*. After intraperitoneal infection with *E. coli*, IL-23, which is produced by resident macrophages through TLR4, induce IL-17 production by Vδ1+ γδ T cells. IL-17-producing Vδ1+ γδ T cells contribute to host defense by inducing neutrophil infiltrations. LPS : lipopolysaccharide, Mϕ : macrophage.

Cytokines produced by γδ T cells exert various immunoregulatory roles depending on their condition. For example, IFN-γ-producing γδ T cells contribute to host defense by inducing a cytotoxic function, which is enhanced following the Th1 response [36], whereas IL-10-producing γδ T cells are often found to dampen excessive inflammations in later stages of bacterial infection [37]. In addition, skin-resident γδ T cells produce fibroblast growth factors and keratinocyte growth factors in wound repair. By finding IL-17-producing γδ T cell lineages, a novel function of γδ T cells was revealed.

DEVELOPMENTAL PATHWAY AND DIVERSITY OF IL-17 PRODUCING γδ T CELLS

Depending on the use of Vγ chains, timing of development within the thymus and tissue distribution of γδT cells are tightly regulated during ontogeny. Vδ1+ cells paired with Vγ5 or Vγ6 chains as the first T cell lineage develop in the early fetal thymus after which Vγ5+ cells migrate into the skin, while Vγ6+ cells migrate into reproductive organs and peritoneal cavities. We have recently revealed that Vγ6+ γδ T cells functionally developed into IL-17 producers within the thymus and became CD25-positive in peripheral tissues such as the peritoneal cavity and uterus [15]. Vγ6+ IL-17-producing γδ T cells like Th17 cells could produce TNF-α but neither IFN-γ nor IL-4. However, IL-17 production was not detected in Vγ5+ γδ T cells in the thymus or its periphery. These results imply that the function of producing IL-17 is imprinted only on Vγ6+ γδ T cells within the fetal thymus, but the mechanism whereby Vγ5+ and Vγ6+ γδ T cells develop differently is not clear (Fig. **2**). Other γδ T cell repertoires such as Vγ1, Vγ4 and Vγ7 start to develop from a late stage of ontogeny in the fetal thymus. Vγ4+ cells are relatively abundant in the lung and contain IL-17-producing γδ T cells, although the mechanisms of functional

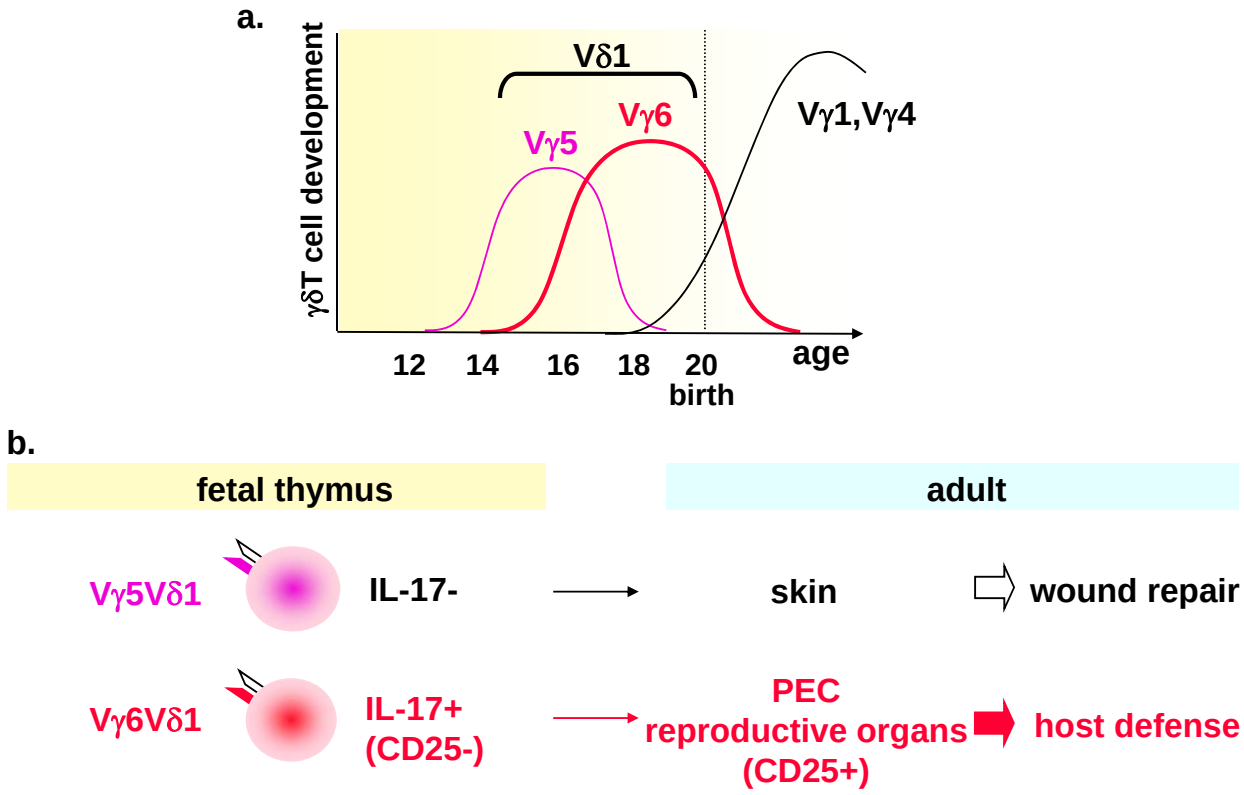

Fig. (2). Vγ6+ γδ T cells functionally develop into IL-17 producers within the fetal thymus. (**a**) Developments of γδ T cells in the fetal thymus are shown. (**b**) Fetal thymus-derived Vγ5Vδ1+ or Vγ6Vδ1+ γδ T cells are migrated into each tissue exerting different functions.

differentiation remain to be clarified [33, 35]. These data indicate a relationship between tissue distribution of γδ T cell repertoires and their IL-17-producing function. It has recently been reported that CD122-negative γδ T cells having naïve phenotypes in the thymus and spleen produced IL-17; on the other hand, antigen-specific CD122-positive γδ T cells produced IFN-γ [34]. Consistent with this, we have found that CD25-positive CD122-negative γδ T cells in the peritoneal cavity of naive mice were able to produce IL-17, while the Vγ6+ IL-17-producing γδ T cells in thymus did not express CD25 [15]. The Vγ6+ IL-17-producing γδ T cells were still found in IL-2-deficient mice albeit at reduced numbers, suggesting that the IL-2 signal is not required for development in the thymus but contributes to the maintenance of Vγ6+ IL-17-producing γδ T cells in the periphery. On the other hand, Vγ4+ IL-17-producing γδ T cells in the spleen did not express CD25. Therefore, there might be different mechanisms in Vγ6+ and Vγ4+ cells to differentiate into IL-17 producers or to be maintained in the periphery.

It is generally accepted that the thymus is an important place to generate T cells through interaction with thymic epithelial cells (TECs). Indeed, Vδ1+ γδ T cells also cannot develop in athymic mice. Vγ5+ and Vγ6+ γδ T cells sharing Vδ1 chains develop in the early fetal thymus where the tissue distribution and the functions of these cells may be differently determined. Therefore, different signals from TECs in fetal thymus might explain different functions of Vγ5+ and Vγ6+ γδ T cells, although we cannot exclude the possibility that different precursors exist. Thus, studies in thymic environments will be informative to understand the ontogeny of IL-17-producing γδ T cells.

MECHANISMS OF IL-17 PRODUCTION BY γδ T CELLS

We previously reported that IL-17 production was produced in a TLR4-dependent manner against *E. coli* infection [13]. Furthermore, IL-17 production by γδ T cells was found to be induced in response to endogenous IL-23 released by macrophages through TLR4 stimulation. Indeed, peritoneal γδ T cells were able to produce IL-17 in response to exogenous IL-23 *in vitro*. IL-23-induced IL-17 production by γδ T cells was abolished in tyk2-deficient mice [38]. Consistently, in pulmonary *Mycobacterium tuberculosis* infection, IL-17 production from γδ T cells was induced by an *M. tuberculosis*-infected dendritic cell-derived IL-23 *in vivo* and *in vitro* [11]. Stark *et al*. also showed that dendritic cell-derived IL-23 was a stimulating molecule for IL-17 production in response to LPS [10]. These results suggest that IL-17-producing γδ T cells express IL-23 receptors which signal through tyk2 to induce IL-17 production. However, other signaling molecules involved in IL-23-mediated IL-17 production in γδ T cells remain to be determined.

Crosslinking of γδ TCR by mAb can induce IL-17 production, indicating that signaling from γδTCR is important for IL-17 production. However, ligands to the γδTCR remain unclear. IL-17-producing γδ T cells in the peritoneal cavity and uterus express canonical TCRs rearranged with Vγ6 and Vδ1 chains, raising the possibility that IL-17-producing γδ T cells might recognize endogenous proteins induced by infection. The implication of roles of IL-17-producing γδ T cells awaits elucidation of the molecular

mechanisms for γδ TCRs, especially in the identification of ligands.

Th17 cells are induced by TCR stimulation in the presence of TGF-β and IL-6 *in vivo* and *in vitro* [39]. To elucidate the functional differentiation mechanism, Vγ6+ IL-17-producing γδ T cells functionally developed in fetal thymus were analyzed by using a fetal thymus organ culture system in the presence of anti-TGF-β and anti-IL-6 mAbs. However, functional differentiation to IL-17-producing γδ T cells was not blocked (unpublished observation). Consistent with this, IL-17-producing γδ T cells in the spleen were found in the absence of IL-6 signaling [40]. IL-21 has also been reported as an important molecule for Th17 differentiation [41]. However, IL-17-producing γδ T cells were equally found in IL-21 receptor KO mice in the periphery suggesting that an IL-21-mediated signal was not required for differentiation of IL-17-producing γδ T cells (unpublished observation). Recently RORγt was identified as a transcription factor for Th17 cells [42]. RORγt directly binds to IL-17 promoter regions to control IL-17 production in Th17 cells [43]. However, it remains unclear whether RORγt has a similar function in IL-17-producing γδ T cells.

FUTURE PERSPECTIVES

IL-17-producing γδ T cells appear in different timing of ontogeny and in different tissue from Th17 cells. These features suggest a possibility that IL-17-producing γδ T cells not only function at different stages but also undergo different developmental pathways from Th17 cells. In contrast to Th17 cells, the molecular mechanisms of development in the thymus and functional differentiation of IL-17-producing γδ T cells remain mostly unknown. It is expected that intensive studies on γδ T cells will allow host defense mechanisms to be understand and applied in clinical studies.

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