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REVIEW

γδ T cells and IL-17/IL-17R signaling axis in CNS inflammation

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Abstract: Lymphocytes expressing γδ T-cell receptors constitute an entire system of functionally specialized subsets that have been implicated in the regulation of immune responses, including responses to pathogens and allergens, and in tissue repair. γδ T cells represent a small subpopulation of T cells that, unlike αβ T cells, function more as cells of the innate immune system. γδ T cells are known to mediate the production of inflammatory cytokines, including interferon-γ, tumor necrosis factor-α, and interleukin (IL)-17, and thus enable the activation of other subsets of infiltrating effector cells. However, not much attention was paid to γδ T cells until the recent discovery of a distinct $CD4^+$ T helper (T_H) cell, T_H17 cell. $CD4^+$ T cells, upon activation and expansion, develop into different T_H-cell subsets with different cytokine profiles and distinct effector functions. T cells were earlier divided into T_H1 or T_H2 cells, depending on the cytokines they produce. A third subset of IL-17-producing effector T_H cells, called T_H17 cells, has been discovered and characterized recently. Since then the literature on IL-17-producing cells has grown steadily, and several studies have focused on γδ T cells. Cytokine-mediated modulation of central nervous system (CNS) inflammatory diseases by γδ T cells in humans or in animal models is currently the subject of many studies. IL-17 and its receptor IL-17R have been implicated in the pathogenesis of immune-mediated CNS diseases, and attention has been paid to understand the mechanisms by which IL-17 cytokines and it receptor (IL-17R) family mediate the effects at a molecular level. This article reviews the studies that cover earlier aspects of γδ T cell/IL-17 biology and the new dimension of γδ T cells, IL-17, and IL-17/IL-17R signaling axis in CNS inflammation. Understanding the role of γδ T cells, IL-17, and IL-17/IL-17R signaling axis in infection and immunity could open a new avenue for immunomodulation.

Keywords: cytokine, γδ T cells, T_H17 cells, IL-17, IL-17R, multiple sclerosis, EAE, autoimmunity, CNS, viral infection, virus-induced demyelination

Introduction

Interleukin (IL)-17A and its receptor IL-17RA are the founding members of a newly described family of cytokines (IL-17A–IL-17F) and their receptors (IL-17RA–IL-17RE; known as the IL-17R family).[1–3] Receptors belonging to the IL-17R family have unique structural features and mediate signaling events that are surprisingly distinct from those triggered by other cytokine receptors, particularly those usually involved in adaptive immunity. IL-17A plays a critical role in the pathogenesis of many autoimmune diseases, including multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). IL-17 has also been shown to exacerbate autoimmune diseases. T_H17 cells are a newly defined αβ T-cell lineage

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characterized by IL-17 production. However, γδ T cells are often the major source of IL-17.[4,5] Recent studies have demonstrated that γδ T cells play a role in the development of demyelinating central nervous system (CNS) inflammation. As multifaceted cells, γδ T cells have the potential to influence all levels of inflammation by the rapid production of inflammatory mediators, by recruiting inflammatory cells via chemokines, influencing T-cell differentiation by cytokine production, and/or direct killing via production of cytotoxic effectors.[6] Although the roles of γδ T cells and T_H17 cells/IL-17 in EAE and MS are to some extent clear, it is unknown whether the activation cascade of γδ T cells and T_H17 cells/IL-17 has any function in virus-induced demyelination. Very few studies are available on the inflammatory cascade of γδ T cells and T_H17 cells/IL-17 and IL-17/IL-17R signaling mechanisms in virus-induced CNS demyelination. In this review, we have attempted to gather data from published articles and our own findings to examine the role of γδ T cells, IL-17-producing T_H17-cell lineage, and IL-17/IL-17R signaling system in the virus-induced demyelination model of MS.

MS is one of the major chronic inflammatory CNS diseases in humans with heterogeneous clinical presentations and course.[7] The major manifestation of MS is demyelination with and without axonal preservation. Demyelination is a complex process, and while the precise mechanisms of this pathology are unclear, inflammatory demyelination is thought to be the result of adaptive immune-mediated responses to myelin antigens in the myelin sheaths of axons and/or in the myelin-forming oligodendrocytes. However, the contribution of innate immune cells in mediating MS pathogenesis has recently gained attention, as several studies demonstrated the role of various innate immune cells in mediating MS pathogenesis, in particular, the potential anti-inflammatory or proinflammatory function of dendritic cells, microglial cells, natural killer (NK) cells, NKT cells, and γδ T cells along with their interaction among themselves and with myelin.[8–11]

MS is best studied in some experimental models such as EAE, Theiler's murine encephalomyelitis virus (TMEV), and mouse hepatitis virus (MHV). The primary emphasis has been on understanding CD^+ T cell-mediated or T cell and antibody-mediated autoimmune encephalomyelitis. Virtually all types of immune response have been proposed to play important roles in the pathogenesis of EAE[7,12] and TMEV.[13–15] Infection of mice with MHV, strain JHM,[16,17] results in acute and chronic demyelination, mimicking the pathogenesis of the MS. This pathological process is primarily T cell-mediated, and MHV infection of mice lacking B and T cells does not result in demyelination. Contrary to these results, robust demyelination is detected in MHV-infected young nude (athymic) mice, which demonstrates that demyelination in nude mice could be mediated by γδ T cells.[18] γδ T cells, but not conventional CD4 or CD8 αβ T cells, were detected in the CNS of MHV-infected nude mice, and their depletion with neutralizing antibody resulted in an 80% reduction in demyelination. Moreover, demyelination induced by MHV-A59, another neurotropic strain of MHV, has been shown to develop in adult immunocompromised mice lacking B and T cells.[19] It has also been demonstrated that the depletion of $CD4^+$ or $CD8^+$ T cells after the acute stage of infection does not reduce demyelination.[20,21] Indeed, recent studies on MHV-A59 or the demyelination induced by its isogenic spike protein (host-attachment protein) recombinant strain, RSA59, exhibit that inflammatory CNS demyelination consists of a mixed population of inflammatory cells, predominantly macrophages/microglia and a smaller population of T lymphocytes but not conventional $CD4^+$ or $CD8^+$ αβ T cells.[22–24] These results illustrate that γδ T cells can substitute for T cells in a virus model of demyelination, but not much is known about the mechanism of action of effectors.

γδ T cells in infection and immunity

Because of their immune response against viral infection, macrophages, NK cells, and interferons are mostly known as immune effectors, and slow-generating, adaptive Ag-specific αβ T-cell and B-cell responses are known to be often crucial for the clearance of the pathogen and establishment of adaptive immunity. Although the existence of γδ T cells has been known for a long time, their significance in this paradigm of protective immunity has not been well documented until some recent studies have suggested that γδ T cells may play a role in the control of parasitic infections such as malaria and *Eimeria veriformis* and bacterial infections such as *Listeria monocytogenes* and *Klebsiella pneumonia.*[25–34] Information about these cells in viral infections still remains elusive,[35–40] although there is an ongoing critical reappraisal of the protective role of γδ T cells in viral infection. Recently, it has been reported that there is an increased number of γδ T cells in the peripheral blood of individuals infected with HIV and Epstein–Barr virus,[37,41] and some human γδ T cells clones preferentially lyse targets infected with vaccinia virus 3 or herpes simplex virus.[35] In some viral infection, antiviral function of γδ T cells can be substituted and masked by αβ T cells,[28,38,39] which explain why the role of γδ T cells has been concealed in the field of protective immunity. However, with the advent of the novel cytokine IL-17 and a new subset of

T_H17 cells, γδ T cells attain a new dimension in the field of infection and immunity.

In addition to the innate immune function, growing evidence from both human and primate studies suggest that γδ T cells are involved in inducing adaptive immunity by regulating CD8 T-cell memory responses. It has been proposed that in West Nile (WN) virus infection, γδ T cells contribute to the development of adaptive immunity.[42] However, the development of CD8 T-cell memory response to WN virus infection is not fully understood. Several attempts are being made to determine whether γδ T cells can directly link innate and adaptive immunity in viral infection and contribute to memory response, thus playing a potential role in future vaccine development.

γδ T cells are known to have a role in the pathogenesis of various autoimmune diseases and diseases of unknown etiology, as elevated levels of γδ T cells have been reported in rheumatoid arthritis,[43] MS,[44,45] pulmonary sarcoidosis,[46] inflammatory bowel disease,[47] and polymyositis.[48] Some of these diseases might be precipitated or exacerbated by viral infections, and recent evidence has indicated that γδ T cells may contribute to myocarditis in mice infected with encephalomyocarditis virus.[49] Recent studies have also found γδ T cells in the cerebrospinal fluid (CSF) and lesions of patients with MS.[50] These findings showed that γδ T cells may play a role in regulating autoimmune inflammation in the CNS; however, a causal relationship has not yet been established. In summary, γδ T cells are a multifaceted group of cells that might have both innate and adaptive characteristics and functions.

IL-17 in CNS inflammation

IL-17 is a cytokine that plays an important role in orchestrating innate and adaptive immune function.[51] IL-17 has also been shown to exacerbate experimental autoimmune diseases;[52] $CD4^+$ αβ T cells, γδ T cells, NK cells, and LTi-like cells all produce IL-17.[5,53,54] However, γδ T cells are often the major source of IL-17.[4,5] Recently, it has been found that γδ T cells infiltrate the CNS during the development of EAE, and a very high frequency of these cells secretes IL-17.[5]

IL-17A was described earlier,[55] but became a major focus of research only recently, after the discovery of a novel IL-17-A-producing T_H-cell lineage (T_H17).[56–60] $CD4^+$ T cells, upon activation and expansion, develop into various T_H-cell subsets with different cytokine profiles and distinct effector functions. T cells were earlier divided into T_H1 or T_H2 cells, depending on the cytokines they produce. A third subset of IL-17-producing effector T_H cells, called T_H17 cells, has recently been discovered and characterized.[54,61–63] T_H17 cells are generated in response to polarizing cytokines, where TGF-β plus IL-1β, IL-6, or IL-21 act as differentiation factors, IL-23 as growth and stabilization factor, and STAT3, RORγ, and RORα as transcription factors. Although the mechanism of activation of T_H17 cells and $CD4^+$ T cells that secrete IL-17 is known to some extent, much less is known about the ability of innate cell subpopulations to produce IL-17.

The transcription factor RORγt and IL-23 receptor (IL-23R), the master regulator of T_H17-cell differentiation, which has been associated with the development and differentiation of $CD4^+$ T_H17 cells,[64] are also constitutively expressed by NKT cells and $CD4^+CD3^-$ LTi-like cells.[53,64,65] γδ T cells constitutively express IL-23R and the transcription factor RORγt and produce IL-17, in response to activation by IL-1 and IL-23, without T-cell receptor engagement.[65] IL-17-producing γδ T cells were found at high frequency in the brain of mice with EAE. γδ T cells activated by IL-1β and IL-23 promoted IL-17 production by $CD4^+$ T cells and increased susceptibility to EAE, suggesting that γδ T cells act in an amplification loop for IL-17 production by T_H17 cells. γδ T cells activated by IL-1β and IL-23 are an important source of innate IL-17.[65]

Recently published studies on MS and EAE have demonstrated an association between the development of demyelinating plaques and the accumulation of T_H17 cells at the center and periphery of the lesions.[66–68] Similarly, IL-17-producing γδ T cells were also found at high frequency in the brain of mice with EAE.[5]

Like other inflammatory cytokines, IL-17A has both protective and pathogenic roles. IL-17A is important for host defense against infectious organisms.[67,69–71] However, elevated IL-17A levels in several autoimmune diseases, including MS and EAE, contribute to disease pathogenesis.[52,72–74] Deficiency or neutralization of IL-17A in EAE reduces disease susceptibility and clinical severity.[52] IL-17A can induce the expression of a range of inflammatory mediators and thus can modulate the activities of inflammatory cells through production of numerous cytokines and chemokines involved in inflammatory responses.[75,76] Infiltration of inflammatory cells and encephalitogenic T cells in the CNS is the hallmark of EAE.[10] IL-17A expression is increased in lymphocytes derived from EAE mice, and anti-IL-17A antibody treatment during the recovery phase in a relapsing–remitting EAE model delays the onset and reduces incidence and severity of relapses.[77,78] In patients with MS, IL-17A mRNA and protein are increased in both brain lesions and mononuclear cells isolated from blood and

CSF.[79,80] Recently, it was demonstrated that IL-17A produced by T_H17 cells is detectable at the blood–brain barrier in MS lesions and that IL-17A can promote blood–brain barrier disruption in vitro.[81]

IL-17 receptor signaling in CNS inflammation

IL-17A functions through a distinct ligand–receptor signaling system.[2,3] IL-17A is the founding member of a recently described cytokine family with unique sequences and functions in the immune system and elsewhere.[82] These cytokine molecules, consisting of six ligands (IL-17A–F) and five receptors (IL-17RA–IL-17RE) in mammals, has distinct primary amino acid structures with only minimal homology to other cytokine families. By far the best studied of these cytokines are IL-17A and its receptor, IL-17RA. In contrast to the restricted expression of IL-17A, the IL-17RA is ubiquitously expressed, and thus most cells are potential physiological targets of IL-17A.

The unique structural features of IL-17R family receptors are also known to mediate signaling events that are surprisingly distinct from those triggered by other cytokine receptors, particularly those usually involved in adaptive immunity. The signature cytokines involved in the T_H1- and T_H2-cell responses trigger Janus kinase signaling pathways, whereas IL-17R family cytokines mediate signaling through a distinct pathway that depends on ACT1 (also known as CIKS), resulting in the activation of proinflammatory mediators that are usually associated with innate immune signaling, such as nuclear factor-κB. Thus, because of the unusual signaling properties of IL-17, T_H17 cells act as a bridge between adaptive and innate immunity. Studies have been initiated to define the architecture of the IL-17R family with its ligand–receptor relationships and signal transduction pathways. Current discoveries in the field of IL-17 cytokine receptor biology and its potential implications with respect to emerging therapeutics have been discussed elegantly in a very recent reviews by Gaffen.[1,83]

IL-17RA is a widely expressed receptor that binds IL-17A with high affinity.[2,3] Leukocytes from mice lacking IL-17RA fail to bind IL-17A, and antibodies against IL-17RA inhibit the activity of IL-17A on human epithelial cells, indicating that IL-17RA is critical for IL-17A function.[84] Recently, it has been demonstrated that in infectious models in which neutrophils are crucial for host defense, IL-17RA deficiency results in reduced chemokine levels, reduced neutrophil numbers, and increased susceptibility to infection.[67,71] IL-17RA signaling is implicated in both innate and adaptive elements of infectious and autoimmune diseases;[72] however, little is known about its signaling in the CNS. One reason may be that IL-17RA is expressed in the CNS at a very low level. Expression of IL-17RA in the CNS of healthy human subjects is undetectable by immunofluorescence, but the receptor was expressed in CNS endothelial cells within heavily infiltrated MS lesions.[81] Given the important role that IL-17A plays in autoimmune diseases of the CNS, it is important to understand responses of CNS cells to IL-17RA signaling.

Human CNS cells express very little IL-17 receptors.[81] Recently, IL-17RA expression in the mouse CNS was documented and compared between control and EAE mice using RT-PCR, in situ hybridization, and immunohistochemistry.[85] Results indicated increased IL-17RA expression in the CNS of mice with EAE and constitutive expression of functional IL-17RA in mouse CNS tissue. In humans, it has been demonstrated that IL-17RA is expressed on CNS endothelial cells in MS lesions although it has not been possible to detect IL-17RA expression in situ in healthy CNS.[81] CNS cell type–specific expression of IL-17RA was examined in a highly purified, isolated astrocytes and microglial cell cultures (culture technique was adopted from Marek et al[86]), and cytokine/chemokine production was measured in IL-17A-treated cultures to evaluate the functional status of IL-17RA. Experiment on isolated glial cells demonstrated that astrocyte and microglia specifically express IL-17RA in vitro, and IL-17A treatment induces biological responses in these cells, including significant upregulation of monocyte chemotactic protein (MCP-1), MCP-5, macrophage inflammatory protein-2, and KC chemokine secretion. Exogenous IL-17A does not significantly alter the expression of IL-17RA in glial cells, suggesting that upregulation of chemokines by glial cells is due to IL-17A signaling through constitutively expressed IL-17RA. The cellular response elicited in glial cells by IL-17A will likely differ depending on the inflammatory status of the tissue. In addition, cross-communication between IL-17A and other cytokine signaling systems would likely modify the response of glial cells to IL-17A.

Conclusions

Constitutive expression of IL-17RA in mouse CNS, upregulation during EAE, and its expression on astrocytes and microglia suggest a role for glial IL-17A signaling in mediating CNS inflammation and may be a potential pathway to be targeted by therapeutic interventions. Infiltration of IL-17A-secreting T cells (γδ T cells and T_H17 cells) has clearly been demonstrated to be a pathogenic event in EAE. The resultant cellular and chemokine milieu and its effect on IL-17RA signaling in glial

cells warrant detailed study in the future. Moreover, to date, the fundamental signaling mechanisms used by the IL-17R complex are still unclear. Although the current structure–function studies have primarily focused on the IL-17RA subunit, recent research indicates that the IL-17RC subunit plays a key role in modulating IL-17 responses.[87] Proper regulation of the IL-17 signaling axis results in effective host defense against extracellular pathogens, while aberrant signaling can drive autoimmune pathology. Elucidating the molecular mechanisms underlying IL-17 signal transduction can enhance our understanding of inflammatory immune processes and also create an avenue for therapeutic intervention in the treatment of IL-17-dependent diseases. Recent studies have focused on the role of γδ T cells/T_H17 cells and their possible contribution in T_H17/IL-17 inflammation in MS and EAE. Understanding the role of γδ T cells in concurrence with T_H17 cells/IL-17 in virus-induced CNS inflammation also require immediate attention. In sum, T_H17 cells has opened up a new framework for future studies on IL-17 and γδ T cells in infection and immunity.

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Disclosure

The author reports no conflict of interest.

References

1. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol*. 2009;9:556–567.
2. Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev*. 2003; 14:155–174.
3. Yao Z, Fanslow WC, Seldin MF, et al. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity*. 1995;3:811–821.
4. Roark CL, Simonian PL, Fontenot AP, et al. gammadelta T cells: an important source of IL-17. *Curr Opin Immunol*. 2008;20:353–357.
5. Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. *Immunity*. 2009;31:331–341.
6. Ottones F, Dornand J, Naroeni A, Liautard JP, Favero J. V gamma 9V delta 2 T cells impair intracellular multiplication of *Brucella suis* in autologous monocytes through soluble factor release and contact-dependent cytotoxic effect. *J Immunol*. 2000;165:7133–7139.
7. Sospedra M, Martin R. Immunology of multiple sclerosis. *Annu Rev Immunol*. 2005;23:683–747.
8. Gandhi R, Laroni A, Weiner HL. Role of the innate immune system in the pathogenesis of multiple sclerosis. *J Neuroimmunol.* 2010;221: 7–14.
9. Konigshofer Y, Chien YH. Gammadelta T cells – innate immune lymphocytes? *Curr Opin Immunol*. 2006;18:527–533.
10. McFarland HF, Martin R. Multiple sclerosis: a complicated picture of autoimmunity. *Nat Immunol*. 2007;8:913–919.
11. O'Brien K, Fitzgerald DC, Naiken K, Alugupalli KR, Rostami AM, Gran B. Role of the innate immune system in autoimmune inflammatory demyelination. *Curr Med Chem*. 2008;15:1105–1115.
12. Steinman L. Myelin-specific CD8 T cells in the pathogenesis of experimental allergic encephalitis and multiple sclerosis. *J Exp Med*. 2001;194:F27–F30.
13. Miller SD, Vanderlugt CL, Begolka WS, et al. Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. *Nat Med*. 1997;3:1133–1136.
14. Rodriguez M, Sriram S. Successful therapy of Theiler's virus-induced demyelination (DA strain) with monoclonal anti-Lyt-2 antibody. *J Immunol*. 1988;140:2950–2955.
15. Yamada M, Zurbriggen A, Fujinami RS. Monoclonal antibody to Theiler's murine encephalomyelitis virus defines a determinant on myelin and oligodendrocytes, and augments demyelination in experimental allergic encephalomyelitis. *J Exp Med*. 1990;171:1893–1907.
16. Haring JS, Pewe LL, Perlman S. Bystander CD8 T cell-mediated demyelination after viral infection of the central nervous system. *J Immunol*. 2002;169:1550–1555.
17. Wang FI, Stohlman SA, Fleming JO. Demyelination induced by murine hepatitis virus JHM strain (MHV-4) is immunologically mediated. *J Neuroimmunol*. 1990;30:31–41.
18. Dandekar AA, Perlman S. Virus-induced demyelination in nude mice is mediated by gamma delta T cells. *Am J Pathol*. 2002;161: 1255–1263.
19. Matthews AE, Lavi E, Weiss SR, Paterson Y. Neither B cells nor T cells are required for CNS demyelination in mice persistently infected with MHV-A59. *J Neurovirol*. 2002;8:257–264.
20. Sutherland RM, Chua MM, Lavi E, et al. $CD4^+$ and $CD8^+$ T cells are not major effectors of mouse hepatitis virus A59-induced demyelinating disease. *J Neurovirol*. 1997;3:225–228.
21. Wu GF, Dandekar AA, Pewe L, Perlman S. CD4 and CD8 T cells have redundant but not identical roles in virus-induced demyelination. *J Immunol*. 2000;165:2278–2286.
22. Das Sarma J, Kenyon LC, Hingley ST, Shindler KS. Mechanisms of primary axonal damage in a viral model of multiple sclerosis. *J Neurosci*. 2009;29:10272–10280.
23. Shindler KS, Kenyon LC, Dutt M, Hingley ST, Das Sarma J. Experimental optic neuritis induced by a demyelinating strain of mouse hepatitis virus. *J Virol*. 2008;82:8882–8886.
24. Das Sarma J. A mechanism of virus-induced demyelination. *Interdiscip Perspect Infect Dis*. 2010;2010:109239.
25. D'Souza CD, Cooper AM, Frank AA, Mazzaccaro RJ, Bloom BR, Orme IM. An anti-inflammatory role for gamma delta T lymphocytes in acquired immunity to *Mycobacterium tuberculosis*. *J Immunol*. 1997; 158:1217–1221.
26. Emoto M, Danbara H, Yoshikai Y. Induction of gamma/delta T cells in murine salmonellosis by an avirulent but not by a virulent strain of Salmonella choleraesuis. *J Exp Med*. 1992;176:363–372.
27. Findly RC, Roberts SJ, Hayday AC. Dynamic response of murine gut intraepithelial T cells after infection by the coccidian parasite Eimeria. *Eur J Immunol*. 1993;23:2557–2564.
28. Hayday AC. [gamma][delta] Cells: a right time and a right place for a conserved third way of protection. *Annu Rev Immunol*. 2000;18: 975–1026.
29. Ladel CH, Blum C, Dreher A, Reifenberg K, Kaufmann SH. Protective role of gamma/delta T cells and alpha/beta T cells in tuberculosis. *Eur J Immunol*. 1995;25:2877–2881.
30. Mombaerts P, Arnoldi J, Russ F, Tonegawa S, Kaufmann SH. Different roles of alpha beta and gamma delta T cells in immunity against an intracellular bacterial pathogen. *Nature*. 1993;365:53–56.
31. Moore TA, Moore BB, Newstead MW, Standiford TJ. Gamma delta-T cells are critical for survival and early proinflammatory cytokine gene expression during murine Klebsiella pneumonia. *J Immunol*. 2000;165: 2643–2650.
32. Salerno A, Dieli F. Role of gamma delta T lymphocytes in immune response in humans and mice. *Crit Rev Immunol*. 1998;18:327–357.

33. Seixas EM, Langhorne J. gammadelta T cells contribute to control of chronic parasitemia in *Plasmodium chabaudi* infections in mice. *J Immunol*. 1999;162:2837–2841.
34. Tsuji M, Mombaerts P, Lefrancois L, Nussenzweig RS, Zavala F, Tonegawa S. Gamma delta T cells contribute to immunity against the liver stages of malaria in alpha beta T-cell-deficient mice. *Proc Natl Acad Sci U S A*. 1994;91:345–349.
35. Bukowski JF, Morita CT, Brenner MB. Recognition and destruction of virus-infected cells by human gamma delta CTL. *J Immunol*. 1994; 153:5133–5140.
36. Carding SR, Allan W, Kyes S, Hayday A, Bottomly K, Doherty PC. Late dominance of the inflammatory process in murine influenza by gamma/delta + T cells. *J Exp Med*. 1990;172:1225–1231.
37. de Paoli P, Gennari D, Martelli P, et al. A subset of gamma delta lymphocytes is increased during HIV-1 infection. *Clin Exp Immunol*. 1991;83:187–191.
38. Johnson RM, Lancki DW, Sperling AI, et al. A murine CD4$^-$, CD8$^-$ T cell receptor-gamma delta T lymphocyte clone specific for herpes simplex virus glycoprotein I. *J Immunol*. 1992;148:983–988.
39. Sciammas R, Kodukula P, Tang Q, Hendricks RL, Bluestone JA. T cell receptor-gamma/delta cells protect mice from herpes simplex virus type 1-induced lethal encephalitis. *J Exp Med*. 1997;185:1969–1975.
40. Wallace M, Malkovsky M, Carding SR. Gamma/delta T lymphocytes in viral infections. *J Leukoc Biol*. 1995;58:277–283.
41. de Paoli P, Gennari D, Martelli P, Cavarzerani V, Comoretto R, Santini G. Gamma delta T cell receptor-bearing lymphocytes during Epstein-Barr virus infection. *J Infect Dis*. 1990;161:1013–1016.
42. Wang T, Gao Y, Scully E, et al. Gamma delta T cells facilitate adaptive immunity against West Nile virus infection in mice. *J Immunol*. 2006; 177:1825–1832.
43. Olive C, Gatenby PA, Serjeantson SW. T-cell receptor gamma/delta usage in rheumatoid arthritis. Persistence of oligoclonality in the periphery. *Ann N Y Acad Sci*. 1995;756:183–185.
44. Freedman MS, Ruijs TC, Selin LK, Antel JP. Peripheral blood gamma-delta T cells lyse fresh human brain-derived oligodendrocytes. *Ann Neurol*. 1991;30:794–800.
45. Nick S, Pileri P, Tongiani S, Uematsu Y, Kappos L, de Libero G. T cell receptor gamma delta repertoire is skewed in cerebrospinal fluid of multiple sclerosis patients: molecular and functional analyses of antigen-reactive gamma delta clones. *Eur J Immunol*. 1995;25:355–363.
46. Tamura N, Holroyd KJ, Banks T, Kirby M, Okayama H, Crystal RG. Diversity in junctional sequences associated with the common human V gamma 9 and V delta 2 gene segments in normal blood and lung compared with the limited diversity in a granulomatous disease. *J Exp Med*. 1990;172:169–181.
47. Soderstrom K, Bucht A, Halapi E, Grönberg A, Magnusson I, Kiessling R. Increased frequency of abnormal gamma delta T cells in blood of patients with inflammatory bowel diseases. *J Immunol*. 1996; 156:2331–2339.
48. Hohlfeld R, Engel AG, Ii K, Harper MC. Polymyositis mediated by T lymphocytes that express the gamma/delta receptor. *N Engl J Med*. 1991;324:877–881.
49. Huber SA, Moraska A, Choate M. T cells expressing the gamma delta T-cell receptor potentiate coxsackievirus B3-induced myocarditis. *J Virol*. 1992;66:6541–6546.
50. Blink SE, Miller SD. The contribution of gammadelta T cells to the pathogenesis of EAE and MS. *Curr Mol Med*. 2009;9:15–22.
51. Yu JJ, Gaffen SL. Interleukin-17: a novel inflammatory cytokine that bridges innate and adaptive immunity. *Front Biosci*. 2008;13: 170–177.
52. Komiyama Y, Nakae S, Matsuki T, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J Immunol*. 2006;177:566–573.
53. Takatori H, Kanno Y, Watford WT, et al. Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. *J Exp Med*. 2009;206: 35–41.
54. Sutton C, Brereton C, Keogh B, et al. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J Exp Med*. 2006;203:1685–1691.
55. Aggarwal S, Gurney AL. IL-17: prototype member of an emerging cytokine family. *J Leukoc Biol*. 2002;71:1–8.
56. Bettelli E, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T (H) 17 cells. *Nature*. 2008;453:1051–1057.
57. Bettelli E, Oukka M, Kuchroo VK. T (H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol*. 2007;8:345–350.
58. Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4$^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*. 2005;6:1123–1132.
59. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med*. 2005;201:233–240.
60. Park H, Li Z, Yang XO, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol*. 2005;6: 1133–1141.
61. Chen Z, O'Shea JJ. Regulation of IL-17 production in human lymphocytes. *Cytokine*. 2008;41:71–78.
62. Veldhoen M, Hocking RJ, Atkins CJ, et al. Taffeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity*. 2006;24:179–189.
63. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol*. 2007;25:821–852.
64. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 2006;126:1121–1133.
65. Rachitskaya AV, Hansen AM, Horai R, et al. Cutting edge: NKT cells constitutively express IL-23 receptor and RORgammat and rapidly produce IL-17 upon receptor ligation in an IL-6-independent fashion. *J Immunol*. 2008;180:5167–5171.
66. Aranami T, Yamamura T. Th17 Cells and autoimmune encephalomyelitis (EAE/MS). *Allergol Int*. 2008;57:115–120.
67. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17 A for systemic anti-Candida albicans host defense in mice. *J Infect Dis*. 2004;190:624–631.
68. Segal BM. Th17 cells in autoimmune demyelinating disease. *Semin Immunopathol*. 32:71–77.
69. Kelly MN, Kolls JK, Happel K, et al. Interleukin-17/interleukin-17 receptor-mediated signaling is important for generation of an optimal polymorphonuclear response against *Toxoplasma gondii* infection. *Infect Immun*. 2005;73:617–621.
70. Ye P, Garvey PB, Zhang P, et al. Interleukin-17 and lung host defense against *Klebsiella pneumoniae* infection. *Am J Respir Cell Mol Biol*. 2001;25:335–340.
71. Yu JJ, Ruddy MJ, Wong GC, et al. An essential role for IL-17 in preventing pathogen-initiated bone destruction: recruitment of neutrophils to inflamed bone requires IL-17 receptor-dependent signals. *Blood*. 2007;109:3794–3802.
72. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity*. 2004;21:467–476.
73. Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest*. 1999;103:1345–1352.
74. Vaknin-Dembinsky A, Balashov K, Weiner HL. IL-23 is increased in dendritic cells in multiple sclerosis and down-regulation of IL-23 by antisense oligos increases dendritic cell IL-10 production. *J Immunol*. 2006;176:7768–7774.
75. Forlow SB, Schurr JR, Kolls JK, Bagby GJ, Schwarzenberger PO, Ley K. Increased granulopoiesis through interleukin-17 and granulocyte colony-stimulating factor in leukocyte adhesion molecule-deficient mice. *Blood*. 2001;98:3309–3314.
76. Linden A, Adachi M. Neutrophilic airway inflammation and IL-17. *Allergy*. 2002;57:769–775.

77. Chen Y, Langrish CL, McKenzie B, et al. Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis. *J Clin Invest*. 2006;116:1317–1326.
78. Hofstetter HH, Ibrahim SM, Koczan D, et al. Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. *Cell Immunol*. 2005;237:123–130.
79. Lock C, Hermans G, Pedotti R, et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat Med*. 2002;8:500–508.
80. Matusevicius D, Kivisakk P, He B, et al. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult Scler*. 1999;5:101–104.
81. Kebir H, Kreymborg K, Ifergan I, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med*. 2007;13:1173–1175.
82. Kawaguchi M, Adachi M, Oda N, Kokubu F, Huang SK. IL-17 cytokine family. *J Allergy Clin Immunol*. 2004;114:1265–1273; quiz 1274.
83. Gaffen SL. An overview of IL-17 function and signaling. *Cytokine*. 2008;43:402–407.
84. McAllister F, Henry A, Kreindler JL, et al. Role of IL-17A, IL-17F, and the IL-17 receptor in regulating growth-related oncogene-alpha and granulocyte colony-stimulating factor in bronchial epithelium: implications for airway inflammation in cystic fibrosis. *J Immunol*. 2005;175:404–412.
85. Das Sarma J, Ciric B, Marek R, et al. Functional interleukin-17 receptor A is expressed in central nervous system glia and upregulated in experimental autoimmune encephalomyelitis. *J Neuroinflammation*. 2009;6:14.
86. Marek R, Caruso M, Rostami A, Grinspan JB, Das Sarma J. Magnetic cell sorting: a fast and effective method of concurrent isolation of high purity viable astrocytes and microglia from neonatal mouse brain tissue. *J Neurosci Methods*. 2008;175:108–118.
87. Ho AW, Gaffen SL. IL-17RC: a partner in IL-17 signaling and beyond. *Semin Immunopathol*. 2010;32:33–42.