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Life before Seventeen: Cloning of the IL-17 Receptor

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It is often said that pathogens know more about the immune system than we do. For example, nearly all viruses have evolved some means of evading or counteracting viral pattern recognition receptor and IFN signaling pathways (1, 2). Many large DNA viruses, such as herpesviruses and poxviruses, encode homologs of cytokines and chemokines or their receptors, which may function as either agonists or antagonists. In most cases, we do not understand precisely how these proteins benefit the virus. However, exploiting this knowledge has been a fruitful means of discovering new pathways important for microbial pathogenesis, as well as identifying potential therapeutic strategies that may be harnessed for clinical benefit (3).

IL-17 is another cytokine with an interesting but so far unexplained viral connection. IL-17 was cloned in 1993 from a subtractive rodent cDNA library and termed CTLA8 (4) [the gene was later shown to be of rat origin (5)]. The possibility that CTLA8 encoded a cytokine was inferred from the presence of AU-rich elements in its 3′ UTR, a common feature of cytokine and growth factor genes, as well as the observation that CTLA8 expression was restricted to T cell hybridomas. A particularly novel aspect of this discovery was the 57% identity between CTLA8 and ORF13 in *Herpesvirus saimiri* (HVS), a T cell tropic γ-herpesvirus that causes a lymphoproliferative syndrome in New World primates. However, the original report describing CTLA8 did not identify any functional activity for this molecule. The homology to ORF13 (HVS13), although intriguing, was not illuminating in terms of CTLA8 biology.

Following the description of CTLA8, Melanie Spriggs' group at Immunex used an antiserum specific for HVS13 to identify a secreted glycosylated protein produced by HVS-infected owl monkey kidney cells, and similar proteins were observed in HVS13-transfected CV1 cells. Using degenerate PCR primers, they also cloned the mouse and human homologs of CTLA8, which were renamed IL-17 (and later, IL-17A) (5, 6). Like other cytokines, IL-17 had a predicted site of *N*-glycosylation and several conserved cysteines, but its sequence did not resemble that of any members of known cytokine families. The cloning of IL-17 coincided with the sequencing of mammalian genomes, which led to the discovery of many new cytokines through in silico data mining. On the basis of homology with IL-17, several other IL-17–like cytokines were identified, including IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F (7, 8). The first crystal structure of an IL-17 family member (IL-17F) revealed unexpected similarity to cysteine-knot growth factors such as NGF (9). However, the sequence homology of IL-17-family cytokines to each other but not other proteins confirmed the notion that the IL-17 family constitutes a distinct class of cytokines and raised the interesting possibility that they might have unique immunological activities.

To clone the CTLA8/IL-17R, Yao et al. (5) screened an EL4 cDNA expression library with an HVS13.Fc fusion protein. The resulting clone encoded a single-pass, ubiquitously expressed type I transmembrane receptor of 864 aa. Like its ligand, the IL-17R exhibited a striking lack of homology with any known proteins, hinting that it might be the founding member of a new receptor family. Subsequent studies identified four additional receptors with homology to IL-17R (now termed IL-17RA) (8). One of these, IL-17RC, was found to be an obligate coreceptor for IL-17 and IL-17F signaling in fibroblasts (10) and was recently confirmed to be essential in a variety of IL-17–dependent disease settings (11, 12). The crystal structure of the human IL-17RA extracellular domain verified the unique nature of the receptor's overall architecture (13).

The biological effects of cytokines are mediated through signaling pathways activated by their cognate receptors. Its lack of sequence homology with other receptors meant that it was not possible to predict a priori the signaling pathways that IL-17RA might induce. However, IL-17RA has an unusually long cytoplasmic tail (521 aa), which suggested considerable potential for activation of signal transduction, perhaps by novel mechanisms. As a first step to defining signaling, Yao et al. (5) demonstrated activation of NF-κB in 3T3 fibroblasts, as well as IL-17–induced secretion of IL-6, an NF-κB–dependent gene product. A landmark 2003 bioinformatic study identified a region located within IL-17R family cytoplasmic tails homologous to Toll-IL-1R (TIR) domains, dubbed a "SEFIR" (14). This report further noted the presence of a SEFIR domain in Act1, a signaling intermediate previously linked to regulation of NF-κB by BAFF and CD40 (14, 15). Proof that Act1 was indeed essential for IL-17R signaling soon followed with studies of EAE and IL-17 signaling in Act1$^{-/-}$ mice (16, 17). Act1 is both an adaptor for TRAFs and an E3 ubiquitin ligase necessary for NF-κB activation by IL-17 (18). Although the SEFIR is conserved among IL-17R family members throughout evolution (19), empirical mapping studies of IL-17RA and IL-17RC revealed that substantial nonconserved sequences downstream of the SEFIR are additionally required

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Abbreviation used in this article: HVS, *Herpesvirus saimiri*.

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for IL-17 signaling (11, 20, 21). IL-17RA also pairs with IL-17RB to form the IL-25/IL-17E receptor (22) and may participate in other receptor complexes. Thus, IL-17RA may be analogous to common signaling subunits in other receptor families such as γc and gp130. A variety of studies evaluating IL-17R signal transduction are beginning to reveal the detailed modes of action of this intriguing receptor family (23, 24). However, much is still unknown, including mechanisms of synergy with other cytokines and the full array of ligand-receptor relationships within the IL-17 extended family.

A finding often overlooked in Yao et al. was the observation that IL-17 and its viral homolog could stimulate T cell proliferation in the presence of suboptimal PHA, which could be blocked by a soluble IL-17R.Fc. To date, very little follow-up has been done on the role of IL-17 activation of T cells, although direct effects in B lymphocytes have been convincingly documented (25, 26). The authors speculated that IL-17's ability to promote T cell proliferation might underlie HVS-induced lymphoproliferative disease. However, later studies showed that deletion of ORF13 from *H. saimiri* did not impact viral replication, T cell transformation capacity, or viral pathogenicity (27). Thus, it is a fascinating mystery why HVS has co-opted IL-17, and it remains the only virus known to have done so. In terms of evolution, the IL-17 and receptor family predates the origins of recombined Ag receptors, with homologs in sea lamprey, oysters, and zebrafish (28–31). This finding may suggest an evolutionary advantage of IL-17 that could shed light on the role of viral IL-17.

These days it goes without saying that IL-17 is most famous for its role as the signature cytokine of Th17 cells, which have emerged as major mediators of both autoimmunity and immunity against extracellular pathogens (32). The discovery of this subset in 2005 triggered a more nuanced appreciation of T cell immunology (33, 34), reviewed extensively elsewhere (35). IL-17 is produced not only by $CD4^+$ Th cells but also by a variety of innate lymphocytes, including γδT and NKT cells (36), and is a major regulator of the neutrophil response (37, 38). These features of IL-17 are consistent with its rapid action in primary infections, first documented for *Klebsiella pneumoniae* (39) but since observed in numerous infectious disease settings (40). Rare immunodeficiency syndromes impacting IL-17 expression have shed light on the major role of IL-17 in humans. Patients with *AIRE* deficiency develop neutralizing autoantibodies against IL-17A and IL-17F, but surprisingly their only disease manifestation is mucocutaneous candidiasis, caused by the commensal fungus *Candida albicans* (41). Similarly, individuals with inherited defects in IL-17F, IL-17RA, or STAT3 (required for Th17 differentiation) also exhibit mucosal candidiasis and cutaneous staphylococcal infections (42, 43), consistent with prior mouse studies (44–47). Conversely, Th17 cells and IL-17 itself promote pathology in autoimmune disease models, inspiring clinical trials of anti–IL-17A Abs as therapies for various autoimmune disorders (48, 49).

Who knows? Eventually we might figure out the secrets of IL-17 that *H. saimiri* knew all along.

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References

1. Bowie, A. G., and L. Unterholzner. 2008. Viral evasion and subversion of pattern-recognition receptor signalling. *Nat. Rev. Immunol.* 8: 911–922.
2. Randall, R. E., and S. Goodbourn. 2008. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *J. Gen. Virol.* 89: 1–47.
3. Rahman, M. M., A. R. Lucas, and G. McFadden. 2009. Viral TNF inhibitors as potential therapeutics. *Adv. Exp. Med. Biol.* 666: 64–77.
4. Rouvier, E., M.-F. Luciani, M.-G. Mattéi, F. Denizot, and P. Golstein. 1993. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a *Herpesvirus saimiri* gene. *J. Immunol.* 150: 5445–5456.
5. Yao, Z., W. C. Fanslow, M. F. Seldin, A.-M. Rousseau, S. L. Painter, M. R. Comeau, J. I. Cohen, and M. K. Spriggs. 1995. Herpesvirus saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 3: 811–821.
6. Yao, Z., S. L. Painter, W. C. Fanslow, D. Ulrich, B. M. Macduff, M. K. Spriggs, and R. J. Armitage. 1995. Human IL-17: a novel cytokine derived from T cells. *J. Immunol.* 155: 5483–5486.
7. Aggarwal, S., and A. L. Gurney. 2002. IL-17: prototype member of an emerging cytokine family. *J. Leukoc. Biol.* 71: 1–8.
8. Moseley, T. A., D. R. Haudenschild, L. Rose, and A. H. Reddi. 2003. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev.* 14: 155–174.
9. Hymowitz, S. G., E. H. Filvaroff, J. P. Yin, J. Lee, L. Cai, P. Risser, M. Maruoka, W. Mao, J. Foster, R. F. Kelley, et al. 2001. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. *EMBO J.* 20: 5332–5341.
10. Toy, D., D. Kugler, M. Wolfson, T. Vanden Bos, J. Gurgel, J. Derry, J. Tocker, and J. J. Peschon. 2006. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. *J. Immunol.* 177: 36–39.
11. Ho, A. W., F. Shen, H. R. Conti, N. Patel, E. E. Childs, A. C. Peterson, N. Hernández-Santos, J. K. Kolls, L. P. Kane, W. Ouyang, and S. L. Gaffen. 2010. IL-17RC is required for immune signaling via an extended SEF/IL-17R signaling domain in the cytoplasmic tail. *J. Immunol.* 185: 1063–1070.
12. Hu, Y., N. Ota, I. Peng, C. J. Refino, D. M. Danilenko, P. Caplazi, and W. Ouyang. 2010. IL-17RC is required for IL-17A- and IL-17F-dependent signaling and the pathogenesis of experimental autoimmune encephalomyelitis. *J. Immunol.* 184: 4307–4316.
13. Ely, L. K., S. Fischer, and K. C. Garcia. 2009. Structural basis of receptor sharing by interleukin 17 cytokines. *Nat. Immunol.* 10: 1245–1251.
14. Novatchkova, M., A. Leibbrandt, J. Werzowa, A. Neubüser, and F. Eisenhaber. 2003. The STIR-domain superfamily in signal transduction, development and immunity. *Trends Biochem. Sci.* 28: 226–229.
15. Qian, Y., J. Qin, G. Cui, M. Naramura, E. C. Snow, C. F. Ware, R. L. Fairchild, S. A. Omori, R. C. Rickert, M. Scott, et al. 2004. Act1, a negative regulator in CD40- and BAFF-mediated B cell survival. *Immunity* 21: 575–587.
16. Chang, S. H., H. Park, and C. Dong. 2006. Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. *J. Biol. Chem.* 281: 35603–35607.
17. Qian, Y., C. Liu, J. Hartupee, C. Z. Altuntas, M. F. Gulen, D. Jane-Wit, J. Xiao, Y. Lu, N. Giltiay, J. Liu, et al. 2007. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. *Nat. Immunol.* 8: 247–256.
18. Liu, C., W. Qian, Y. Qian, N. V. Giltiay, Y. Lu, S. Swaidani, S. Misra, L. Deng, Z. J. Chen, and X. Li. 2009. Act1, a U-box E3 ubiquitin ligase for IL-17 signaling. *Sci. Signal.* 2: ra63.
19. Ryzhakov, G., K. Blazek, and I. A. Udalova. 2011. Evolution of vertebrate immunity: sequence and functional analysis of the SEFIR domain family member Act1. *J. Mol. Evol.* 72: 521–530.
20. Maitra, A., F. Shen, W. Hanel, K. Mossman, J. Tocker, D. Swart, and S. L. Gaffen. 2007. Distinct functional motifs within the IL-17 receptor regulate signal transduction and target gene expression. *Proc. Natl. Acad. Sci. USA* 104: 7506–7511.
21. Onishi, R., S. Park, W. Hanel, A. Maitra, and S. Gaffen. 2010. The SEFIR is not enough: An extended region downstream of the interleukin-17RA SEFIR domain is required for IL-17-dependent signal transduction. *J. Biol. Chem.* 285: 32751–32759.
22. Rickel, E. A., L. A. Siegel, B. R. Yoon, J. B. Rottman, D. G. Kugler, D. A. Swart, P. M. Anders, J. E. Tocker, M. R. Comeau, and A. L. Budelsky. 2008. Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. *J. Immunol.* 181: 4299–4310.
23. Gaffen, S. L. 2009. Structure and signalling in the IL-17 receptor family. *Nat. Rev. Immunol.* 9: 556–567.
24. Iwakura, Y., H. Ishigame, S. Saijo, and S. Nakae. 2011. Functional specialization of interleukin-17 family members. *Immunity* 34: 149–162.
25. Hsu, H. C., P. Yang, J. Wang, Q. Wu, R. Myers, J. Chen, J. Yi, T. Guentert, A. Tousson, A. L. Stanus, et al. 2008. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. *Nat. Immunol.* 9: 166–175.

26. Doreau, A., A. Belot, J. Bastid, B. Riche, M. C. Trescol-Biemont, B. Ranchin, N. Fabien, P. Cochat, C. Pouteil-Noble, P. Trolliet, et al. 2009. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. *Nat. Immunol.* 10: 778–785.
27. Knappe, A., C. Hiller, H. Niphuis, F. Fossiez, M. Thurau, S. Wittmann, E. M. Kuhn, S. Lebecque, J. Banchereau, B. Rosenwirth, et al. 1998. The interleukin-17 gene of herpesvirus saimiri. *J. Virol.* 72: 5797–5801.
28. Roberts, S., Y. Gueguen, J. de Lorgeril, and F. Goetz. 2008. Rapid accumulation of an interleukin 17 homolog transcript in Crassostrea gigas hemocytes following bacterial exposure. *Dev. Comp. Immunol.* 32: 1099–1104.
29. Tsutsui, S., O. Nakamura, and T. Watanabe. 2007. Lamprey (*Lethenteron japonicum*) IL-17 upregulated by LPS-stimulation in the skin cells. *Immunogenetics* 59: 873–882.
30. Pancer, Z., W. E. Mayer, J. Klein, and M. D. Cooper. 2004. Prototypic T cell receptor and CD4-like coreceptor are expressed by lymphocytes in the agnathan sea lamprey. *Proc. Natl. Acad. Sci. USA* 101: 13273–13278.
31. Tsang, M., R. Friesel, T. Kudoh, and I. B. Dawid. 2002. Identification of Sef, a novel modulator of FGF signalling. *Nat. Cell Biol.* 4: 165–169.
32. Steinman, L. 2007. A brief history of T(H)17, the first major revision in the T(H) 1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat. Med.* 13: 139–145.
33. Park, H., Z. Li, X. O. Yang, S. H. Chang, R. Nurieva, Y. H. Wang, Y. Wang, L. Hood, Z. Zhu, Q. Tian, and C. Dong. 2005. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat. Immunol.* 6: 1133–1141.
34. Harrington, L. E., R. D. Hatton, P. R. Mangan, H. Turner, T. L. Murphy, K. M. Murphy, and C. T. Weaver. 2005. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.* 6: 1123–1132.
35. Korn, T., E. Bettelli, M. Oukka, and V. K. Kuchroo. 2009. IL-17 and Th17 cells. *Annu. Rev. Immunol.* 27: 485–517.
36. Cua, D. J., and C. M. Tato. 2010. Innate IL-17-producing cells: the sentinels of the immune system. *Nat. Rev. Immunol.* 10: 479–489.
37. Kolls, J. K., and A. Lindén. 2004. Interleukin-17 family members and inflammation. *Immunity* 21: 467–476.
38. Yu, J. J., and S. L. Gaffen. 2008. Interleukin-17: a novel inflammatory cytokine that bridges innate and adaptive immunity. *Front. Biosci.* 13: 170–177.
39. Ye, P., F. H. Rodriguez, S. Kanaly, K. L. Stocking, J. Schurr, P. Schwarzenberger, P. Oliver, W. Huang, P. Zhang, J. Zhang, et al. 2001. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J. Exp. Med.* 194: 519–527.
40. Peck, A., and E. D. Mellins. 2010. Precarious balance: Th17 cells in host defense. *Infect. Immun.* 78: 32–38.
41. Puel, A., C. Picard, S. Cypowyj, D. Lilic, L. Abel, and J. L. Casanova. 2010. Inborn errors of mucocutaneous immunity to *Candida albicans* in humans: a role for IL-17 cytokines? *Curr. Opin. Immunol.* 22: 467–474.
42. Puel, A., S. Cypowyj, J. Bustamante, J. F. Wright, L. Liu, H. K. Lim, M. Migaud, L. Israel, M. Chrabieh, M. Audry, et al. 2011. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* 332: 65–68.
43. Holland, S. M., F. R. DeLeo, H. Z. Elloumi, A. P. Hsu, G. Uzel, N. Brodsky, A. F. Freeman, A. Demidowich, J. Davis, M. L. Turner, et al. 2007. STAT3 mutations in the hyper-IgE syndrome. *N. Engl. J. Med.* 357: 1608–1619.
44. Schwarzenberger, P., and J. K. Kolls. 2002. Interleukin 17: an example for gene therapy as a tool to study cytokine mediated regulation of hematopoiesis. *J. Cell. Biochem. Suppl.* 38: 88–95.
45. Conti, H. R., F. Shen, N. Nayyar, E. Stocum, J. N. Sun, M. J. Lindemann, A. W. Ho, J. H. Hai, J. J. Yu, J. W. Jung, et al. 2009. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J. Exp. Med.* 206: 299–311.
46. Kagami, S., H. L. Rizzo, S. E. Kurtz, L. S. Miller, and A. Blauvelt. 2010. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against *Candida albicans*. *J. Immunol.* 185: 5453–5462.
47. Cho, J. S., E. M. Pietras, N. C. Garcia, R. I. Ramos, D. M. Farzam, H. R. Monroe, J. E. Magorien, A. Blauvelt, J. K. Kolls, A. L. Cheung, et al. 2010. IL-17 is essential for host defense against cutaneous *Staphylococcus aureus* infection in mice. *J. Clin. Invest.* 120: 1762–1773.
48. Hueber, W., D. D. Patel, T. Dryja, A. M. Wright, I. Koroleva, G. Bruin, C. Antoni, Z. Draelos, M. H. Gold, P. Durez, et al. 2010. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci. Transl. Med. 2:52ra72.
49. Genovese, M. C., F. Van den Bosch, S. A. Roberson, S. Bojin, I. M. Biagini, P. Ryan, and J. Sloan-Lancaster. 2010. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study. *Arthritis Rheum.* 62: 929–939.