ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY FOR OTHER INFLAMMATORY DISEASES

Case reports have also indicated that anti-IL-6RAb is effective for graft-versus-host disease and TNF-receptor-associated periodic syndrome (TRAPS). A patient with graft-versus-host disease presenting with abdominal pain and diarrhea had been refractory to all known treatments, but after anti-IL-6RAb was administered at 8 mg kg^{-1} every 2 weeks, symptoms improved in conjunction with histological improvement (145). TRAPS is a rare autosomal, predominantly inherited autoinflammatory disease caused by missense mutations of the 55-kDa TNF receptor superfamily 1A and characterized by recurrent episodes of fever, myalgia, arthralgia, migrating erysipelas, and serositis (146). One patient with TRAPS, whose anti-TNF inhibitor or IL-1R antagonist treatment could not be continued, was treated with anti-IL-6RAb. The antibody aborted an evolving acute attack and prevented further attacks of TRAPS (147). These case reports also indicate that anti-IL-6RAb can be effective for other (auto)inflammatory diseases.

CELLULAR AND MOLECULAR MECHANISM OF THE THERAPEUTIC EFFECT OF ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY

Anti-IL-6RAb blocks the binding of IL-6 with 80-kDa transmembrane IL-6R and neutralizes sIL-6R but not IL-6 itself. Anti-IL-6RAb administration initially produces a transient increase in the serum levels of IL-6, but continuous administration subsequently results in a tendency for IL-6 to decrease along with amelioration of the disease activity (33, 148). This suggests that blockade of IL-6 signaling may be able to correct the underlying fundamental immune defects present in various autoimmune and inflammatory diseases. During the past five years, many studies have shown that a balance of new CD4 T cell subsets consisting of Th17 and Treg is important for the pathogenesis of autoimmune diseases. IL-17 produced by Th17 mediates tissue inflammation by promoting synthesis of proinflammatory cytokines including IL-6, whereas it is involved in the elimination of extracellular bacteria through the recruitment and activation of neutrophils and macrophages (8). More importantly, Th17, as opposed to Th1, has been recently recognized as the primary effector cell responsible for the development of autoimmune diseases. In contrast, Treg play a critical role in maintaining immune homeostasis and preventing the development of autoimmune diseases (149); therefore, a balance between Th17 and Treg is crucial for immune homeostasis, whereas an imbalance (Th17$\gg$Treg) causes the onset of various autoimmune and chronic inflammatory diseases. IL-6 in combination with TGF-β promotes the differentiation of naïve T cells into Th17 but inhibits TGF-β-induced Treg differentiation, indicating that IL-6 is an important factor in determining Th17/Treg balance. Dysregulated IL-6 production leads to predominance of Th17 over Treg, whereas anti-IL-6RAb can repair this imbalance (**Figure 3**) (9, 18). Indeed, in several animal disease models, anti-IL-6RAb suppresses antigen-specific Th17 differentiation but induces antigen-specific Treg differentiation (90, 143, 144, 150).

Nuclear receptors, retinoid-related orphan receptors (ROR)γt and RORα, which are induced by IL-6-mediated STAT3 activation, are essential for the induction of Th17 (8). Interestingly, however, IL-27 inhibits Th17 differentiation but does not downregulate the expression of RORγt or RORα (151, 152), suggesting that other nuclear receptor or transcriptional factor may be involved in this differentiation. Stimulation of murine naïve T cells with IL-6 and TGF-β, which are essential for the induction of Th17, induced a marked expression of aryl hydrocarbon receptor (Ahr) (153), which is known as a dioxin receptor. Ahr is present in cytoplasm, and, upon binding with a ligand, it translocates to the nucleus and dimerizes with the Ahr nuclear translocator (Arnt). The resultant Ahr-Arnt complex then binds to specific sequences, designated as xenobiotic

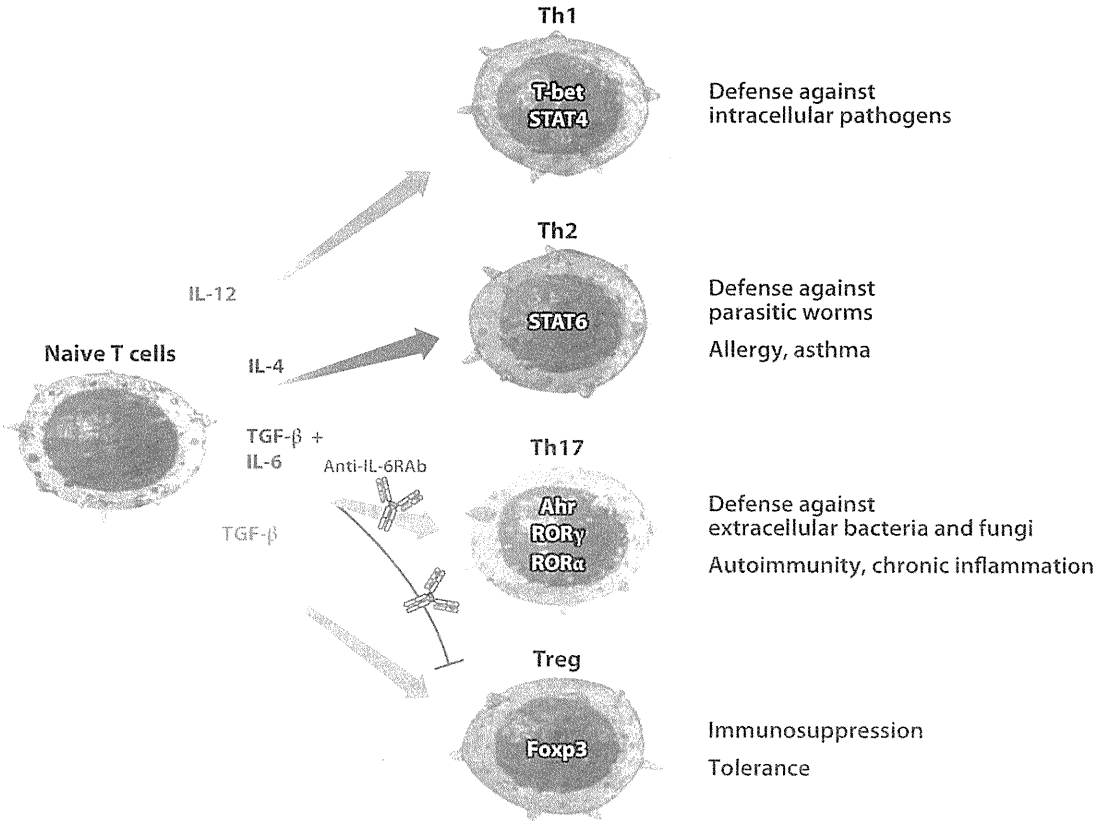

Figure 3

Anti-interleukin-6 receptor antibody (anti-IL-6RAb) may be able to repair Th17/Treg imbalance. When $CD4^+$ naïve T cells are primed, a specific cytokine directs their differentiation into an effector T cell subset. IL-6 in combination with TGF-β preferentially induces Th17 development, whereas IL-6 inhibits TGF-β-induced Treg differentiation, thus leading to Th17/Treg imbalance. This imbalance is pathologically important for the development of autoimmune and chronic inflammatory diseases. Anti-IL-6RAb may be able to repair this imbalance. Abbreviations: Ahr, aryl hydrocarbon receptor; Foxp3, forkhead box P3; ROR, retinoid-related orphan receptor; STAT, signal transducer and activator of transcription; T-bet, Th1-specific T box transcription factor; TGF-β, transforming growth factor β; Th17, IL-17-producing T helper cells; Treg, regulatory T cells.

responsive elements, and exerts a variety of biological effects (154). Moreover, Ahr induced by IL-6 plus TGF-β in T cells interacts with STAT1 and STAT5 but not with STAT3. As reported, STAT3 positively regulates Th17 development by inducing RORγt and RORα, but STAT1 and STAT5 negatively regulate this differentiation. IL-27 or IFN-γ reportedly activates STAT1 (151, 155), and IL-2 activates STAT5, resulting in the suppression of Th17 development by these cytokines (156). These experiments demonstrate that Ahr interacts with both STAT1 and STAT5 and negatively regulates their activities, thus leading to the augmentation of Th17 differentiation by the removal of its negative regulators. As expected, AhrKO mice showed a significant decrease in Th17 development (153) and failed to develop collagen-induced arthritis (157). The induction of EAE is also inhibited in AhrKO mice (158). All these results indicate the importance of the IL-6-Ahr-Th17 axis in the development of autoimmune diseases. Of equal importance is that anti-IL-6RAb may be able to disrupt this axis and repair the Th17/Treg imbalance.

Roll et al. (159) examined 16 RA patients for the in vivo effect of anti-IL-6RAb on the B cell compartment and found that anti-IL-6RAb induced a significant reduction of peripheral preswitch and postswitch memory B cells. As described elsewhere, anti-IL-6RAb treatment leads to a reduction of pathological $CD38^{high}CD19^{low}IgD^{-}$ plasma cells in SLE patients (57), and anti-IL-6RAb can diminish survival of the plasmablast population, which produces mainly AQP4 antibody in NMO (94). These findings suggest that the clinical effect of anti-IL-6RAb is also mediated through its inhibition of pathological autoantibody production.

CONCLUSION AND FUTURE PERSPECTIVES

IL-6 participates in the host defense against environmental pathogens and is involved in a broad spectrum of biological events, such as immune responses, hematopoiesis, and acute-phase reactions, whereas dysregulation of IL-6 production has been implicated in the pathogenesis of various autoimmune and chronic inflammatory diseases. Therapeutic targeting of the IL-6R is therefore considered to be a rational treatment strategy for various diseases (**Table 1**). Although this review has focused on the effects and potential uses of anti-IL-6RAb for autoimmune and inflammatory

Table 1 Therapeutic targeting of the interleukin-6 receptor for various autoimmune and inflammatory diseases

Autoimmune diseases
Rheumatoid arthritis (approved[a] in more than 90 countries worldwide)
Systemic lupus erythematosus
Systemic sclerosis
Polymyositis
Takayasu arteritis and giant cell arteritis
Crohn's disease
Relapsing polychondritis
Acquired hemophilia A
Multiple sclerosis and neuromyelitis optica
Chronic inflammatory diseases
Castleman's disease (approved in Japan)
Systemic and polyarticular juvenile idiopathic arthritis (approved in Japan)
Adult-onset Still's disease
Amyloid A amyloidosis
Polymyalgia rheumatica
RS3PE
Spondyloarthritides
Behçet's disease
Uveitis
Graft-versus-host disease
Autoinflammatory diseases (TRAPS)

[a]Anti-interleukin-6 receptor antibody (anti-IL-6RAb) has been approved as a biological drug for the treatment of rheumatoid arthritis, Castleman's disease, and juvenile idiopathic arthritis and is expected to be applicable to various other autoimmune and inflammatory diseases.
Abbreviations: RS3PE, remitting seronegative, symmetrical synovitis with pitting edema; TRAPS, tumor necrosis factor (TNF)-receptor-associated periodic syndrome.

diseases, it also shows that it is potentially useful for the treatment of malignant diseases including multiple myeloma, renal cancer, prostate cancer, and mesothelioma (17). Clinical trials to evaluate the efficacy and safety of anti-IL-6RAb for these diseases and clarification of the mechanism(s) through which IL-6R blockade exerts its clinical effects constitute important issues for future studies.

SUMMARY POINTS

1. IL-6 plays a significant pathological role in the development of various autoimmune and chronic inflammatory diseases.
2. Humanized anti-IL-6RAb is a first-in-class biologic response modifier with an action different from that of other biologics.
3. Anti-IL-6RAb has proven to be effective for the treatment of RA, juvenile idiopathic arthritis, and Castleman's disease and has been approved for the treatment of these diseases.
4. Anti-IL-6RAb is a promising biologic for various other autoimmune and inflammatory diseases.

FUTURE ISSUES

1. Further clinical trials to evaluate the efficacy and safety of anti-IL-6RAb for various diseases are required.
2. In murine models of autoimmune diseases, anti-IL-6RAb induced Treg and inhibited Th17 and/or Th1 differentiation. However, whether anti-IL-6RAb can repair Th17/Treg imbalance in human diseases remains unknown. The mechanisms through which anti-IL-6RAb is effective for the treatment of diseases need to be elucidated.

DISCLOSURE STATEMENT

Tadamitsu Kishimoto holds a patent for tocilizumab and receives royalties for Actemra®. The other authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors thank The Program of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation.

LITERATURE CITED

1. Hirano T, Yasukawa K, Harada H, Taga T, Watanabe Y, et al. 1986. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature* 324:73–76
2. Kishimoto T. 1989. The biology of interleukin-6. *Blood* 74:1–10
3. Kishimoto T. 2005. Interleukin-6: from basic science to medicine—40 years in immunology. *Annu. Rev. Immunol.* 23:1–21
4. Heinrich PC, Castell JV, Andus T. 1990. Interleukin-6 and the acute phase response. *Biochem. J.* 265:621–36

5. Siewert E, Bort R, Kluge R, Heinrich PC, Castell J, Jover R. 2000. Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. *Hepatology* 32:49–55
6. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, et al. 2004. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J. Clin. Investig.* 113:1271–76
7. Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. 2005. Clinical aspects of systemic amyloid diseases. *Biochim. Biophys. Acta* 1753:11–22
8. Korn T, Bettelli E, Oukka M, Kuchroo VK. 2009. IL-17 and Th17 cells. *Annu. Rev. Immunol.* 27:485–517
9. Kimura A, Kishimoto T. 2010. IL-6: regulator of Treg/Th17 balance. *Eur. J. Immunol.* 40:1830–35
10. Okada M, Kitahara M, Kishimoto S, Matsuda T, Hirano T, Kishimoto T. 1988. IL-6/BSF-2 functions as a killer helper factor in the in vitro induction of cytotoxic T cells. *J. Immunol.* 141:1543–49
11. Akira S, Takeda K. 2004. Toll-like receptor signalling. *Nat. Rev. Immunol.* 4:499–511
12. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, et al. 2010. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464:104–7
13. Hirano T, Taga T, Yasukawa K, Nakajima K, Nakano N, et al. 1987. Human B-cell differentiation factor defined by an anti-peptide antibody and its possible role in autoantibody production. *Proc. Natl. Acad. Sci. USA* 84:228–31
14. Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, et al. 1989. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 74:1360–67
15. Hirano T, Matsuda T, Turner M, Miyasaka N, Buchan G, et al. 1988. Excessive production of interleukin 6/B cell stimulatory factor-2 in rheumatoid arthritis. *Eur. J. Immunol.* 18:1797–801
16. Akira S, Taga T, Kishimoto T. 1993. Interleukin-6 in biology and medicine. *Adv. Immunol.* 54:1–78
17. Nishimoto N, Kishimoto T. 2006. Interleukin-6: from bench to bedside. *Nat. Clin. Pract. Rheumatol.* 2:619–26
18. Tanaka T, Narazaki M, Kishimoto T. 2011. Anti-interleukin-6 receptor antibody, tocilizumab, for the treatment of autoimmune diseases. *FEBS Lett.* In press
19. Kotake S, Sato K, Kim KJ, Takahashi N, Udagawa N, et al. 1996. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J. Bone Miner. Res.* 11:88–95
20. Palmqvist P, Persson E, Conaway HH, Lerner UH. 2002. IL-6, leukemia inhibitory factor, and oncostatin M stimulate bone resorption and regulate the expression of receptor activator of NF-κB ligand, osteoprotegerin, and receptor activation of NF-κB in mouse calvariae. *J. Immunol.* 169:3353–62
21. Nakahara H, Song J, Sugimoto M, Hagihara K, Kishimoto T, et al. 2003. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. *Arthritis Rheum.* 48:1521–29
22. Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, et al. 1989. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. *Proc. Natl. Acad. Sci. USA* 86:6367–71
23. Duncan MR, Berman B. 1991. Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. *J. Investig. Dermatol.* 97:686–92
24. Yamasaki K, Taga T, Hirata Y, Yawata H, Kawanishi Y, et al. 1988. Cloning and expression of the human interleukin-6 (BSF-2/IFN-β2) receptor. *Science* 241:825–28
25. Hibi M, Murakami M, Saito M, Hirano T, Taga T, et al. 1990. Molecular cloning and expression of an IL-6 signal transducer, gp130. *Cell* 63:1149–57
26. Narazaki M, Yasukawa K, Saito T, Ohsugi Y, Fukui H, et al. 1993. Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130. *Blood* 82:1120–26
27. Murakami M, Hibi M, Nakagawa N, Nakagawa T, Yasukawa K, et al. 1993. IL-6-induced homodimerization of gp130 and associated activation of a tyrosine kinase. *Science* 260:1808–10
28. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC. 2003. Hexameric structure and assembly of the interleukin-6/IL-6 α-receptor/gp130 complex. *Science* 300:2101–4
29. Kishimoto T, Akira S, Taga T. 1992. Interleukin-6 and its receptor: a paradigm for cytokines. *Science* 258:593–97

30. Kishimoto T, Akira S, Narazaki M, Taga T. 1995. Interleukin-6 family of cytokines and gp130. *Blood* 86:1243–54
31. Pflanz S, Hibbert L, Mattson J, Rosales R, Vaisberg E, et al. 2004. WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J. Immunol.* 172:2225–31
32. Tanaka T, Ogata A, Narazaki M. 2010. Tocilizumab for the treatment of rheumatoid arthritis. *Expert Rev. Clin. Immunol.* 6:843–54
33. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. 2008. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 112:3959–64
34. Frey N, Grange S, Woodworth T. 2010. Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. *J. Clin. Pharmacol.* 50:754–66
35. Schmitt C, Kuhn B, Zhang X, Kivitz AJ, Grange S. 2011. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. *Clin. Pharmacol. Ther.* 89:735–40
36. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. 2007. New therapies for treatment of rheumatoid arthritis. *Lancet* 370:1861–74
37. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, et al. 2007. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomized controlled trial of tocilizumab. *Ann. Rheum. Dis.* 66:1162–67
38. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, et al. 2008. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 58:2968–80
39. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, et al. 2008. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomized placebo controlled trial. *Ann. Rheum. Dis.* 67:1516–23
40. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, et al. 2008. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet* 371:987–97
41. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi, T, et al. 2009. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod. Rheumatol.* 19:12–19
42. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, et al. 2010. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann. Rheum. Dis.* 69:88–96
43. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, et al. 2011. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum.* 63:609–21
44. Singh JA, Beg S, Lopez-Olivo MA. 2010. Tocilizumab for rheumatoid arthritis. *Cochrane Database Syst. Rev.* July 7(7):CD008331
45. Nishimoto N, Ito K, Takagi N. 2010. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. *Mod. Rheumatol.* 20:222–32
46. Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. 2011. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systemic literature review and meta-analysis of randomized controlled trials. *Rheumatology* 50:552–62
47. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. 2003. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.* 48:2122–27

48. Okada M, Kita Y, Kanamaru N, Hashimoto S, Uchiyama Y, et al. 2011. Anti-IL-6 receptor antibody causes less promotion of tuberculosis infection than anti-TNF-α antibody in mice. *Clin. Dev. Immunol.* 2011:404929
49. Ogata A, Mori M, Hashimoto S, Yano Y, Fujikawa T, et al. 2010. Minimal influence of tocilizumab on IFN-γ synthesis by tuberculosis antigens. *Mod. Rheumatol.* 20:130–33
50. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. 2001. Systemic lupus erythematosus. *Lancet* 357:1027–32
51. Linker-Israeli M, Deans RJ, Wallace DJ, Prehn J, Ozeri-Chen T, Klinenberg JR. 1991. Elevated levels of endogenous IL-6 in systemic lupus erythematosus: a putative role in pathogenesis. *J. Immunol.* 147:117–23
52. Iwano M, Dohi K, Hirata E, Kurumatani N, Horii Y, et al. 1993. Urinary levels of IL-6 in patients with active lupus nephritis. *Clin. Nephrol.* 40:16–21
53. Hirohata S, Miyamoto T. 1990. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. *Arthritis Rheum.* 33:644–49
54. Pflegerl P, Vesely P, Hantusch B, Schlederer M, Zenz R, et al. 2009. Epidermal loss of JunB leads to a SLE phenotype due to hyper IL-6 signaling. *Proc. Natl. Acad. Sci. USA* 106:20423–28
55. Mihara M, Takagi N, Takeda Y, Ohsugi Y. 1998. IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F_1 mice. *Clin. Exp. Immunol.* 112:397–402
56. Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XY. 2006. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. *Immunology* 119:296–305
57. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, et al. 2010. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum.* 62:542–52
58. Gabrielli A, Avvedimento EV, Krieg T. 2009. Scleroderma. *N. Engl. J. Med.* 360:1989–2003
59. Hasegawa M, Sato S, Fujimoto M, Ihn H, Kikuchi K, et al. 1998. Serum levels of interleukin 6 (IL-6), oncostatin M, soluble IL-6 receptor, and soluble gp130 in patients with systemic sclerosis. *J. Rheumatol.* 25:308–13
60. Gallucci RM, Lee EG, Tomasek JJ. 2006. IL-6 modulates α-smooth muscle actin expression in dermal fibroblasts from IL-6-deficient mice. *J. Investig. Dermatol.* 126:561–68
61. Shima Y, Kuwahara Y, Murota H, Kitaba S, Kawai M, et al. 2010. The skin of patients with systemic sclerosis softened during the treatment with anti-IL-6 receptor antibody tocilizumab. *Rheumatology* 49:2408–12
62. Dalakas MC. 2010. Immunotherapy of myositis: issues, concerns and future prospects. *Nat. Rev. Rheumatol.* 6:129–37
63. Lundberg I, Ulfgren AK, Nyberg P, Andersson U, Klareskog L. 1997. Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies. *Arthritis Rheum.* 40:865–74
64. Lepidi H, Frances V, Figarella-Branger D, Bartoli C, Machado-Baeta A, Pellissier JF. 1998. Local expression of cytokines in idiopathic inflammatory myopathies. *Neuropathol. Appl. Neurobiol.* 24:73–79
65. Scuderi F, Mannella F, Marino M, Provenzano C, Bartoccioni E. 2006. IL-6-deficient mice show impaired inflammatory response in a model of myosin-induced experimental myositis. *J. Neuroimmunol.* 176:9–15
66. Okiyama N, Sugihara T, Iwakura Y, Yokozeki H, Miyasaka N, Kohsaka H. 2009. Therapeutic effects of interleukin-6 blockade in a murine model of polymyositis that does not require interleukin-17A. *Arthritis Rheum.* 60:2505–12
67. Narazaki M, Hagihara K, Shima Y, Ogata A, Kishimoto T, Tanaka T. 2011. Therapeutic effect of tocilizumab on two patients with polymyositis. *Rheumatology* 50:1344–46
68. Salvarani C, Cantini F, Hunder GG. 2008. Polymyalgia rheumatica and giant-cell arteritis. *Lancet* 372:234–45
69. Noris M, Daina E, Gamba S, Bonazzola S, Remuzzi G. 1999. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? *Circulation* 100:55–60
70. Nishimoto N, Nakahara H, Yoshio-Hoshino N, Mima T. 2008. Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum.* 58:1197–200

71. Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. 2011. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med. Wkly.* 141:w13156
72. Ito H. 2004. Novel therapy for Crohn's disease targeting IL-6 signaling. *Expert Opin. Ther. Targets* 8:287–94
73. Mitsuyama K, Toyonaga A, Sasaki E, Ishida O, Ikeda H, et al. 1995. Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. *Gut* 36:45–49
74. Hosokawa T, Kusugami K, Ina K, Ando T, Shinoda M, et al. 1999. Interleukin-6 and soluble interleukin-6 receptor in the colonic mucosa of inflammatory bowel disease. *J. Gastroenterol. Hepatol.* 14:987–96
75. Yamamoto M, Yoshizaki K, Kishimoto T, Ito H. 2000. IL-6 is required for the development of Th1 cell-mediated murine colitis. *J. Immunol.* 164:4878–82
76. Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, et al. 2004. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 126:989–96
77. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, et al. 2009. IL-6 and STAT3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* 15:103–13
78. Van Vollenhoven RF, Keystone EC, Furie R, Blesch A, Wang C, et al. 2009. Gastrointestinal safety in patients with rheumatoid arthritis treated with tocilizumab: data from Roche clinical trials. *EULAR 2009 Congr., Copenhagen*
79. Rapini RP, Warner NB. 2006. Relapsing polychondritis. *Clin. Dermatol.* 24:482–85
80. Stabler T, Piette JC, Chevalier X, Marini-Portugal A, Kraus VB. 2004. Serum cytokine profiles in relapsing polychondritis suggest monocyte/macrophage activation. *Arthritis Rheum.* 50:3663–67
81. Kawai M, Hagihara K, Hirano T, Shima Y, Kuwahara Y, et al. 2009. Sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in two patients with refractory relapsing polychondritis. *Rheumatology* 48:318–19
82. Collins PW, Percy CL. 2010. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br. J. Haematol.* 148:183–94
83. Miao CH. 2010. Immunomodulation for inhibitors in hemophilia A: the important role of Treg cells. *Expert Rev. Hematol.* 3:469–83
84. Nishida S, Kawasaki T, Kashiwagi H, Morishima A, Hishitani Y, et al. 2011. Successful treatment of acquired hemophilia A, complicated by chronic GVHD, with tocilizumab. *Mod. Rheumatol.* 21:420–22
85. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. 2010. Mechanisms underlying inflammation in neurodegeneration. *Cell* 140:918–34
86. Steinman L. 2008. Nuanced roles of cytokines in three major human brain disorders. *J. Clin. Investig.* 118:3557–63
87. Maimone D, Gregory S, Arnason BG, Reder AT. 1991. Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. *J. Neuroimmunol.* 32:67–74
88. Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, et al. 2002. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med.* 8:500–8
89. Gijbels K, Van Damme J, Proost P, Put W, Carton H, Billiau A. 1990. Interleukin 6 production in the central nervous system during experimental autoimmune encephalomyelitis. *Eur. J. Immunol.* 20:233–35
90. Serada S, Fujimoto M, Mihara M, Koike N, Ohsugi Y, et al. 2008. IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis. *Proc. Natl. Acad. Sci. USA* 105:9041–46
91. Jarius S, Wildemann B. 2010. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. *Nat. Rev. Neurol.* 6:383–92
92. Uzawa A, Mori M, Arai K, Sato Y, Hayakawa S, et al. 2010. Cytokine and chemokine profiles in neuromyelitis optica: significance of interleukin-6. *Mult. Scler.* 16:1443–52
93. Içöz S, Tüzün E, Kürtüncü M, Durmuş H, Mutlu M, et al. 2010. Enhanced IL-6 production in aquaporin-4 antibody positive neuromyelitis optica patients. *Int. J. Neurosci.* 120:71–75
94. Chihara N, Aranami T, Sato W, Miyazaki Y, Miyake S, et al. 2011. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proc. Natl. Acad. Sci. USA* 108:3701–6
95. Brandt SJ, Bodine DM, Dunbar CE, Nienhuis AW. 1990. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. *J. Clin. Investig.* 86:592–99

96. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, et al. 1995. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood* 86:1276–80
97. Aoki Y, Narazaki M, Kishimoto T, Tosato G. 2001. Receptor engagement by viral interleukin-6 encoded by Kaposi sarcoma-associated herpesvirus. *Blood* 98:3042–49
98. Beck JT, Hsu SM, Wijdenes J, Bataille R, Klein B, et al. 1994. Brief report: alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. *N. Engl. J. Med.* 330:602–5
99. Nishimoto N, Sasai M, Shima Y, Nakagawa M, Matsumoto T, et al. 2000. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 95:56–61
100. Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, et al. 2005. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 106:2627–32
101. Yokota S, Kishimoto T. 2010. Tocilizumab: molecular intervention therapy in children with systemic juvenile idiopathic arthritis. *Expert Rev. Clin. Immunol.* 6:735–43
102. De Benedetti F, Pignatti P, Gerloni V, Massa M, Sartirana P, et al. 1997. Differences in synovial fluid cytokine levels between juvenile and adult rheumatoid arthritis. *J. Rheumatol.* 24:1403–9
103. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, et al. 2005. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 52:818–25
104. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, et al. 2008. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 371:998–1006
105. De Benedetti F, Brunner H, Ruperto N, Wright S, Kenwright A, et al. 2010. From biology to classification and targeted therapy in juvenile idiopathic arthritis. *Ann. Rheum. Dis.* 69(Suppl. 3):146
106. Bergad PL, Schwarzenberg SJ, Humbert JT, Morrison M, Amarasinghe S, et al. 2000. Inhibition of growth hormone action in models of inflammation. *Am. J. Physiol. Cell Physiol.* 279:C1906–17
107. Fautrel B. 2008. Adult-onset Still disease. *Best Pract. Res. Clin. Rheumatol.* 22:773–92
108. Iwamoto M, Nara H, Hirata D, Minota S, Nishimoto N, Yoshizaki K. 2002. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. *Arthritis Rheum.* 46:3388–89
109. Nakahara H, Mima T, Yoshino-Hoshino N, Matsushita M, Hashimoto J, Nishimoto N. 2009. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. *Mod. Rheumatol.* 19:69–72
110. De Bandt M, Saint-Marcoux B. 2009. Tocilizumab for multirefractory adult-onset Still's disease. *Ann. Rheum. Dis.* 68:153–54
111. Cunha ML, Wagner J, Osawa A, Scheinberg M. 2010. The effect of tocilizumab on the uptake of ^{18}FDG-PET imaging in patients with adult-onset Still's disease. *Rheumatology* 49:1014–16
112. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. 2001. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 358:24–29
113. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, et al. 2007. Natural history and outcome in systemic AA amyloidosis. *N. Engl. J. Med.* 356:2361–71
114. Hagihara K, Nishikawa T, Isobe T, Song J, Sugamata Y, Yoshizaki K. 2004. IL-6 plays a critical role in the synergistic induction of human serum amyloid A (SAA) gene when stimulated with proinflammatory cytokines as analyzed with an SAA isoform real-time quantitative RT-PCR assay system. *Biochem. Biophys. Res. Commun.* 314:363–69
115. Hagihara K, Nishikawa T, Sugamata Y, Song Y, Isobe T, et al. 2005. Essential role of STAT3 in cytokine-driven NF-κB-mediated serum amyloid A gene expression. *Genes Cells* 10:1051–63
116. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, et al. 2004. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* 50:1761–69
117. Okuda Y, Takasugi K. 2006. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. *Arthritis Rheum.* 54:2997–3000
118. Nishida S, Hagihara K, Shima Y, Kawai M, Kuwahara Y, et al. 2009. Rapid improvement of AA amyloidosis with humanised anti-interleukin 6 receptor antibody treatment. *Ann. Rheum. Dis.* 68:1235–36

119. Sato H, Sakai T, Sugaya T, Otaki Y, Aoki K, et al. 2009. Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis. *Clin. Rheumatol.* 28:1113–16
120. Inoue D, Arima H, Kawanami C, Takiuchi Y, Nagano S, et al. 2010. Excellent therapeutic effect of tocilizumab on intestinal amyloid A deposition secondary to active rheumatoid arthritis. *Clin. Rheumatol.* 29:1195–97
121. Alvarez-Rodríguez L, Lopez-Hoyos M, Mata C, Marin MJ, Calvo-Alen J, et al. 2010. Circulating cytokines in active polymyalgia rheumatica. *Ann. Rheum. Dis.* 69:263–69
122. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. 1997. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. *Arthritis Rheum.* 40:1873–78
123. Hagihara K, Kawase I, Tanaka T, Kishimoto T. 2010. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. *J. Rheumatol.* 37:1075–76
124. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. 1985. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. *JAMA* 254:2763–67
125. Oide T, Ohara S, Oguchi K, Maruyama M, Yazawa M, et al. 2004. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in Nagano, Japan: clinical, radiological, and cytokine studies of 13 patients. *Clin. Exp. Rheumatol.* 22:91–98
126. Arima K, Origuchi T, Tamai M, Iwanaga N, Izumi Y, et al. 2005. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. *Ann. Rheum. Dis.* 64:1653–55
127. Tanaka T, Hagihara K, Shima Y, Narazaki M, Ogata A, et al. 2010. Treatment of a patient with remitting seronegative, symmetrical synovitis with pitting oedema with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Rheumatology* 49:824–26
128. Reveille JD, Arnett FC. 2005. Spondyloarthritis: update on pathogenesis and management. *Am. J. Med.* 118:592–603
129. Wu IB, Schwartz RA. 2008. Reiter's syndrome: the classic triad and more. *J. Am. Acad. Dermatol.* 59:113–21
130. Metsarinne KP, Nordstrom DC, Konttinen YT, Teppo AM, Fyhrquist FY. 1992. Plasma interleukin-6 and renin substrate in reactive arthritis, rheumatoid arthritis, and systemic lupus erythematosus. *Rheumatol. Int.* 12:93–96
131. Singh R, Aggarwal A, Misra R. 2007. Th1/Th17 cytokine profiles in patients with reactive arthritis/undifferentiated spondyloarthropathy. *J. Rheumatol.* 34:2285–90
132. Tanaka T, Kuwahara Y, Shima Y, Hirano T, Kawai M, et al. 2009. Successful treatment of reactive arthritis with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Arthritis Rheum.* 61:1762–64
133. Wendling D, Racadot E, Toussirot E, Wijdenes J. 1996. Combination therapy of anti-CD4 and anti-IL6 monoclonal antibodies in a case of severe spondylarthropathy. *Br. J. Rheumatol.* 35:1330
134. Henes JC, Horger M, Guenaydin I, Kanz L, Koetter I. 2010. Mixed response to tocilizumab for ankylosing spondylitis. *Ann. Rheum. Dis.* 69:2217–18
135. Wendling D, Bossert M, Prati C. 2010. Short-term effect of IL-6 inhibition in spondylarthritis. *Jt. Bone Spine* 77:624–25
136. Brulhart L, Nissen MJ, Chevallier P, Gabay C. 2010. Tocilizumab in a patient with ankylosing spondylitis and Crohn's disease refractory to TNF antagonists. *Jt. Bone Spine* 77:625–26
137. Shima Y, Tomita T, Ishii T, Morishima A, Maeda Y, et al. 2011. Tocilizumab, a humanized anti-interleukin-6 receptor antibody, ameliorated clinical symptoms and MRI findings of a patient with ankylosing spondylitis. *Mod. Rheumatol.* 21:436–39
138. Mendes D, Correia M, Barbedo M, Vaio T, Mota M. 2009. Behçet's disease—a contemporary review. *J. Autoimmun.* 32:178–88
139. Mege JL, Dilsen N, Sanguedolce V, Gul A, Bongrand P, et al. 1993. Overproduction of monocyte derived tumor necrosis factor α, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. *J. Rheumatol.* 20:1544–49
140. Hirohata S, Isshi K, Oguchi H, Ohse T, Haraoka H, et al. 1997. Cerebrospinal fluid interleukin-6 in progressive Neuro-Behçet's syndrome. *Clin. Immunol. Immunopathol.* 82:12–17

141. Hirano T, Ohguro N, Hohki S, Hagihara K, Shima Y, et al. 2011. A case of Behçet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod. Rheumatol.* In press
142. Caspi RR. 2010. A look at autoimmunity and inflammation in the eye. *J. Clin. Investig.* 120:3073–83
143. Hohki S, Ohguro N, Haruta H, Nakai K, Terabe F, et al. 2010. Blockade of interleukin-6 signaling suppresses experimental autoimmune uveoretinitis by the inhibition of inflammatory Th17 responses. *Exp. Eye Res.* 91:162–70
144. Haruta H, Ohguro N, Fujimoto M, Hohki S, Terabe F, et al. 2011. Blockade of interleukin-6 signaling suppresses not only Th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis. *Investig. Ophthalmol. Vis. Sci.* 52:3264–71
145. Gergis U, Arnason J, Yantiss R, Shore T, Wissa U, et al. 2010. Effectiveness and safety of tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, in a patient with refractory GI graft-versus-host disease. *J. Clin. Onocol.* 28:e602–4
146. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, et al. 1999. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 97:133–44
147. Vaitla PM, Radford PM, Tighe PJ, Powell RJ, McDermott EM, et al. 2011. Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the anti-interleukin-6 receptor monoclonal antibody tocilizumab. *Arthritis Rheum.* 63:1151–55
148. Nishimoto N, Japanese MRA Study Group for RA. 2010. Drug free remission after cessation of Actemra monotherapy (DREAM study). *EULAR 2010 Congr., Rome*
149. Wing K, Sakaguchi S. 2010. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat. Immunol.* 11:7–13
150. Fujimoto M, Serada S, Mihara M, Uchiyama Y, Yoshida H, et al. 2008. Interleukin-6 blockade suppresses autoimmune arthritis in mice by the inhibition of inflammatory Th17 responses. *Arthritis Rheum.* 58:3710–19
151. Stumhofer JS, Laurence A, Wilson EH, Huang E, Tato CM, et al. 2006. Interleukin 27 negatively regulates the development of interleukin 17–producing T helper cells during chronic inflammation of the central nervous system. *Nat. Immunol.* 7:937–45
152. El-behi M, Ciric B, Yu S, Zhang GX, Fitzgerald DC, Rostami A. 2009. Differential effect of IL-27 on developing versus committed Th17 cells. *J. Immunol.* 183:4957–67
153. Kimura A, Naka T, Nohara K, Fujii-Kuriyama Y, Kishimoto T. 2008. Aryl hydrocarbon receptor regulates Stat1 activation and participates in the development of Th17 cells. *Proc. Natl. Acad. Sci. USA* 105:9721–26
154. Puga A, Tomlinson CR, Xia Y. 2005. Ah receptor signals cross-talk with multiple developmental pathways. *Biochem. Pharmacol.* 69:199–207
155. Kimura A, Naka T, Kishimoto T. 2007. IL-6-dependent and -independent pathways in the development of interleukin 17–producing T helper cells. *Proc. Natl. Acad. Sci. USA* 104:12099–104
156. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, et al. 2007. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 26:371–81
157. Nakahama T, Kimura A, Nguyen NT, Chinen I, Hanieh H, et al. 2011. Aryl hydrocarbon receptor deficiency in T cells suppresses the development of collagen-induced arthritis. *Proc. Natl. Acad. Sci. USA.* 108:14222–27
158. Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, et al. 2008. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature* 453:106–9
159. Roll P, Muhammad K, Schumann M, Kleinert S, Einsele H, et al. 2011. In vivo effect of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment. *Arthritis Rheum.* 63:1255–64

Annual Review of Pharmacology and Toxicology

Volume 52, 2012

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Pharmacology and Toxicology* articles may be found at http://pharmtox.annualreviews.org/errata.shtml

総　説

分類不能型免疫不全症 Update

森尾友宏

Common variable immunodeficiency: an update on etiology, pathophysiology, and classification

Tomohiro MORIO, M.D., Ph.D.

Department of Developmental Biology and Pediatrics, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences

(Received December 8, 2011)

summary

Common variable immunodeficiency is one of the most common primary immunodeficiency that is categorized into primary antibody deficiency. The responsible genes identified so far include *ICOS*, *TACI*, *CD19*, *CD20*, *CD21*, *CD81* and *BAFF-R*; and most of the CVID-causing genes are yet to be identified. *TACI* mutation is the most common one; however the direct contribution of TACI mutation to pathogenesis of CVID is not yet clear. One third to a half of the patients with CVID shows autoimmunity as well as malignancy in their course. It is of importance to develop diagnostic measure, to identify the disease causing genes, and to develop the optimal therapy.

Key words——Common variable immunodeficiency (CVID); classification; KRECs; TRECs; whole exome sequencing

抄　録

分類不能型免疫不全症は Common variable immunodeficiency (CVID) と呼ばれ，最も頻度の高い先天性免疫不全症，かつ最も頻度の高い抗体産生不全型免疫不全症である．今までに判明した責任遺伝子には *ICOS*, *TACI*, *CD19*, *CD20*, *CD21*, *CD81*, *BAFF-R* などがあるが，いずれもその頻度は低く，*TACI* ではその変異が直接的にかつ単一で病態に関わっているかどうか不明である．臨床症状としては感染症，自己免疫疾患や悪性腫瘍の合併などがあり，成人型の免疫不全症としてきわめて重要な位置を占める．特に単一遺伝子異常に基づく，易感染性，自己免疫疾患・悪性腫瘍の発症という点で，様々な疾患の免疫異常基盤探索においても重要な疾患である．鑑別診断に加え，病態に応じた分類，責任遺伝子の究明，至適治療法の開発が重要である．

はじめに

Common variable immunodeficiency (CVID) は従来分類不能型免疫不全症と訳されていたが，症例数が多く (common)，多彩な臨床症状をとる (variable)，分類不能な疾患であるために，暫定的につけられた名称がそのまま用いられている．抗体産生不全を主体とする疾患群であり，成人領域で判明する原発性免疫不全症としては数が最も多い．疫学的には 10,000 人から 100,000 人に 1 人とされているが，私たちが 2009 年に行った我が国における全国調査においても 200 名程度の患者が存在することが明らかになっている[1~6]．その数は欧米をはじめとして少しずつ増加しており，これも awareness campaign によるところが大きいと考えられている．ヨーロッパにおける J-Project，英国の "Is it PIS?" キャンペーン，ドイツの FIND ID などがそれにあたる．表 1 には免疫不全症の診断の遅れを防ぐために，Jeffery Modell Foundation が中心となって作成した PID の 10 awareness warning signs をあげた．成人領域においても，感染症の頻度が高い，感染症が重症化あるいは遷延化した，稀な感染症を起こした，などというエピソードをもつ患者ではまず一般的な血算と共に，IgG, A, M, E を測定することが重要であり，今後その数はますます増加する可能性がある．

東京医科歯科大学大学院発生発達病態学分野

I. CVID の定義

CVID は，欧州免疫不全症学会 (European Society for Immunodeficiencies : ESID) によれば，「2 歳

表1 Ten warning signs

1-1E) 10 Warning Signs of PID-General

1) Four or more new ear infections within 1 year.
2) Two or more serious sinus infections within 1 year.
3) Two or more months on antibiotics with little effect.
4) Two or more pneumonias within 1 year.
5) Failure of an infant to gain weight or grow normally.
6) Recurrent, deep skin or organ abscesses.
7) Persistent thrush in mouth or fungal infection on skin.
8) Need for intravenous antibiotics to clear infections.
9) Two or more deep-seated infections including septicemia.
10) A family history of PI.

1-1J) 原発性免疫不全症を疑う10の徴候（日本語版）

1) 乳児で呼吸器・消化管感染症を繰り返し，体重増加不良や発育不良が見られる．
2) 1年に2回以上肺炎にかかる．
3) 気管支拡張症を発症する．
4) 2回以上，髄膜炎，骨髄炎，蜂窩織炎，敗血症や，皮下膿瘍，臓器内膿瘍などの深部感染症にかかる．
5) 抗菌薬を服用しても2ヶ月以上感染症が治癒しない．
6) 重症副鼻腔炎を繰り返す．
7) 1年に4回以上，中耳炎にかかる．
8) 1歳以降に，持続性の鵞口瘡，皮膚真菌症，重度・広範な疣贅（いぼ）がみられる．
9) BCGによる重症副反応（骨髄炎など），単純ヘルペスウイルスによる脳炎，髄膜炎菌による髄膜炎，EBウイルスによる重症血球貪食症候群に罹患したことがある．
10) 家族が乳幼児期に感染症で死亡するなど，原発性免疫不全症候群を疑う家族歴がある．

1-2) 成人で免疫不全症を疑う6の徴候

The 6 ESID warning signs for ADULT primary immunodeficiency diseases

1. Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)
2. Recurring infections or infection requiring prolonged antibiotic therapy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
4. Two or more radiologically proven pneumonia within 3 years
5. Infection with unusual localization or unusual pathogen
6. PID in the family

表2 除外すべき疾患群（Diseases to be excluded : DE）

	責任遺伝子
1. XLA（X連鎖γグロブリン血症）：男性	*BTK*
その他のB細胞欠損症（IGHM, CD79A, CD70B, BKNK…）は稀	
2. XLP（X連鎖リンパ増殖症候群）：男性	*SAP*
3. X-HIGM（X連鎖高IgM症候群）：男性	*CD40L*
その他の高IgM症候群（*AID*, *UNG*）	
4. Good's syndrome（胸腺腫を伴う免疫不全症）	
5. 非典型的SCID（後期発症複合型免疫不全症）	*ADA*, *LIGIV*, *XLF1*…
CD4＜200/mm³で疑う	
6. Bone-marrow failure（骨髄不全症候群：Fanconi貧血，先天性角化異常症など）	
7. Lymphoma/leukemia（白血病，リンパ腫）	
8. Protein loss via the kidney（腎疾患における蛋白漏出）	
9. Protein loss via the gastrointestinal tract（腸管疾患における蛋白漏出）screening with alpha-1-antitrypisin in stool	
10. 薬剤	

以上（多くは10歳代以降）で発症する低γグロブリン血症で，同種血球凝集素の欠損，あるいはワクチンへの低反応を示し，既知の免疫不全症ではない疾患」と定義されている．疾患概念は不明瞭かつ様々な疾患群を含んでいることは間違いない[1~6]．

現時点において基本的には除外診断となっているが，特徴的な疾患群が存在することもまた確かである．表2に除外すべき疾患とその責任遺伝子などの

情報につき記載した．特に注意すべき点は以下の通りである．

X連鎖無γグロブリン血症では*BTK*変異部位などによりB細胞の完全欠損や，無γグロブリン血症ではなく低γグロブリン血症となることがあり，男性ではまず否定が必要である．男性では同様に特にEBVへの脆弱性（血球貪食症候群など）を伴った場合には，*SH2D1A*あるいは*XIAP*を検討しておくべきである．また高IgM症候群の約2/3では実際にIgMが高値になっておらず，IgG, IgAは低値を示す．従って男性ではCD40Lを，また男女いずれの場合もAIDは検査しておいて良い．さらに，胸腺腫を伴う免疫不全症（Good症候群）もその数は比較的多く，年長での発症及びB細胞がほぼ欠損することが特徴であるが，年長者では胸腺腫を確認しておく必要がある[1~6]．最後に，原因不明（他の疾患の除外）という点では自己矛盾する内容であるが，CVIDの責任遺伝子として後述するものについても，いずれも稀な疾患であり，すぐに検査する必要はない．

II. CVIDの臨床症状

CVIDの症状は様々である．身体的特徴としては，肝脾腫を呈する症例が比較的多い程度であり，皮疹（アトピー様乾癬様，多型滲出性紅斑様など），神経症状，発達遅滞などの合併も認める．ただし発達遅滞を認めるCVIDが真のCVIDであるかは検証が必要である．感染症としては，いわゆるsino-pulmonary diseaseが多いが，Epstein Barrウイルス（EBV）感染症，サイトメガロウイルス（CMV）感染症，パピローマウイルス感染症などT細胞機能不全を疑わせる症例も散見される．全国調査においては，自己免疫疾患を合併するものは全体で19％，40歳以上で36％，悪性腫瘍の合併は全体で10％，40歳以上で19％であった．自己免疫疾患として最も多いのは，自己免疫性溶血性貧血や自己免疫性血小板減少症であるが，関節リウマチ，炎症性腸疾患，多発筋炎などさまざまな疾患を認める．悪性腫瘍ではリンパ系悪性腫瘍が多いが，甲状腺腫瘍，子宮頸癌，消化器系腫瘍も散見される．臨床症状には大きな差があり，全く無症状のままに他疾患のスクリーニングの中で発見されることもある．Bodo Grimbacherらのgroupは CVIDの重症度について表3に示すようなスコアリングシステムを提唱している[5]．

III. CVIDの病態

CVIDの病態は様々であり，あらゆる異常が報告されていると言っても良い．たとえば胸腺からのT細胞新生能の低下，T細胞増殖能の低下，T細胞シグナル伝達異常，サイトカイン産生異常，アポトーシスの異常や，TCR Vbeta repertoireの偏り，CD40L発現の低下等が報告されており，また樹状細胞の機能不全や，数の低下などを示す報告もある[7~9]．テロメア長の短縮を認める症例もある[10]．B細胞については，クラススイッチ記憶B細胞数

表3 分類不能型免疫不全症の重症度スコアリングシステム

Points	1	2	3	4
1. Chronic sinusitis	Absent	Present		
2. Past meningitis or encephalitis	Absent	One bout	Two bouts	>Two bouts
3. Past pneumonia	Absent	One bout	Two bouts	>Two bouts
4. Bronchiectasis	Absent	One bout	Two bouts	>Two bouts
5. Other parenchymal lung pathology such as fibrosis, LIP, BOOP, *etc*.	Absent	Suspected		Confirmed
6. Lung surgery (lobectomy or pneumonectomy)	Absent			Performed
7. Splenomegly	Absent	11–14.9 cm	15–20 cm	>20 cm
8. Splenectomy	Absent			Performed
9. Lymphadenopathy (largest node)	Absent	<2 cm	2–3 cm	>3 cm
10. CVID enteropathy	Absent	Intermittent	Chronic but mild	Severe
11. Autoimmune condition	Absent	Suspected		Confirmed
12. Other rheumatological complaints such as arthralgia	Absent	Suspected	Confirmed	
13. Granulomata	Absent	Skin only	Lung, liver or spleen	CNS (incl. eye)
14. Lymphoma	Absent			Present
15. Cancer (solid tumors)such as bowel, skin or stomach	Absent			Present

文献5)より改変

や形質芽球数の減少は明らかであるが，B 細胞数が 1%未満というものもあり，B 細胞欠損症との異同も明確ではない．これらの混乱した情報は，CVID の一群を取り上げて，その欠陥を一般化しようとする研究から生じたものであり，CVID は heterogenous な疾患群から成り立っているというコンセンサスの元により本質的な病態解明が望まれる．

今井，野々山らはこれらの混乱を鑑みて，CVID を B 細胞欠損型，T 細胞欠損型，B/T 欠損型，B/T 正常の真の CVID に分類することを提唱している（表 4）．ここでは B 細胞新生能，B 細胞数の代替え指標として，sjKRECs（signal joint kappa-deleting recombination excision circles），cjKRECs（coding joint KRECs）を[11]，T 細胞新生能の指標として，TRECs（T-cell receptor excision circles）を用いている[12,13]．この系は realtime PCR にて簡単に測定することができるが，B 細胞では CD19/CD20 陽性細胞数が cjKRECs の，また CD4＋CD45RA＋（＋CD31＋）細胞が recent thymic emigrant cells として TRECs の，代替えとして用いることができる．一方，CD19/CD20 は sjKRECs を反映しない．

B 細胞数の減少あるいは，sjKRECs の減少を除

表 4　分類不能型免疫不全症の亜群（Subgroup of CVID: SC）

SC-A.	B 細胞新生能正常，naïve T 細胞数正常
SC-B.	B 細胞新生能減少，naïve T 細胞数正常
SC-C.	B 細胞新生能正常，naïve T 細胞数減少
SC-D.	B 細胞新生能減少，naïve T 細胞数減少

B 細胞数として CD19，CD20 を用いる以外に，cjKRECs（Kappa-deleting recombination excision circles）を B 細胞数の，sjKRECs を B 細胞新生能の指標として用いる提言がある（今井，野々山ら）．Naïve T 細胞（CD4＋CD45RA＋）の代替えとしては，T 細胞新生能として TRECs（T-cell receptor excision circles）を用いることがある．

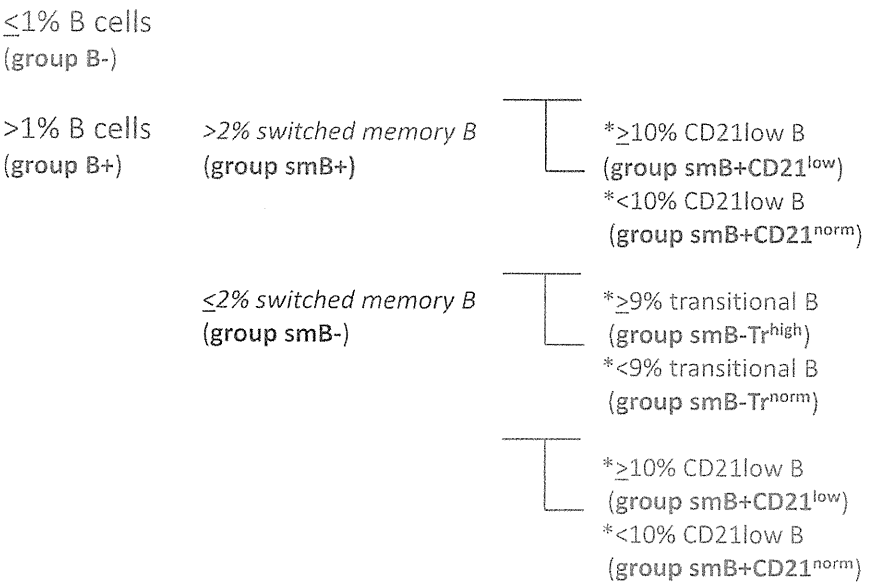

図 1　EURO Class of CVID（文献 14）より改変）

	B+	SmB+	SmB-	SmB+ 21low	SmB+ 21norm	SmB- Trhigh	SmB- Trnorm	SmB- 21low	SmB- 21norm
No of patients or %	303	42%	58%	33% of SmB+	67% of SmB+	19% of SmB-	81% of SmB-	49% of SmB-	51% of SmB-
Splenomegaly	41%	24%	52%	50%	14%	54%	51%	54%	51%
Lymphoadenopathy	26%	22%	24%	17%	20%	57%	22%	57%	22%
Granuloma	12%	4%	17%	14%	2%	24%	16%	24%	16%
Autoimmunity	20%	19%	21%	15%	10%	19%	26%	17%	26%

図 2　EURO Class of CVID と臨床症状（文献 14）より改変）

表5 いわゆる分類不能型免疫不全症に含まれる病態（Classification of CVID: CC）

1. 選択的IgM欠損症
2. 選択的IgA欠損症
3. IgG欠損症及びIgGサブクラス異常症
4. 特異抗体欠損症
5. 高IgM症候群
6. IgG/IgA（IgMの程度は様々）：真のCVID
7. その他の低γグロブリン血症

それぞれに対し
Type (a) asymptomatic
Type (b) with recurrent infections
Type (c) without infections but with other associated pathology

文献5)より改変

表6 分類不能型免疫不全症における特徴的表現型

1.	低身長，小頭症，発達遅滞	DE5, DE6を示唆
2.	悪性腫瘍の合併	DE4, 5, 6, 7の除外が必要
3.	自己免疫疾患が前面にでる疾患	
4.	特定の感染症への脆弱性	DE2類似疾患など

DEは表2を参照

いた群においては，患者B細胞はCD20＋CD27＋IgM−IgD−のswitched memory群の減少を示す．時に抗体が関与すると思われる自己免疫疾患があるが，これらの症例における免疫グロブリンレパートア解析は今後の課題である．B細胞がoligoclonalな場合も想定される．

その他のCVID分類の試みとして，どの免疫グロブリンサブクラスが主に障害を受けるのかと，臨床症状に着目するものがある（表5）．このような分類に至った1つの理由として，IgA欠損症がCVIDと相互移行することがあるという事実がある．実際にIVで記載する責任遺伝子の一部についてもその欠陥によりIgA欠損症あるいはCVIDを呈している．その他IgMが比較的高値でIgG, IgAが低値の症例は高IgM症候群variantでクラススイッチ異常がベースにあり，IgMのみが低値という場合なども想定できる[5]．

ヨーロッパなどではさらに，B細胞数，記憶B細胞の割合，transitional B細胞の比率，CD21の発現低下の有無，などによりCVIDを分類する試みもある（図1及び図2）[14,15]．ここでは臨床症状との対比を行っているが，脾腫はクラススイッチ記憶B細胞が少ない群，比較的保たれているがCD21low細胞が多い群により頻繁に認められる．リンパ節腫大は一方クラススイッチ記憶B細胞が少なく，CD21low細胞が多い群あるいはtransitional B細胞が多い群に頻繁に認められる．

表6に，特徴的な臨床症状と除外診断の関連についてまとめた．

IV. 現在までに明らかになっているCVIDの責任遺伝子

1. CD19/CD21/CD81欠損症

CD19/CD21/CD81は複合体を作っており，B細胞への抗原刺激においては，抗原とC3dが会合し，B細胞受容体とCD19/CD21/CD81複合体の両者からのシグナルが伝達されることになる．いわゆるB細胞におけるdual signaling modelである．CD19欠損においては，B細胞数は正常で，クラススイッチした記憶B細胞数は減少している[16,17]．IgGは低値で，特異抗体産生能は低下しており，小児期から感染症を反復する．抗原受容体刺激によるCa流入は低下している．CD21欠損症においては，IgG, IgAは低値であるものの，抗原特異的抗体産生能は比較的保たれていた．比較的軽症なCVID群である[15]．CD81欠損症ではIgG低値，IgAやや低下，IgM正常であり，血管性紫斑病が認められた．CD81はCD19の表出にも重要であり，欠損症ではCD19発現は低下し，CD19欠損症と同様のB細胞分化異常とシグナル異常が認められた[19]．

2. CD20欠損症

CD20は代表的なB細胞抗原であり，骨髄のearly pre-Bから発現が認められる．ノックアウトマウスではB細胞数や抗体産生も正常であったが，Ca流入に異常を認める．ヒトでは低IgG（IgM, IgA正常）の患者でCD20異常が同定されている[20]．クラススイッチした記憶B細胞が減少し，抗原刺激によるCa流入に欠陥があることから，CD19/CD21/CD81欠損症と類似した状態ということができる．このように1, 2はCaシグナルに異常のある群とも捕らえることができるが，そのシグナル系に関係する分子異常がCVIDの新規責任遺伝子として同定される可能性がある．

3. ICOS欠損症

ICOSはCD28ファミリーに属する共刺激分子で，

CD28, CTLA-4, PD-1 などがその群に属する．活性化されたT細胞に発現し，T細胞分化，サイトカイン産生，T細胞依存性抗体産生などに重要とされている．ICOS 欠損症は分子異常が示された初めての CVID である．今までに同定された遺伝子変異は 2 種類だけであり，稀な CVID ということができる[21~24]．

患者では小児期から成人期に発症する様々な感染症を呈し，結節性リンパ様増生，間質性肺炎，自己免疫疾患（血球減少，炎症性腸疾患，関節リウマチ，乾癬など），パピローマウイルスによる子宮頸癌など，CVID が呈するほとんどの症状を示している．IgG は低下し，しかし IgM, IgA の低下の程度は様々である．IgM が比較的高値・IgA 低値のクラススイッチ異常パターンをとるケースも認められた．日本の症例の検討では Th1, Th2, Th17 サイトカインの産生低下，記憶 CD4T 細胞の減少，Treg サブセットの減少が認められ，さらに T-bet, GATA-3, MAF, RORC induction にも欠陥があることが示された．CTLA-4 の発現誘導にも問題がある．従って，ICOS 欠損症では，活性型及び抑制性両者の T 細胞の分化あるいは維持に問題があり，そのいずれが主に侵されるかによって，感染症が主体となるか，自己免疫疾患が主体となるかが決定される可能性がある．実際に ICOS 欠損マウスを用いた実験ではエフェクター T 細胞の機能低下が報告されているが，逆に autoimmunity への傾向を示唆した論文も少数認められる．CVID における易感染性と自己免疫疾患のバランスに関与する分子機構として興味深い．

4. TACI 異常症

TACI 異常症と IgA 欠損症，CVID との関連は 2005 年に示されたが，その因果関係は複雑である．ヘテロ異常で健常者と患者が混在する家系や，複合ヘテロ接合体異常，ホモ異常などが報告されているが，おそらく単独の因子ではなく，修飾因子が加わって発症するのではないかと考えられている[22~30]．TACI は transmembrane activator and calcium-modulating cyclophilin ligand interactor の略で，TNF 受容体スーパーファミリーに属し，BAFF（B cell activating factor), BCMA（B cell maturation antigen）や APRIL（a proliferation-inducing ligand）などをリガンドとしている．リガンドとの会合により，B 細胞ではクラススイッチが誘導される．多くの患者では TACI mutation があっても発現が認められることも解析を困難にしている．

患者ではしかし，CVID の大半の症状を呈しており，今までに 600 名近い患者が同定されている．B 細胞数は正常であるが，時に激減した患者も散見される．クラススイッチ記憶 B 細胞の減少は CVID 全般の傾向とかわらない．IgA, IgM は低値をとることが多いが，IgA が正常であったり，高 IgM となったりすることもある．両アリルでの変異では APRIL への会合が低下することが示されているが，最も頻度の高い変異は片アリルでの C104R, A181E であり，健常人でも同じ変異を有する集団が 2%程度存在する[27,31]．新たな変異では（あるいは既知のヘテロ変異でも）病的意義を検証することが難しい疾患群である．

5. BAFF-R 欠損症

BAFF-R 欠損症は姉弟例で報告されているのみである．BAFF-R は TNF 受容体スーパーファミリーに属し（TNFRSF13C），B 細胞に表出され，BAFF（B cell activation factor）によって刺激が入り，NFkB の誘導→抗アポトーシスに働き，B 細胞の生存に深く関与している．BAFF-R 欠損症では IgG, IgM の低下を認め，IgA は正常であった．しかし IgG の低下は一例ではごく軽度であった．姉弟での表現型の差異などから，BAFF-R 以外の因子が貢献するところが大きいと考えられている[32]．実際に，BAFF-R のリガンドは BAFF のみであるが，BAFF のリガンドとしては，先述の TACI, BCMA, APRIL などがある．

T 細胞依存性抗体産生は正常であるが，T 非依存的抗体産生に欠陥がある．また自己免疫やリンパ増殖などは認めていない．可溶性 BAFF-R が減少する CVID の一群があり，BAFF-R の調節領域異常があるのではと推測されている．

6. Msh5 異常症

Msh5 は DNA ミスマッチ修復や，減数分裂での相同組換えに関与するが，クラススイッチ組換えでの役割も明らかになっている．2 つの SNP の組み合わせ（L85F/P786S）が IgA 欠損症や CVID と関連していると報告されている[33]．

V. 病因へのアプローチ

CVID では家族例や遺伝歴のある症例が少なく