Immunol Res (2007) 38:347–352
DOI 10.1007/s12026-007-0006-2

Inherited human IRAK-4 deficiency: an update

Capucine Picard · Horst von Bernuth · Cheng-Lung Ku · Kun Yang · Anne Puel · Jean-Laurent Casanova

Published online: 9 June 2007

Abstract Interleukin-1 receptor-associated kinase-4 (IRAK-4), a member of the IRAK family, plays an essential role in Toll-like receptor- and IL-1 receptor-mediated signaling. We briefly review inherited human IRAK-4 deficiency, a recently described primary immunodeficiency leading to recurrent, invasive, pyogenic bacteria infection, and invasive pneumococcal disease in particular.

Keywords Primary immunodeficiency · NF-κB · Toll-like receptors · Interleukin-1 receptors · Tumor necrosis factor receptors · Inflammation · *Streptococcus pneumoniae*

Several primary immunodeficiencies (PIDs) affecting NF-κB signaling and conferring susceptibility to pyogenic bacteria have recently been described. The patients bear mutations in *NEMO*, *IKBA* or *IRAK4* [1, 2]. Patients with anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) carry either X-linked recessive hypomorphic mutations in

Presented at the First Robert A Good Society Symposium, St. Petersburg, FL 2006.

C. Picard
Centre d'étude des déficits immunitaires, Hôpital Necker-Enfants Malades, 149 Rue de Sèvres, Paris 75015, France, EU

C. Picard (✉)
Laboratoire de Génétique Humaine des Maladies Infectieuses, Institut National de la Santé et de la Recherche Médicale, U550, Paris, France, EU
e-mail: picardc@necker.fr

C. Picard · H. von Bernuth · C.-L. Ku · K. Yang · A. Puel · J.-L. Casanova
Université Paris Descartes, Faculté Médecine Necker, Paris, France, EU

J.-L. Casanova
Unité d'Immunologie et d'Hématologie Pédiatriques, Hôpital Necker-Enfants Malades, 149 Rue de Sèvres, Paris 75015, France, EU

NEMO, which encodes a component of the NF-κB kinase IKK complex, or autosomal dominant hypermorphic mutation in *IKBA*, which encodes the inhibitor IκBα [1–5]. The NEMO-NF-κB signaling pathway is used by several receptors involved in development (e.g., EDAR, RANK, and VEGFR-3) and immunity (e.g., members of the TNF receptor superfamily and members of the Toll-like and interleukin-1 receptor (TIR) superfamily) [1, 2]. Patients with mutations in *NEMO* or *IKBA* present EDA and are susceptible to many different infectious agents, including pyogenic bacteria, mycobacteria, fungi, and viruses [1, 2]. In contrast, IRAK-4-deficient patients present a purely immunological defect, with specific impairment of the TIR-interleukin-1 receptor-associated kinase (IRAK) signaling pathway but no developmental defects [6]. Interleukin-1 receptor-associated kinase-4 (IRAK-4)-deficient patients seem to be specifically prone to invasive systemic and peripheral pyogenic bacterial diseases, including pneumococcal and staphylococcal diseases in particular [6].

IRAK-4 is the fourth member of the IRAK family to be described, IRAK-1, IRAK-2, and IRAK-M having been described previously [7, 8]. Like other IRAKs, IRAK-4 contains two structural domains: a death domain (DD) that mediates the molecular recognition of other DD-containing proteins, and a catalytic kinase domain (KD) [7, 8]. Two IRAK molecules, IRAK-2 and IRAK-M, are devoid of kinase activity and operate as regulators [8]. IRAK-4 plays an essential role in mediating cellular activation in response to Toll-like receptor (TLR) agonists and at least two members of the IL-1/IL-18 superfamily [7, 9]. Following the binding of TLR agonists or IL-1/IL-18, TIRs recruit the adaptor molecule Myd88, which then recruits IRAK-4 through DD interaction (Fig. 1) [7, 10]. IRAK-4 promotes IRAK-1 activation and its recruitment to the IL-1 receptor (IL-1R) complex [9, 11]. Overexpression of IRAK-4 proteins with truncations in the KD can suppress

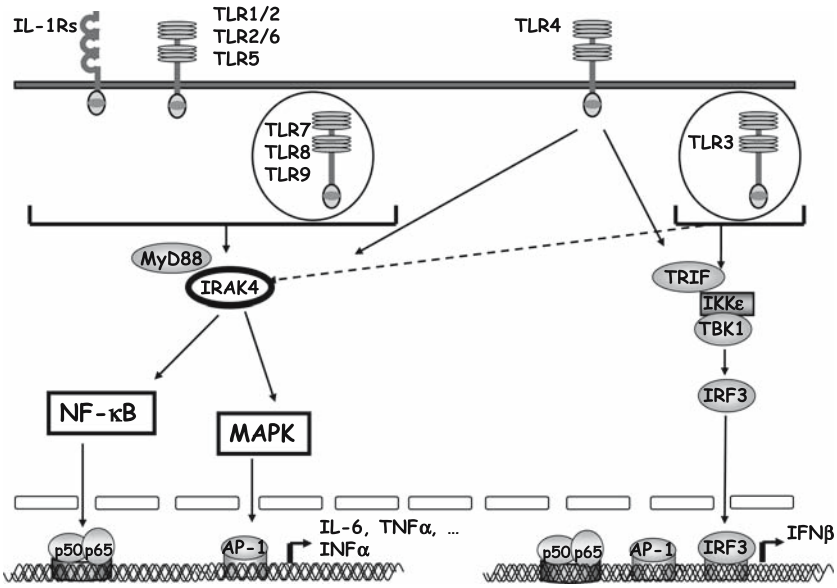

Fig. 1 IRAK-4, in association with MyD88, mediates activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways in response to IL-1, IL-18, TLR1/2, TLR4, TLR5, TLR2/6, TLR7, TLR8 and TLR9 agonists. The production of IFN-α is induced by the IRAK-4 signaling pathway in response to TLR7–9 agonists. In contrast, the induction of IFN-β in response to TLR3 and TLR4 agonists is mediated by the TRIF signaling pathway

IL-1-inductible recruitment of wild-type IRAK-4 to the IL-1R complex and its association with IRAK-1 while enabling sequestration of Myd88 [12]. In contrast, kinase-inactive mutant IRAK-4 can restore IL-1-mediated signaling in human IRAK-4-deficient cells and, to a lesser extent, in mouse IRAK-4-deficient cells [9, 11]. The kinase activity of IRAK-4 does not seem to be necessary for IL-1-induced IRAK phosphorylation and signaling. Interestingly, impairment of the kinase activity of both IRAK-1 and IRAK-4 is required to abolish the IL-1 response, demonstrating that the kinase activity of IRAK-1 and IRAK-4 is redundant for IL-1-mediated signaling [11]. However, it remains unclear whether this is relevant in vivo and in response to other stimuli, such as TLR. The resolution of this issue will require the generation of KD knock-in mice.

IRAK-4 deficiency (OMIM 607676) is an autosomal recessive disorder first described in three unrelated patients, shortly after the discovery of IRAK-4 [6]. We are aware of a total of 28 IRAK-4 deficient patients worldwide [6, 13–22] (unpublished data). All mutations tested are null because of a lack of protein expression. The patients are homozygous (n = 24) or compound heterozygous (n = 4) for *IRAK4* mutations. Blood cells from the patients fail to produce pro-inflammatory cytokines upon stimulation with IL-1β, IL-18 and all TLR agonists tested. In fibroblasts, IL-6 induction, NF-κB- and mitogen-activated protein kinase (MAPK) pathways are impaired in response to IL-1, but normal in response to the TLR3 non-specific agonist poly(I:C). IRAK-4 is thus crucial for the early induction of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, by agonists from pyogenic bacteria, via TLR1/2, TLR4, TLR5, TLR2/6 and TLR9 (Fig. 1) [6, 18]. However, it is redundant for the TLR3 induction of IL-6 in fibroblasts [6, 18]. IRAK-4 is also redundant for the TLR3 non specific and TLR4-mediated induction of antiviral interferons in blood cells and fibroblasts (Fig. 1) [6, 18]. In contrast, human TLR7-9-induced-IFNα/β secretion is strictly IRAK-4-dependent (in blood and EBV-transformed B cells) (Fig. 1) [18]. Routine immunological evaluations of these patients have typically been unremarkable, with the exception of two IRAK-4-deficient patients with impaired antibody responses to polysaccharide antigens [15, 22, 23]. We recently described a method for diagnosing IRAK-4 deficiency based on the detection of L-selectin (CD62L) cleavage on the surface of granulocytes following the stimulation of blood cells with a TLR4 agonist and a TLR7/8 agonist [21].

Clinically, IRAK-4-deficient patients suffer from recurrent infections caused by pyogenic bacteria, mostly Gram-positive, with weak fever and poor initial inflammatory responses. S*treptococcus pneumoniae* is the leading pathogen in these subjects, and has been detected in the majority of patients with proven IRAK-4 deficiency, in whom it caused blood-borne invasive diseases (septicemia, meningitis, or arthritis) [6, 13–23] (unpublished data). The second most frequently detected infectious organism is *Staphylococcus aureus*, often responsible for skin infections, but occasionally also for liver infections or septicemia. Invasive diseases caused by Gram-negative bacteria have been diagnosed in some patients [13, 17, 19]. All invasive infections occurred before the age of 14 years. IRAK-4 deficiency is a life-threatening disease, resulting in the deaths of 12 of the 28 known patients, all of whom died before the age of 8 years [6, 13–23] (unpublished data). There is an overall trend towards improvement with age, as shown by the four adult patients doing well with no treatment at the ages of 22, 24 and 33 years [13, 17] (unpublished data). Known patients with IRAK-4 deficiency display no particular susceptibility to mycobacterial, fungal or viral infections. Delayed separation of the umbilical cord has been described in IRAK-4-deficient patients [20]. IRAK-4-deficient patients should receive monthly prophylactic administrations of immunoglobulins at least until the age of 10 years. Prophylactic antibiotics should also be given (oral TMP-SMX and

penicillin), and an intensive vaccination program followed, including conjugated and non-conjugated vaccines against encapsulated bacteria.

The immunological phenotype of IRAK-4-deficient mice is consistent with that of the patients. Not all the TLR agonists have been tested in *Irak4* knockout (ko) mouse models. In macrophages, the production of pro-inflammatory cytokines is abolished in response to IL-1β, TLR2, TLR4 and TLR9 agonists and to the TLR3 agonist poly(I:C) [10, 24]. The IRF-3 dimerization is normal upon the TLR4 agonist LPS, as is the upregulation of CD40, CD86 and CD80 molecules in dendritic cells, while this up-regulation is impaired upon TLR9 activation [24]. Still in macrophages, the IFN-β mRNA induction and the IP-10 production are impaired upon stimulation with a TLR4 agonist [24]. In fibroblasts, IL-6 induction, NF-κB- and MAPK pathways are impaired in response to IL-1β [10]. IFN-β mRNA induction, GARG16 and IP-10 production and NF-κB-pathway in fibroblasts are impaired in response to TLR4 agonist [24]. The cytokine production by the fibroblasts in response to poly(I:C) has not yet been explored. Finally, Irak4-deficient T cells do not respond to IL-18 [25]. However, there are differences between IRAK-4-deficient patients and ko mouse models. In particular, Irak-4 ko mice seem to display defects in T-cell receptor function, including impaired TCR-induced IL-2 production and proliferation, whereas these defects have not been observed in patients [26] (unpublished data).

For the determination of the infectious phenotype, mice deficient for Irak-4 have been challenged only with LCMV and *S. aureus* [10]. Irak4 deficient mice challenged with LMCV displayed lower than normal levels of IFN-γ production by NK cells, but no loss of cytolytic function [10]. The outcome of the infection was not reported. These mice are resistant to lethal doses of LPS and, like IRAK-4 deficient patients, are particularly susceptible to staphylococcal infection [10]. Mice with deficiencies in other components of the TIR-signaling pathway (e.g., MyD88, TLR2) are susceptible not only to pyogenic bacteria (notably *S. aureus* and *S. pneumoniae*), but also to a broader spectrum of infections than IRAK-4-deficient patients [6, 27]. Based on the broad infectious phenotype of MyD88-deficient mice, it is expected that Irak-4-deficient mice are equally vulnerable. A discrepancy between Irak-4-deficient mice and IRAK-4-deficient patients is thus expected in terms of infectious phenotypes, despite the most similar immunological phenotypes. This would be reminiscent of the narrow infectious phenotype of patients with germline mutations in the IL-12-IFN-γ circuit [28, 29] or in UNC-93B [30], when compared with the corresponding mutant mice. We elsewhere argued that such differences probably reflect the different constraints operating on experimental infections in animal models and natural infections in human [31]. Studies of infection in Irak4 deficient mice are required to define more accurately the protective role of IRAK-4 in the mouse. A comparison of the infection phenotypes of mice and humans with IRAK-4 deficiency should provide important insight into the genetic control of immunity to infection [31, 32].

Acknowledgments We would like to thank Laurent Abel and all the members of our laboratory for helpful discussions and for critical reading of this text, and our collaborators at Necker and worldwide for their trust and patience over the years, in particular RA. Good, NK. Day, A. Ozinsky, X. Li, SN. Vogel, JI. Gallin, SM Holland, D. Lammas, G. Davies, H. Chapel, S. Al Hajjar, I. Zaid Al Moshen, D. Davidson, D. Speert, C. Roifman, A. Issekutz, C. Rodriguez-Gallego, L. Marodi, B. Zion Garty, K. Schwarz, S. Ehl, H. Takada, T. Hara, J. Smart, M. Tang, O. Levy, R. Geha, CK. Cunningham, X. Bossyut, F. Barrat and RL. Coffman. Needless to say, we are much indebted to the patients and their families. HvB was supported by grants from the *Deutsche Forschungsgemeinschaft*, Bonn, Germany (DFG n°-995/1 and -995/2). This work was supported by the Fondation BNP-Paribas, the Fondation Schlumberger, and EU grant number QLK2-CT-2002–00846. JLC is an International Scholar of the Howard Hughes Medical Institute.

References

1. Puel A, Picard C, Ku CL, Smahi A, Casanova JL. Inherited disorders of NF-kappaB-mediated immunity in man. Curr Opin Immunol 2004;34–41
2. Ku CL, Yang K, Bustamante J, et al. Inherited disorders of human Toll-like receptor signalling: immunological implications. Immunol Rev 2005;10–20
3. Doffinger R, Smahi A, Bessia C, et al., X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nat Genet 2001;277–85
4. Jain A, Ma CA, Liu S, et al. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. Nat Immunol 2001;223–8
5. Courtois G, Smahi A, Reichenbach J, et al. A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest 2003;1108–15
6. Picard C, Puel A, Bonnet M, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 2003;2076–9
7. Li S, Strelow A, Fontana EJ, Wesche H. IRAK-4: a novel member of the IRAK family with the properties of an IRAK-kinase. Proc Natl Acad Sci USA 2002;5567–72
8. Janssens S, Beyaert R. Functional diversity and regulation of different interleukin-1 receptor-associated kinase (IRAK) family members. Mol Cell 2003;293–302
9. Lye E, Mirtsos C, Suzuki N, Suzuki S, Yeh WC. The role of interleukin 1 receptor-associated kinase-4 (IRAK-4) kinase activity in IRAK-4-mediated signaling. J Biol Chem 2004;40653–8
10. Suzuki N, Suzuki S, Duncan GS, et al. Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4. Nature 2002;750–6
11. Qin J, Jiang Z, Qian Y, Casanova JL, Li X. IRAK4 kinase activity is redundant for interleukin-1 (IL-1) receptor-associated kinase phosphorylation and IL-1 responsiveness. J Biol Chem 2004;26748–53
12. Medvedev AE, Thomas K, Awomoyi A, et al. Cutting Edge: expression of IL-1 receptor-associated kinase-4 (IRAK-4) proteins with mutations identified in a patient with recurrent bacterial infections alters normal IRAK-4 interaction with components of the IL-1 receptor complex. J Immunol 2005;6587–91
13. Medvedev AE, Lentschat A, Kuhns DB, et al. Distinct mutations in IRAK-4 confer hyporesponsiveness to lipopolysaccharide and interleukin-1 in a patient with recurrent bacterial infections. J Exp Med 2003;521–31
14. Enders A, Pannicke U, Berner R, et al. Two siblings with lethal pneumococcal meningitis in a family with a mutation in Interleukin-1 receptor-associated kinase 4. J Pediatr 2004;698–700
15. Day N, Tangsinmankong N, Ochs H, et al. Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody responses. J Pediatr 2004;524–6
16. Currie AJ, Davidson DJ, Reid GS, et al. Primary immunodeficiency to pneumococcal infection due to a defect in Toll-like receptor signaling. J Pediatr 2004;512–8
17. Chapel H, Puel A, von Bernuth H, Picard C, Casanova JL. Shigella sonnei meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. Clin Infect Dis 2005;1227–31
18. Yang K, Puel A, Zhang S, et al. Human TLR-7-, -8-, and -9-mediated induction of IFN-alpha/beta and -lambda Is IRAK-4 dependent and redundant for protective immunity to viruses. Immunity 2005; 465–78
19. Cardenes M, von Bernuth H, Garcia-Saavedra A, et al. Autosomal recessive interleukin-1 receptor-associated kinase 4 deficiency in fourth-degree relatives. J Pediatr 2006;549–51
20. Takada H, Yoshikawa H, Imaizumi M, et al. Delayed separation of the umbilical cord in two siblings with Interleukin-1 receptor-associated kinase 4 deficiency: rapid screening by flow cytometer. J Pediatr 2006;546–8
21. von Bernuth H, Ku CL, Rodriguez-Gallego C, et al. A fast procedure for the detection of defects in early Toll-like-receptor signaling. Pediatrics 2006;2498–503
22. Ku CL, Picard C, Erdos M, et al. IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. J Med Genet 2007;16–23
23. Haraguchi S, Day NK, Nelson RP, et al. Interleukin 12 deficiency associated with recurrent infections. Proc Natl Acad Sci USA 1998;13125–9
24. Suzuki N, Suzuki S, Eriksson U, et al. IL-1R-associated kinase 4 is required for lipopolysaccharide-induced activation of APC. J Immunol 2003;6065–71
25. Suzuki N, Chen NJ, Millar DG, et al. IL-1 receptor-associated kinase 4 is essential for IL-18-mediated NK and Th1 cell responses. J Immunol 2003;4031–5

26. Suzuki N, Suzuki S, Millar DG, et al. A critical role for the innate immune signaling molecule IRAK-4 in T cell activation. Science 2006;1927–32
27. Albiger B, Sandgren A, Katsuragi H, et al. Myeloid differentiation factor 88-dependent signalling controls bacterial growth during colonization and systemic pneumococcal disease in mice. Cell Microbiol 2005;1603–15
28. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 2002;581–620
29. Abel L, Casanova JL. Human genetics of infectious diseases: fundamental insights from clinical studies. Semin Immunol 2006;327–9
30. Casrouge A, Zhang SY, Eidenschenk C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 2006;308–12
31. Casanova JL, Abel L. The human model: a genetic dissection of immunity to infection in natural conditions. Nat Rev Immunol 2004;55–66
32. Casanova JL, Abel L. Inborn errors of immunity to infection: the rule rather than the exception. J Exp Med 2005;197–201