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Review

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Experimental and natural infections in MyD88- and IRAK-4-deficient mice and humans

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Most Toll-like-receptors (TLRs) and interleukin-1 receptors (IL-1Rs) signal via myeloid differentiation primary response 88 (MyD88) and interleukin-1 receptor-associated kinase 4 (IRAK-4). The combined roles of these two receptor families in the course of experimental infections have been assessed in MyD88- and IRAK-4-deficient mice for almost fifteen years. These animals have been shown to be susceptible to 46 pathogens: 27 bacteria, eight viruses, seven parasites, and four fungi. Humans with inborn MyD88 or IRAK-4 deficiency were first identified in 2003. They suffer from naturally occurring life-threatening infections caused by a small number of bacterial species, although the incidence and severity of these infections decrease with age. Mouse TLR- and IL-1R-dependent immunity mediated by MyD88 and IRAK-4 seems to be vital to combat a wide array of experimentally administered pathogens at most ages. By contrast, human TLR- and IL-1R-dependent immunity mediated by MyD88 and IRAK-4 seems to be effective in the natural setting against only a few bacteria and is most important in infancy and early childhood. The roles of TLRs and IL-1Rs in protective immunity deduced from studies in mutant mice subjected to experimental infections should therefore be reconsidered in the light of findings for natural infections in humans carrying mutations as discussed in this review.

Keywords: Invasive pyogenic infections · IRAK4 · MyD88 · Primary immunodeficiency · Toll-like receptors

Introduction

MyD88 was first described as a "macrophage differentiation marker" for which mRNA accumulated in murine M1 myeloleukemic cells upon activation with IL-6 [1, 2]. Human

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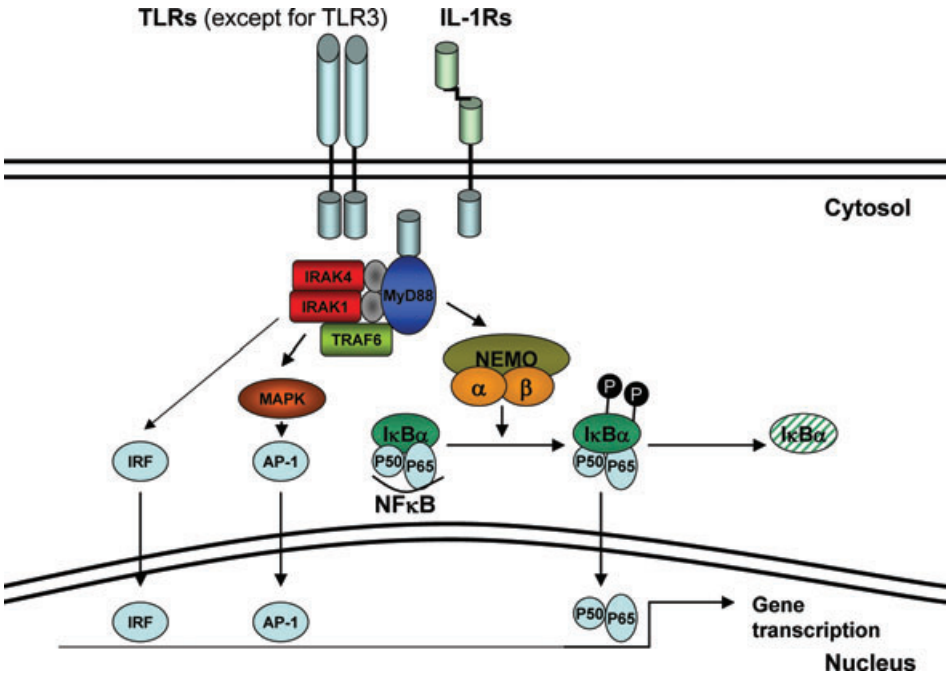

Figure 1. MyD88- and IRAK-4-signaling pathways. The TIR superfamily (TLRs/IL-1Rs) is dependent on MyD88 and IRAK-4 signaling for its regulation of gene transcription. MyD88 and IRAK-4 control IRF (Interferon regulatory factors), MAPK (map kinases), and NEMO (NF-κB essential modulator) that regulate AP-1 and NF-κB (p50/p65); the latter by stimulating the phosphorylation and degradation of IκBα so releasing NF-κB from the inactive NF-κB/IκBα complex. MyD88 also controls IRF5- and IRF7-dependent signaling (not shown).

MYD88 maps to chromosome 3p22-p21.3 and contains five exons [1]. The full-length cDNA for human *MYD88* encodes 296 amino acids forming a 33 kDa protein [2]. Murine *Myd88* maps to chromosome 9q119. It also has five exons and the full-length cDNA encodes 296 amino acids forming a 33-kDa protein. The MyD88 protein includes an *N*-terminal "death domain" (DD) and a *C*-terminal Toll-interleukin receptor (TIR) domain, similar to the intracellular domains of TLRs and members of the IL-1R superfamily, collectively referred to as TIR receptors [2–6]. Human *IRAK4* maps to chromosome 12q12 and contains 13 exons. The full-length cDNA for human IRAK-4 encodes 460 amino acids, forming a 52 kDa protein. The murine *Irak4* gene maps to chromosome 15q94 and also contains 13 exons. The corresponding full-length cDNA encodes 459 amino acids, forming a 52 kDa protein. The IRAK-4 protein contains an *N*-terminal DD and a central kinase domain [7].

MyD88 and IRAK-4 are essential for signaling via all TLRs with the exception of TLR3 and, to some extent, TLR4, and for signaling via most IL-1Rs, including IL-1R1, IL-18R, and IL-33R (ST2) [8–17]. Following its activation, MyD88 binds to the IL-1Rs and TLRs via its TIR domain, forming an oligomer; it then recruits IRAK-4 to the receptor via its DD [5, 18–21], mediating the activation of various transcription factors, including IRF5 and IRF7, AP-1, and NF-κB, depending in part on the cell type and the cell surface receptor stimulated [22] (Fig. 1). Thus, TIR-MyD88-IRAK-4-mediated signaling appears to be important for the innate recognition of pathogens and the ignition of inflammation, and, as such, is indispensable for the induction of protective immunity.

However, most demonstrations of the importance of TIR-MyD88-IRAK-4-dependent pathways for protective immunity have been based on studies of experimental infections in mice in which protective immunity against a broad range of infectious agents has been shown; however, the essential nature of the role of TIR signaling in such broad-ranging immunity has been called into question by both clinical genetic and evolutionary genetic studies [23–28]. In particular, the identification of human IRAK-4 and MyD88 deficiencies as immunological and clinical phenocopies has provided considerable insights [29, 30]. Detailed immunological and clinical descriptions of a large cohort of patients with these deficiencies have led to a reassessment of the importance of the TIR-MyD88-IRAK-4-dependent pathway for general protective immunity in humans under natural conditions [31].

Impact of MyD88 and IRAK-4 deficiencies on protective immunity in mice

Susceptibility to pathogens in MyD88- and IRAK-4-deficient mice

Myd88-deficient mice are known to be susceptible to experimental infections with 45 pathogens: 27 bacteria [32–77], eight viruses [78–91], seven protozoa [92–107], and four fungi [108–113]. Enhanced pathogen growth in Myd88-deficient mice has been observed for:

i Six Gram-positive bacteria: *Bacillus anthracis* (spores injected subcutaneously (s.c.)) [77], *Listeria monocytogenes* after i.v. or i.p. injection or infection via gavage [33, 34, 38, 59], *Staphylococcus aureus* after i.v. or s.c. injection [32, 50], *Streptococcus agalacticae* after s.c. or i.p. injection [37], *Streptococcus pneumoniae* after i.v. or i.n. infection [45, 48], *Streptococcus pyogenes* after s.c. injection [72];

Table 1. Forty-six pathogens displaying higher growth rates in vivo in MyD88-deficient mice than in wild-type controls in experimental conditions

Pathogen group	Strain	References
Gram-positive bacteria	*Bacillus anthracis*	[77]
	Listeria monocytogenes	[33, 34, 38, 59]
	Staphylococcus aureus	[32, 50]
	Streptococcus agalacticae	[37]
	Streptococcus pneumoniae	[45, 48]
	Streptococcus pyogenes	[72]
Gram-negative bacteria	Anaplasmataceae	[73]
	Borrelia burgdorferi	[42, 43, 51]
	Borrelia hermsii	[52]
	Brucella abortus	[46, 64]
	Burkholderia pseudomallei	[67]
	Campylobacter jejuni	[60]
	Chlamydia muridarum	[71]
	Chlamydia pneumoniae	[47]
	Citrobacter koseri	[76]
	Citrobacter rodentium	[61, 62]
	Francisella tularensis	[53, 68]
	Haemophilus influenzae	[49, 66]
	Klebsiella pneumoniae	[69]
	Legionella pneumoniae	[54, 55]
	Mycoplasma pneumoniae	[74]
	Neisseria meningitidis	[56]
	Pseudomonas aeruginosa	[36, 44, 57, 63]
	Salmonella typhimurium	[70, 75]
Mycobacteria	*Mycobacterium avium*	[35]
	Mycobacterium bovis	[39]
	Mycobacterium tuberculosis	[40, 41, 58, 65]
Viruses	*Herpes simplex virus* 1	[80]
	Herpes simplex virus 2	[83]
	Influenza A virus	[84]
	Lymphocytic choriomeningitis virus	[81, 85]
	Murine cytomegalovirus	[78, 79, 82, 86]
	Rabies virus	[90, 91]
	SARS coronavirus	[89]
	Vesicular stomatitis virus	[87, 88]
Parasites	*Cryptosporidium parvum*	[101]
	Enterocytozoon bieneusi	[107]
	Leishmania braziliensis	[104]
	Leishmania major	[94, 95, 105]
	Toxoplasma gondii	[92, 93, 96, 98, 103, 106]
	Trypanosoma brucei	[99]
	Trypanosoma cruzii	[97, 100, 102]
Fungi	*Aspergillus* spp.	[108]
	Candida albicans	[108, 109, 112]
	Cryptococcus neoformans	[110, 111]
	Paracoccidioides brasiliensis	[113]

ii Eighteen Gram-negative bacteria: *Anaplasmataceae* after i.p. injection [73], *Borrelia burgdorferi* after intradermal (i.d.) inoculation [42, 43, 51], *Borrelia hermsii* after i.p. injection [52], *Brucella abortus* after i.p. injection [46, 64], *Burkholderia pseudomallei* after i.n. inoculation [67], *Campylobacter jejunii* after stomach gavage [60], *Chlamydia muridarum* after i.n. inoculation [71], *Chlamydia pneumoniae* after i.n. application [47], *Citrobacter koseri* after the direct inoculation of live bacteria into the brain parenchyma by stereotactic injection [76], *Citrobacter rodentium* after ingestion of a suspension of the bacterium or gavage [61, 62], *Franciscella tularensis* after i.n. inoculation and i.d. deposition [53, 68], *Haemophilus influenzae* after i.n. inoculation or i.p. injection [49, 66], *Klebsiella pneumoniae* after intratracheal (i.t.) inoculation [69], *Legionella pneumoniae* after exposure to aerosols or after i.n. inoculation [54, 55], *Mycoplasma pneumoniae* after i.n. inoculation [74], *Neisseria meningitidis* after i.p. injection [56], *Pseudomonas aeruginosa* after exposure to aerosolized bacteria or i.n. inoculation [36, 44, 57, 63], and *Salmonella typhimurium* after i.v. injection [70, 75];

iii Three mycobacteria after i.v., i.n., or aerogenic exposure (*Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium tuberculosis*) [35, 39–41, 58, 65];

iv Eight viruses: Herpes simplex virus type 1 after aerogenic exposure [80], Herpes simplex virus type 2 after vaginal challenge [83], Influenza A virus after i.n. inoculation [84], Lymphocytic choriomeningitis virus after i.v. injection [81, 85], murine cytomegalovirus after i.p. injection [78, 79, 82, 86], rabies virus after intracranial injection [90, 91], SARS coronavirus after i.n. inoculation [89], and vesicular stomatitis virus after i.n. inoculation or i.v. injection [87, 88];

v Seven parasites: *Cryptosporidium parvum* after gavage [101], *Enterocytozoon bieneusi* after oral inoculation [107], *Leishmania braziliensis* after the s.c. injection of stationary-phase promastigotes [104], *Leishmania major* after the s.c. injection of stationary-phase promastigotes [94, 95, 105], *Toxoplasma gondii* after i.p. injection [92, 93, 96, 98, 103, 106], *Trypanosoma brucei* after i.p. infection [99], *Trypanosoma cruzii* after i.p. injection [97, 100, 102];

vi Four fungi: *Aspergillus* after i.v. infection [108], *Candida albicans* after i.v or intragastric injection [108, 109, 112], *Cryptococcus neoformans* after i.n. inoculation or i.p. injection [110, 111], *Paracoccidioides brasiliensis* after i.t. inoculation [113] (see Table 1).

IRAK-4-deficient mice showed enhanced pathogen growth when challenged with *S. aureus* i.p. [17].

Survival of MyD88- and IRAK-4-deficient mice

Survival of deficient mice

As greater pathogen growth in vivo is not always correlated with lower levels of survival, we consider here the published mortality data for experimental infections of MyD88-deficient mice. Mortality due to experimental infections was greater in MyD88-deficient mice than in wild-type mice for 33 pathogens:

Table 2. Thirty-three pathogens for which the mortality of MyD88-deficient mice in vivo was greater than that of wild-type controls in experimental conditions

Pathogen group	Strain	References
Gram-positive bacteria	*Bacillus anthracis*	[77]
	Listeria monocytogenes	[33]
	Staphylococcus aureus	[32]
	Streptococcus agalacticae	[37]
	Streptococcus pneumoniae	[45, 48]
	Streptococcus pyogenes	[72]
Gram-negative bacteria	Anaplasmataceae	[73]
	Borrelia hermsii	[52]
	Burkholderia pseudomallei	[67]
	Chlamydia muridarum	[71]
	Chlamydia pneumoniae	[47]
	Francisella tularensis	[53, 68]
	Klebsiella pneumoniae	[69]
	Pseudomonas aeruginosa	[36, 44, 57, 63]
Mycobacteria	*Mycobacterium avium*	[35]
	Mycobacterium bovis	[39]
	Mycobacterium tuberculosis	[40, 41, 58, 65]
Viruses	*Herpes simplex virus* 1	[80]
	Herpes simplex virus 2	[83]
	Influenza A virus	[84]
	Lymphocytic choriomeningitis virus	[81, 85]
	Murine cytomegalovirus	[78, 82]
	Rabies virus	[90, 91]
	SARS coronavirus	[89]
	Vesicular stomatitis virus	[87, 88]
Parasites	*Cryptosporidium parvum*	[101]
	Toxoplasma gondii	[92, 93, 96, 98, 103, 106]
	Trypanosoma brucei	[99]
	Trypanosoma cruzii	[97, 102]
Fungi	*Aspergillus* spp.	[108]
	Candida albicans	[108, 109, 112]
	Cryptococcus neoformans	[110, 111]
	Paracoccidioides brasiliensis	[113]

i Six Gram-positive bacteria: *B. anthracis* after i.p. injection of the toxin [77], *L. monocytogenes* after i.v injection [33], *S. aureus* after i.v injection [32], *S. agalacticae* after s.c. or i.p. injection [37], *S. pneumoniae* after i.v. or i.n. infection [45, 48], *S. pyogenes* after s.c. injection [72];

ii Eight Gram-negative bacteria: *Anaplasmataceae* after i.p. injection [73], *B. hermsii* after i.p. injection [52], *B. pseudomallei* after i.n. inoculation [67], *C. muridarum* after i.n. inoculation [71], *C. pneumoniae* after i.n. application [47], *F. tularensis* after i.n. inoculation and i.d. deposition [53, 68], *K. pneumoniae* after i.t. inoculation [69], *P. aeruginosa* after exposure to aerosolized bacteria or i.n. inoculation [36, 44, 57, 63];

iii Three mycobacteria after i.v., i.n., or aerogenic exposure (*M. avium*, *M. bovis*, *M. tuberculosis*) [35, 39–41, 58];

iv Eight viruses: Herpes simplex virus type 1 after aerogenic exposure [80], herpes simplex virus type 2 after vaginal challenge [83], influenza A virus after i.n. inoculation [84], lymphocytic choriomeningitis virus after i.v. injection [81, 85], murine cytomegalovirus after i.p. injection [78, 82], Rabies virus after intracranial injection [90, 91], SARS coronavirus after i.n. inoculation [89], vesicular stomatitis virus after i.n. inoculation or i.v. injection [87, 88];

v Four parasites: *C. parvum* after gavage [101], *T. gondii* after i.p. injection [92, 93, 96, 98, 103, 106], *T. brucei* after i.p. infection [99], *T. cruzii* after i.p. injection [97, 102];

vi Four fungi: *Aspergillus* after i.v. infection [108], *C. albicans* after i.v. or intragastric injection [108, 109, 112], *C. neoformans* after i.n. inoculation or i.p. injection [110, 111], *P. brasiliensis* after i.t. inoculation [113] (see Table 2).

IRAK-4-deficient mice displayed lower levels of survival than wild-type mice following i.p. challenge with *S. aureus* [17].

Impact of MyD88- and IRAK-4 deficiencies on protective immunity in humans

Susceptibility to pathogens in MyD88- and IRAK-4-deficient patients

The initial description of human IRAK-4 deficiency was based on three patients [29] and that of human MyD88 deficiency was based on nine patients [30]. These patients all carried either homozygous or compound heterozygous mutations of the *IRAK4* or *MYD88* gene that lead to nonfunctional proteins [29, 30]. Given these small numbers of patients, only brief preliminary conclusions could be made concerning the infectious phenotype associated with the absence of MyD88-IRAK-4-dependent signaling. The cumulative evidence from the large number of case reports since published and from the comprehensive description of a cohort of 76 patients (52 with IRAK-4 deficiency and 24 with MyD88 deficiency) allow firmer conclusions about the infectious phenotype in the absence of MyD88-IRAK-4-dependent signaling to be drawn [31, 114–129]. There are also an additional five patients with IRAK-4 deficiency and two patients with MyD88 deficiency for whom no data have yet been published. The infectious phenotype of MyD88- and IRAK-4-deficient patients is dominated by invasive pyogenic infections. The most frequent of such infections are meningitis, sepsis, arthritis, and osteomyelitis, and the principal bacteria isolated in cases of invasive infection are *S. pneumoniae*, *S. aureus*, and *Pseudmomonas aeruginosa* (for a list of all the pathogens isolated from Myd88- and IRAK-4-deficient patients, see Table 3). These patients also typically suffer from deep tissue infections of the upper respiratory tract, such as severe tonsillitis due to *P. aeruginosa* in particular, and superficial skin infections, mostly caused by *S. aureus*.

We cannot rule out the possibility that the predominance of Gram-positive bacteria in patients with MyD88 and IRAK-4 deficiencies results at least in part from a patient recruitment bias.

Table 3. Invasive infections in patients with impaired MyD88-IRAK-4 signaling caused by six Gram-positive and 13 Gram-negative bacteria

Pathogen group	Strain	References
Gram-positive bacteria	*Staphylococcus aureus*	[29–31, 115, 117, 119, 121, 125, 126, 128]
	Streptococcus agalacticae	[30, 31, 127, 128]
	Streptococcus milleri	[125]
	Streptococcus parasanguis	[118]
	Streptococcus pneumoniae	[29–31, 114–126, 128]
	Streptococcus pyogenes	[31, 128]
Gram-negative bacteria	*Acinetobacter baumanii*	[128]
	Citrobacter freundii	[31]
	Clostridium septicum	[31, 114, 116]
	Escherichia coli	[31]
	Haemophilus influenzae	[31]
	Klebsiella pneumoniae	[31]
	Moraxella catarrhalis	[31]
	Neisseria meningitidis	[31, 114, 116, 125]
	Proteus spp.	[30, 31]
	Pseudomonas aeruginosa	[30, 31, 120–122, 125, 128]
	Salmonella enterica	[30, 31]
	Serratia marcescens	[31]
	Shigella sonnei	[31, 119, 125, 127]

No patients with these deficiencies have yet been identified in the Indian subcontinent, in South America or in China. Patients with MyD88- or IRAK-4-deficiencies in these areas of the world might perhaps present a higher frequency of infections with Gram-negative bacteria, as suggested by case reports of invasive infection with *Shigella* spp. during endemic diarrhea outbreaks [119, 127]. However, by contrast to this uncertainty concerning positive associations about the infectious phenotype, we can highlight much more emphatically the negative associations drawn concerning the roles of MyD88 and IRAK-4 in host anti-pathogen defense. Most, if not all, of the 76 patients identified to date have been exposed to mycobacteria, viruses, *Toxoplasma*, *Pneumocystis*, and other fungi, but none of these pathogens caused invasive infection. This strongly suggests that MyD88 and IRAK-4 are dispensable in humans for defense against these pathogens, contrary to expectations based on the results obtained in the mouse model [31].

Survival of MyD88- and IRAK-4-deficient patients

At the time of writing, 26 patients with MyD88 deficiency have been identified (22 published [31], two unpublished (von Bernuth, unpublished)). Nine of these patients have died since identification: five in infancy and four in early childhood. The youngest of these nine patients died at 1 month of age and the oldest died at 4 years of age. The 15 surviving patients are currently four, seven, 11, 14, and 20 years old. Fifty-two patients with IRAK-4 deficiency have been identified [31]. Twenty-one of these patients have died since identification: 10 in infancy and 11 in early childhood. The youngest of these 19 patients was 2 months old, and the oldest was 7 years old, at the time of death; the latter being patient P23 from the large cohort published in 2010 [31] who recently died of *S. pneumoniae* meningitis (unpublished observation). The 31 surviving patients are currently two (two patients), three (one patient), four (one patient), five (two patients), six (two patients), seven (three patients), nine (one patient), 12 (one patient), 13 (two patients), 14 (two patients), 15 (two patients), 16 (two patients), 17 (two patients), 18 (one patient), 20 (one patient), 21 (one patient), 22 (one patient), 30 (one patient), 33 (two patients), and 38 (one patient) years old [31]. Thus, it can clearly be seen that human MyD88- and IRAK-4-deficiencies are life threatening. MyD88 and IRAK-4 are indispensable for survival in infancy and early childhood and, before the advent of vaccines and antibiotics, most if not all children with these defects would have died in the first few years of life. However, several individuals with MyD88 deficiency or its immunological phenocopy, IRAK-4-deficiency, who were given antibiotic prophylaxis and even sometimes IgG substitution following the genetic identification of the disease, have survived into adolescence and adulthood. Many of these patients have since stopped taking regular antibiotic prophylaxis, but have not yet developed invasive pyogenic infections. MyD88-IRAK-4-dependent signaling, therefore, appears to be dispensable for survival after adolescence.

Closing remarks

The notion that TLR- and IL-1R-mediated innate immune recognition is indispensable for survival and protective defense against many pathogens — based largely on findings in mouse models of experimental infections — should be reconsidered in light of the naturally occurring infections in humans with MyD88- or IRAK-4-deficiency. By contrast to the broad susceptibility of MyD88-deficient mice to 46 different bacteria, viruses, protozoa, and fungi (i.e. to almost nearly all the microbes tested), patients with MyD88- or IRAK-4-deficiencies are susceptible to invasive and noninvasive infections with only a few Gram-positive and Gram-negative bacteria. Moreover, MyD88-IRAK-4-mediated TLR and IL-1R immunity is undoubtedly vital in infancy and early childhood, but gradually becomes dispensable, from adolescence onwards. Overall, MyD88-dependent TLR and IL-1R immunity is vital in both mice and humans, but its role in the course of naturally occurring infections in humans seems to be much more restricted than initially inferred from experimental infections in mice, as humans lacking functional MyD88 or IRAK-4 proteins are susceptible to a narrow range of pathogens, and only in infancy

and early childhood. The different outcomes between experimental infections in mice and natural infections in humans may be due to species-specific differences, or more likely to differences in the modes of infection. In that regard, the study of naturally occurring infections in MyD88- and IRAK-4-deficient mice would be insightful, as suggested by preliminary studies [130]. In any case, the studies of MyD88- and IRAK4-deficient humans neatly illustrate the value of dissecting inborn errors of immunity underlying pediatric infectious diseases for deciphering the redundant and nonredundant roles of host defense genes in natura [23–28]. Immunological redundancy is greater in the course of natural infections in outbred human populations than in the course of experimental infections in inbred mice. Genetic studies of this type will facilitate the burgeoning, long-awaited investigation of the contribution of immunity to health, and disease in humans [131–133].

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Abbreviations: **DD**: death domain · **TIR**: Toll-interleukin receptor

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