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REVIEW

Toll-like receptor polymorphisms and susceptibility to human disease

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ABSTRACT

Although several lines of evidence suggest that variation in human inflammation is genetically controlled, the genes which regulate these responses are largely unknown. TLRs (Toll-like receptors) mediate recognition of microbes, regulate activation of the innate immune response and influence the formation of adaptive immunity. Cellular and molecular studies over the past several years have identified a number of common TLR polymorphisms that modify the cellular immune response and production of cytokines *in vitro*. In addition, human genetic studies suggest that some of these polymorphisms are associated with susceptibility to a spectrum of diseases. In this review, we summarize studies of common TLR polymorphisms and how this work is beginning to illuminate the influence of human variation on inflammation and disease susceptibility.

INNATE IMMUNITY AND TLR (TOLL-LIKE RECEPTOR) SIGNALLING IN HOST DEFENCE

A series of studies over the past 50 years indicate that host genetics influences susceptibility to human infection [1–3]. The early death of a biological parent from infection in an adoption study was associated with an increased risk of death of the child from an infectious disease by nearly 6-fold. In contrast, the premature death of an adoptive parent from an infection had no significant effect on the adoptees' risk of a similar cause of death [4]. Previous studies have also shown that genetic factors influence cytokine production by the innate immune system and that individuals can be stratified as high- and low-inflammatory responders [5–8]. Furthermore, these inflammatory phenotypes may correlate with clinical outcome, as suggested by the association of TNF (tumour necrosis factor)-α and IL (interleukin)-10 production with fatal meningococcal disease [6]. In this review, we summarize the evidence that attributes these differences to polymorphisms in critical innate immune response genes.

The innate immune response enables the host to differentiate self from pathogen and provide a rapid inflammatory response, including production of cytokines and chemokines, elaboration of effector molecules, such as NO, and interactions with the adaptive immune response [9]. Molecular understanding of innate immunity was accelerated in the mid-1990s when the *Drosophila* protein Toll was shown to be critical for defending flies against fungal infections [10]. This observation opened the way for the subsequent description of similar proteins, called TLRs, in mammalian cells. The human TLR family consists of ten receptors that are critically

Key words: genetic variation, immunodeficiency, inflammation, innate immunity, polymorphism, Toll-like receptor (TLR).
Abbreviations: CI, confidence interval; dsRNA , double-stranded RNA; EDA-ID, ectodermal dysplasia with immunodeficiency; HEK-293 cell, human embryonic kidney cell; IBD, inflammatory bowel disease; IL, interleukin; IL-1R, IL-1 receptor; IRAK, IL-1R-associated kinase; IκB, inhibitor of NF-κB; IKK, IκB kinase; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response gene 88; Mal, MyD88 adaptor-like; NF-κB, nuclear factor κB; NEMO, NF-κB essential modulator; OMIM, Online Mendelial Inheritance in Man; OR, odds ratio; PBC, primary biliary cirrhosis; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TAK, TGF (transforming growth factor)-β-activated kinase; TAB, TAK-1-binding protein; TB, tuberculosis; TLR, Toll-like receptor; TIR, Toll/IL-1R; TIRAP, TIR-domain-containing adapter; TNF, tumour necrosis factor; TRAF, TNF receptor-associated factor; TRIF, TIR-domain-containing adaptor-inducing interferon β.
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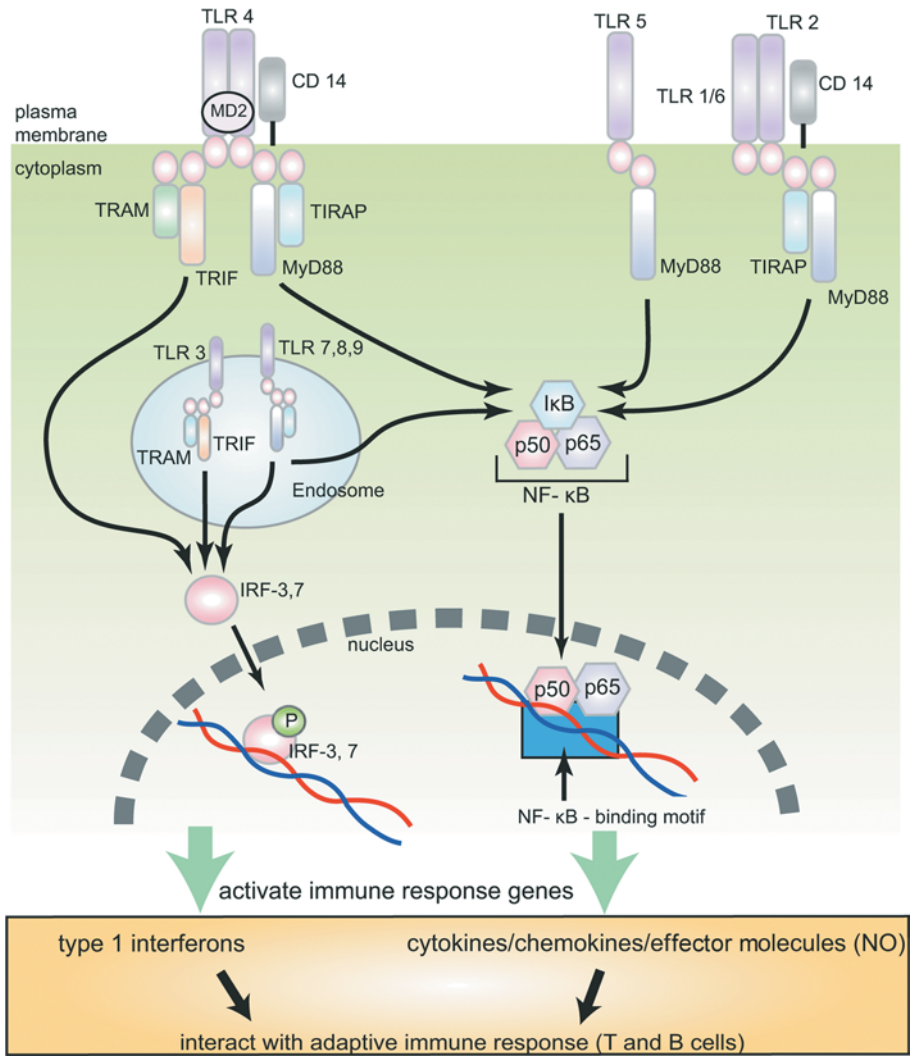

Figure 1 Overview of the human TLR signalling pathway

TLR ligation initiates a signalling cascade that culminates in the translocation of the transcription factors NF-κB and others to the nucleus, generating an acute inflammatory response. The general characteristics of the signalling pathway are depicted. IRF, interferon regulatory factor; TRAM, TRIF-related adaptor molecule.

important for innate immunity [11–13]. TLRs recognize and respond to diverse microbial molecules and enable the innate immune system to discriminate among groups of pathogens and to induce an appropriate cascade of effector responses. Individual TLRs recognize a distinct, but limited, repertoire of conserved microbial products; for example, well-characterized receptor–ligand pairs include TLR4 and LPS (lipopolysaccharide), TLR5 and flagellin, TLR1/TLR2/TLR6 and lipoproteins, and TLR3/TLR7/TLR8/TLR9 and different nucleic acid motifs. Collectively, the complete TLR family allows the host to detect infection by most (if not all) types of microbial pathogens.

TLRs are classified as members of the IL-1R (IL-1 receptor) superfamily on the basis of a shared cytoplasmic region known as the TIR (Toll/IL-1R) domain. The extracellular portions of TLRs are rather diverse, comprising varying numbers of leucine-rich repeats. Following encounter with a microbe, TLRs trigger a complex cascade of events that lead to the induction of a range of proinflammatory genes [11,12,14] (Figure 1). Ligand binding results in the recruitment of several molecules to the receptor complex. These include TIR-domain-containing adaptor molecules such as MyD88 (myeloid differentiation primary response gene 88), TIRAP/Mal (TIR-domain-containing adapter/MyD88 adaptor-like), TICAM1/TRIF (TIR-domain-containing adaptor molecule 1/TIR-domain-containing adaptor-inducing interferon β) and TRAM (TRIF-related adaptor molecule) (Figure 1). Further recruitment of molecules includes IRAKs {IL-1R-associated kinases [IRAK1, 2, 3 (M) and 4]} as well as TRAF6 (TNF receptor-associated factor 6). IRAK1 and TRAF6 then dissociate and bind another complex that consists of TAK1 [TGF

(transforming growth factor)-β-activated kinase 1] and TAB1, 2 and 3 (TAK-1-binding proteins 1, 2 and 3). TAK1 then activates IKK {IκB [inhibitor of NF-κB (nuclear factor κB)] kinase}. The activity of this complex is regulated by IKKγ [also known as NEMO (NF-κB essential modulator)]. IKK-mediated phosphorylation of IκB leads to its degradation, allowing NF-κB to translocate to the nucleus and promote the transcription of multiple proinflammatory genes, including TNF, IL-1β and IL-6.

MENDELIAN INHERITANCE AND MONOGENIC DISORDERS: PRIMARY IMMUNODEFICIENCIES CAUSED BY ABNORMAL TLR SIGNALLING

Genetic mutations in humans that cause extreme immunodeficiency phenotypes present powerful opportunities to determine the relationship between specific immunological defects and human disease processes *in vivo*. Previous studies of human primary immunodeficiencies associated with abnormal TLR signalling demonstrate that this pathway is critical for human defence against infection [15,16]. The genes and immunodeficiencies include IKBKG (IKKγ or NEMO), which causes X-linked hypohydrodric EDA-ID [ectodermal dysplasia with immunodeficiency; OMIM (Online Mendelial Inheritance in Man) #300291], NFKBIA (IκBα), which causes AD-EDA-ID (autosomal-dominant form of EDA-ID), IRAK4 deficiency (OMIN #607676) and Unc93b deficiency [17,18]. These disorders have been summarized elsewhere and will not be the topic of the present review [15,16].

COMPLEX INHERITANCE AND MULTIGENIC DISORDERS: TLR POLYMORPHISMS AND SUSCEPTIBILITY TO COMMON INFECTIONS

Although more than 120 monogenic primary immune deficiency diseases are now recognized, susceptibility to common infectious diseases seldom follows a simple pattern of Mendelian or monogenic inheritance [19]. Mendelian disorders can be ascribed to single gene mutations that abrogate function with high penetrance and often result in severe disease at an early age. In contrast, genetic disorders that follow a pattern of complex inheritance arise from polymorphisms in multiple genes. These disease alleles usually alter gene function more subtly, have lower penetrance, produce milder disease and have variable onset. Susceptibility to most infections follows a mode of polygenic inheritance, with disease arising from an intricate interplay between environmental and genetic factors. Until very recently, the complex inheritance pattern of common infectious diseases has been largely impervious to genetic analysis. However, with recent advances in high-throughput genotyping techniques and bioinformatics, understanding diseases with complex inheritance patterns is becoming feasible. Although humans are identical at most of the 3 billion base pairs in their genome, inter-individual variation is present in approx. 3 million nucleotides (i.e. 0.1 % of the genome). One common type of variation is the SNP (single nucleotide polymorphism), where one of two alternative bases occurs at appreciable frequency (> 1 %) in the population. Previously, studies have utilized SNPs in candidate genes to find associations with susceptibility to different infectious diseases [1,2,20–22]

Studies suggest that genetic variation in specific TLRs alters susceptibility to discrete pathogens. In addition, TLR SNPs have been implicated in susceptibility to non-infectious disorders. Given the complex inheritance patterns of polygenic disorders, the impact of any single allele on disease outcome (penetrance) is often modest. The most convincing association studies of polymorphisms with diseases with complex inheritance patterns include large sample sizes, statistical adjustments for multiple comparison, replication of findings with independent cohorts, multiple study designs (including case-control and family-based studies with use of the transmission disequilibrium testing), adjustment of the analysis for population admixture, and detailed molecular and cellular analyses to determine whether a polymorphism alters function. In the following sections, we review the present findings on TLR polymorphisms and assess the strengths of these studies in light of these features. Details are also summarized in Tables 1 and 2.

TLR4 SNPS AND INFECTION

TLR4 is required for the innate immune response to LPS or endotoxin, a constituent of Gram-negative bacteria. The *Tlr4* gene has two important non-synonymous SNPs (D299G and T399I) that are in linkage disequilibrium and have been intensively examined in functional and genetic association studies. D299G was associated with LPS hyporesponsiveness as measured by bronchospasm in response to *in vivo* inhalation of endotoxin [23]. A separate study found that both D299G and T399I were associated with systemic inflammatory hyporesponsiveness after LPS inhalation [24]. The measured responses included plasma LBP (LPS-binding protein), CRP (C-reactive protein) and white blood cell count. An *in vitro* cellular investigation suggested that 299G was unable to mediate LPS signalling in some cell types, including primary airway epithelial cells, and acted in a dominant fashion with respect to the wild-type 299D allele [23]. A third study found that 299G was associated with impaired IL-12 p70 secretion in PBMCs (peripheral blood mononuclear cells) stimulated with LPS [25]. In contrast, five other studies found no defect in LPS signalling

Table 1 Human TLR pathway polymorphisms, functional studies and susceptibility to infection

See text for references and more details. MS, microsatellite. *Association, summary of reported associations with disease susceptibility in case-control studies. †Validate refers to whether the genetic findings were replicated in another cohort with the same disease; ‡Function refers to whether the variant is associated with altered function of the gene, either through regulation of expression levels (E) or through a non-synonymous coding region polymorphism that alters the signalling function (S). CMV, cytomegalovirus; HCV, heptatis C virus.

TLR	Nucleic (amino) acid variant	Association*	Validate†	Function‡	Comments
TLR1	T1805G (I602S)	Leprosy	No	Yes (S)	In LD with A743G
TLR2	Intron II GT MS	TB	Yes	Possible (E)	
		Reversal reaction in leprosy	No		
	G2258A (R753Q)	Borreliosis	No	Yes (S)	
		TB	No		
		Acute rheumatic fever	No		
		Recurrent febrile infections	No		
		CMV disease	No		
TLR4	A896G (D299G)	Many with variable results.	No	Yes (S *in vivo*) Possible (S *in vitro*)	
	C1196T (T399I)	Many with variable results.	No		In LD with D299G
TLR5	C1174T (R392*)	Yes: *Legionella* No: *Salmonella*	No	Yes (S)	
TLR7	Intron 1, c.1T − 120G	HCV	No	Yes (S)	
TIRAP/Mal	C539T (S180L)	Malaria, pneumococcal empyema, bacteraemia, TB	Yes	Yes (S)	
	C558T (A186A)	TB	No	Possible (S)	

in individuals heterozygous for D299G when whole blood, PBMCs or monocytes were stimulated [26–30]. In addition, a sixth study found no difference in vital signs or plasma IL-6 levels after intravenous administration of LPS [31]. The seemingly contradictory findings in these studies may be explained by different stimulatory conditions (*in vivo* inhaled LPS, *in vivo* intravenous LPS, *ex vivo* PBMCs and *ex vivo* whole blood), the use of small sample sizes that result in differences with borderline statistical significance, comparison of different cell types, use of different doses and types of LPS, measurement of different cytokines and inflammatory markers, and the use of *in vitro* overexpression systems, which may not accurately model signalling pathways in primary cells. Taken together, these studies suggest that SNPs D299G and T399I partially regulate inflammatory pathways under some experimental conditions.

Several genetic studies have examined whether there is an association between TLR4 D299G and bacterial infections or susceptibility to sepsis (Table 2). Although some authors have demonstrated an association between the 299G allele and increased susceptibility to sepsis, this finding has not been observed consistently [32–34] (Table 2). One problem may be that that the aetiology of sepsis is heterogeneous and that TLR4 SNPs would primarily be predicted to alter susceptibility to Gram-negative infections. Two studies support this hypothesis [35,36]; however, other studies of specific Gram-negative bacterial infections have demonstrated mixed results. Two studies found no association of SNP D299G with susceptibility to meningococcal infections [37,38]. In contrast, a third study found an association in children less than 1 year of age [39]. Urinary tract infections, which are predominantly caused by Gram-negative bacteria, had a marginal association with D299G [OR (odds ratio), 2.19; $P = 0.041$] [40]. D299G and T399I are in linkage disequilibrium, with variable degrees of linkage in different populations. Some of the inconsistency of the results in these association studies may be attributable to distinct effects from different TLR4 haplotypes that contain D299G, T399I and other TLR4 polymorphisms. Such differences may also influence interpretation of the signalling studies described above. One study examined rare TLR4 coding variants that were markedly over-represented in patients with systemic meningococcal infections caused by *Neiserria meningiditis*. The functional consequences of these rare coding variants remain unknown [41,42].

Most studies have demonstrated that these two common TLR4 polymorphisms confer an increased risk to some infections; however, this finding is not universal. For example, D299G and T399I are associated with resistance to Legionnaire's disease, a pulmonary infection caused by *Legionella pneumophila*, a flagellated Gram-negative bacterium [43]. It is not known why these TLR4 SNPs are associated with different susceptibility to *Legionella* in comparison with other pathogens, although *Legionella* has an unusual LPS structure that may be recognized predominantly by TLR2 rather than TLR4 [44]. This protective association illustrates that

Table 2 Case-control studies of human TLR polymorphisms and susceptibility to infections

Frequencies listed are denoted by an (a) for allele frequencies and (g) for genotype frequencies that either combines heterozygotes (Aa) with the homozygotes for the minor allele (aa) or the major allele (AA). *C. albicans*, *Candida albicans*; CMV, cytomegalovirus; HCV, hepatitis C virus; HSV, herpes simplex virus; MS, microsatellite; N, no association; ND, polymorphism not detected; NS, not significant ($P > 0.05$); R, associated with resistance; S, polymorphism associated with susceptibility; *S. aureus*, *Staphylococcus aureus*; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection.

				Frequency			
TLR	SNP	Case-control definitions and sample size	Effect (OR)	Case	Control	*P* value	Reference
TLR1	1602S	Leprosy ($n = 57$) compared with control ($n = 90$)	R	0.26 (a)	0.43 (a)	0.004	[98]
	R80T	Aspergillosis ($n = 10$) compared with control ($n = 76$)	S	0.50 (a)	0.12 (a)	< 0.01	[131]
TLR2	R753Q	Gram+ septic shock ($n = 22$) compared with control ($n = 69$)	N	0.09 (a)	0.0 (a)	ND	[132]
	R753Q	TB ($n = 151$) compared with control ($n = 116$)	S	0.093 (g)	0.017 (g)	0.022	[81]
	R753Q	Lyme disease ($n = 155$) compared with control ($n = 349$)	R	0.058 (a)	0.12 (a)	0.037	[80]
	R753Q	*S. aureus* ($n = 420$) compared with control ($n = 696$)	N	0.05 (g)	0.05 (g)	NS	[133]
	R753Q	Rheumatic fever ($n = 61$) compared with control (91)	S	0.459 (a)	0.0495 (a)	< 0.001	[89]
	R753Q	Rheumatic fever ($n = 85$) compared with control ($n = 141$)	N	0.000 (a)	0.01 (a)	ND	[134]
	R753Q	Febrile infections ($n = 52$) compared with control ($n = 91$)	S	0.23 (a)	0.049 (a)	0.000	[135]
	R753Q	CMV after transplant ($n = 24$) compared with control ($n = 68$)	N	0.125 (g)	0.0294 (g)	0.08	[136]
	Intron II MS	TB ($n = 176$) compared with control ($n = 196$), short repeat	S	0.287 (a)	0.223 (a)	0.047	[83]
	Intron II MS	Reversal reaction in leprosy ($n = 54$) compared with no reversal reaction ($n = 79$)	S	0.458 (a)	0.280 (a)	0.001	[84]
	T − 16933A	Gram+ bacteraemia, sepsis ($n = 237$)	S			< 0.04	[94]
	T597C	TB meningitis ($n = 564$) compared with control ($n = 229$)	S	0.140 (g)	0.048 (g)	< 0.001	[86]
	C597T	Reversal reaction in leprosy ($n = 39$) compared with no reversal reaction ($n = 124$)	R	0.325 (a)	0.446 (a)	0.027	[84]
	C1752T	*Meningococcus* ($n = 102$) compared with control ($n = 104$)	R	0.0104 (a)	0.0476 (a)	0.050	[42]
	Haplotype	HSV shedding and lesion rates ($n = 128$)	S			0.008	[137]
TLR4	D299G and T399I	Septic shock ($n = 91$) compared with control ($n = 73$).	N	0.12 (g)	0.11	NS	[36]
		Subgroup with 299G/399T		0.055	0	0.05	
	D299G	Sepsis ($n = 153$) compared with control ($n = 154$)	N	0.065 (g)	0.123 (g)	NS	[34]
	D299G	Sepsis after burns ($n = 228$)	S			0.027	[32]
	D299G	SIRS survival ($n = 94$)	N	0.19 (g)	0.05 (g)	0.076	[33]
	D299G	Gram− sepsis ($n = 79$) compared with control ($n = 39$)	S			0.015	[35]
	Rare variants	*Meningococcus* ($n = 355$) compared with control ($n = 532$)	S	0.058 (a)	0.0042	0.03	[42]
	D299G	*Meningococcus* ($n = 1047$) compared with control ($n = 879$)	N	0.065 (a)	0.059	NS	[38]
	D299G	*Meningococcus* ($n = 252$) compared with control ($n = 251$)	N	0.113 (a)	0.110	NS	[37]
	D299G	*Meningococcus* ($n = 197$) compared with control ($n = 214$)	N (all)	0.094 (a)	0.06	NS (all)	[39]
			Y (< 1 y)	0.163		0.007	
	D299G and T399I	*Legionnella* ($n = 108$) compared with control ($n = 508$)	R	0.025 (a)	0.065	0.025	[43]
	D299G	*Pneumococcus* ($n = 300$) compared with control ($n = 630$)	N	0.163 (a)	0.160	NS	[49]
	D299G	*Pneumococcus* ($n = 300$) compared with control ($n = 178$)	N	0.096 (g)	0.133	NS	[50]
	D299G	TB ($n = 976$) compared with control ($n = 882$)	N	0.208 (a)	0.196	NS	[49]
	D299G	TB ($n = 307$) compared with control ($n = 298$)	N	0.114 (a)	0.114	NS	[51]
	D299G	TB and HIV ($n = 80$) compared with control ($n = 24$)	N	0.208 (g)	0.075	0.06	[52]
	D299G	UTI in children ($n = 103$) compared with control ($n = 235$)		0.08 (a)	0.04 (a)	0.04	[40]
	T399I	Malaria ($n = 290$) compared with control ($n = 290$)	S	0.033 (a)	0.012	0.02	[47]
	D299G	Aspergillosis ($n = 22$) compared with control ($n = 105$)	N			NS	[131]
	D299G	Brucellosis ($n = 198$) compared with control ($n = 111$)	S	0.336 (a)	0.207	< 0.0001	[138]
	D299G	Lymphatic filariasia ($n = 625$)	ND		0		[139]
	D299G	*C. albicans* vaginitis ($n = 88$) compared with control ($n = 134$)	N	0.102 (g)	0.134	NS	[140]
	D299G	*C. albicans* ($n = 43$) compared with control ($n = 166$)	S	0.26	0.10	P < 0.05	[141]
	D299G and T399I	Severe RSV ($n = 99$) compared with control ($n = 90$)	S	0.202 (a)	0.056	0.004	[46]
	D299G	RSV ($n = 236$) compared with control ($n = 106$ and 113)	N	0.40 (a)	0.42 and 0.40	NS	[28]

Table 2 (Contd.)

TLR	SNP	Case-control definitions and sample size	Effect (OR)	Frequency		*P* value	Reference
				Case	Control		
TLR5	R392STOP	*Legionnella* ($n = 108$) compared with control ($n = 508$)	S	0.167 (g)	0.095	0.03	[103]
	R392STOP	Typhoid fever ($n = 565$) compared with control ($n = 281$)	N	0.064 (a)	0.059	NS	[104]
TLR7	Intron 1,	HCV inflammation ($n = 183$) or	R	0.038 (a)	0.098 (a)	0.044	[142]
	c.1T − 120G	Fibrosis ($n = 279$) compared with control ($n = 145$–153)		0.036 (a)	0.117 (a)	0.003	
TLR9	G-1174A	HIV progression ($n = 69$) compared with control ($n = 363$)	S	0.88 (g)	0.66 (g)	0.0007	[116]
	A1635G	HIV progression ($n = 69$) compared with control ($n = 363$)	S	0.89 (g)	0.68 (g)	0.0005	[116]
TIRAP/Mal	S180L	Malaria, bacteraemia, *Pneumococcus* and TB ($n = 6106$ for all cohorts)	R			$< 10^{-7}$	[129]
	C558T	TB ($n = 349$) compared with control ($n = 390$)	S	0.074	0.035	< 0.001	[130]

an innate immune receptor can mediate either beneficial or deleterious inflammatory responses and that these outcomes vary with different pathogens.

A number of studies have looked for associations between TLR4 SNPs and susceptibility to pathogens other than Gram-negative bacteria (Table 2). RSV (respiratory syncytial virus), for example, was shown in one study to stimulate an innate immune response via TLR4 [45]. In a genetic association study, infants with TLR4 polymorphisms were at increased risk of severe RSV bronchiolitis [46]; however, this finding was not replicated in a separate study [28]. In Ghana, SNPs D299G and T399I were associated with severe malaria as well clinical manifestations of malaria during pregnancy [47,48]. There was no evidence of an association between the TLR4 D299G allele and invasive pneumococcal disease [49,50] or TB (tuberculosis) [49,51,52]. There is debate about how TLR4 recognizes pathogens without LPS and whether results from some *in vitro* studies are attributable to LPS contamination of the assays. If TLR4 does not directly recognize these pathogens, one theoretical possibility is that TLR4 may modulate the general inflammatory milieu in response to LPS from a microbial source that is not responsible for the primary infection. Taken together, functional and genetic studies of TLR4 SNPs show a possible association with susceptibility to Gram-negative bacterial infections and perhaps other infections. However, most results have had marginal statistical significance due to small sample sizes and specific positive findings have not been confirmed in validation studies. Additional studies with larger sample sizes, validation cohorts and genotyping that includes more complete haplotype information are essential before the role of TLR4 SNPs in susceptibility to infections will be understood.

TLR4 POLYMORPHISMS AND OTHER DISEASES

TLR4 has also been studied for its role in non-infectious diseases, including atherosclerosis, autoimmune diseases, asthma and cancer [53]. An initial study found that SNP D299G was associated with a decreased risk of atherosclerosis, as measured by intima-media thickness of the carotid artery [54]. In addition, some studies have found an association with susceptibility to cardiovascular disease [32,55–57]; however, other studies have not found either of these associations [58–63]. As several of these studies were large, sample size is an unlikely explanation for some of the discrepant results. One study demonstrated an association of D299G with susceptibility to RA (rheumatoid arthritis), whereas two studies found no association [64–66]. Mixed results have also been found with IBD (inflammatory bowel disease) [67–69] and chronic periodontitis [70–75]. Two studies have examined the role of TLR polymorphisms and susceptibility to asthma and atopic phenotypes [76–78]. Inhalation of environmental endotoxin has been hypothesized to influence development of asthma through stimulation of inflammatory pathways [79]. In a large family-based study from North America, no associations were found between multiple TLR4 SNPs (including D299G) and asthma or atopy-related phenotypes [76]. Similarly, in a study from the U.K., no association was found between SNP D299G and asthma susceptibility [77,78], although there was an association of 299G with an atopy-severity score. The discordant findings in these studies may in part be due to reliance on diverse clinical end points and unequal environmental exposures. For example, in the case of atherosclerosis, the clinical end point of atherogenesis and vessel stenosis is different from that of plaque stabilization and rupture, and may be regulated by different genetic mechanisms. Environmental exposure is probably an important modifier of asthma risk that may need to be incorporated into future analyses of the effect of TLR4 polymorphisms on asthma risk.

TLR2 POLYMORPHISMS AND INFECTIONS

TLR2, as a heterodimer with TLR1 or TLR6, recognizes a number of common bacterial motifs, including bacterial

lipopeptides, peptidoglycan, lipotechoic acid, GPI (glycosylphosphatidylinositol)-linked proteins and zymosan [11]. Among the TLRs, TLR2 recognizes the most diverse set of pathogens, including bacteria, viruses, fungi and parasites. Several TLR2 polymorphisms have been described with functional and genetic association studies. A polymorphism in the TIR domain, R753Q (G2258A), is the best characterized with regards to functional studies and is associated with altered signalling [80]. In HEK-293 cells (human embryonic kidney cells) transfected with TLR2 in an NF-κB assay, the 753Q variant had impaired signalling in comparison with the wild-type variant when stimulated with lipopeptides or lysates of *Borrelia burgdorferi*. Furthermore, cytokine production after *ex vivo* stimulation of whole blood with *Borrelia* lysates was decreased in heterozygous (753RQ) individuals in comparison with wild-type individuals. The frequency of the 753Q variant in 155 patients with serological and clinical evidence of Lyme disease was 5.8 % (nine heterozygous individuals) compareds with 13.5 % in 349 age- and sex-matched controls {OR, 0.393 [95 % CI (confidence interval), 0.17–0.89]; $P = 0.03$}. Furthermore, the protective effect increased when patients with stage III Lyme disease were compared with controls [OR, 0.148 (95 % CI, 0.03–0.65); $P = 0.0028$] [80]. R753Q was associated with pulmonary TB in a Turkish population ($n = 151$ cases and 116 controls) in 753QQ homozygotes [OR, 6.04 (CI, 2.01–20.08), $P = 0.02$] [81]. One limitation of this latter study is that the control group was not in Hardy–Weinberg equilibrium with respect to the G2258A polymorphism, which suggests that population admixture could have confounded these results.

A microsatellite region in intron 2 has been described with variable numbers of GT repeats beginning approx. 100 bp upstream of the translational start site [82]. Functional studies using luciferase assays with variable numbers of GT repeats suggest possible differences in promoter activity that may influence TLR2 signalling. In addition, shorter GT repeats were more common among 176 patients with TB compared with 196 healthy controls (49.4 compared with 37.7 %; $P = 0.02$). This finding was validated by the same authors in a separate cohort of 82 patients with TB [83]. In a study from Ethiopia, the $(GT)_n$ polymorphism, as well as an adjacent second dinucleotide repeat $(CT)_n$, were associated with reversal reaction in leprosy patients [OR, 2.168 (95 % CI, 1.388–3.386), $P = 0.01$] when adjusted for multiple comparisons [84]. Clinically, reversal reaction is characterized by fever, inflammation and neuritis. Immunologically, reversal reaction represents a shift toward the tuberculoid pole of leprosy, and is characterized by a vigorous inflammatory response, containment of the disease, and a Th1 cytokine profile [85].

A synonymous SNP, C597T (N199N), has recently been reported to be associated with TB meningitis as well as with reversal reaction in leprosy [84,86]. In Vietnam, 597CC homozygosity was associated with susceptibility to TB with an OR of 2.22 (compared with 597TT/TC; $P = 0.007$; $n = 358$ patients with TB and 389 controls). The association with TB was almost entirely due to enhanced susceptibility to meningeal as opposed to pulmonary TB (OR, 3.26; $P = 0.0002$). In the same Ethiopian leprosy study described above, 597T was associated with protection from reversal reaction [OR, 0.598 (CI, 0.382–0.937); $P = 0.027$] [84]. A polymorphism in the TLR2 TIR domain (C2029T, R677W) was originally described in the context of an association with susceptibility to lepromatous leprosy [87]. This SNP was later found to be an artifact that resulted from a variant in a duplicated pseudogene region of TLR2 that is present several kilobases upstream of the true gene [88].

TLR2 POLYMORPHISMS AND OTHER DISEASES

TLR2 R753Q was associated with an increased risk of restenosis following percutaneous transcoronary angioplasty, an increased risk of acute rheumatic fever (OR, 97.1; $P < 0.0001$) in a group of 61 adult patients from Turkey and pancolitis in patients with ulcerative colitis [89]. Lee et al. [90] have also studied variation in GT repeats in Koreans with RA and found that patients with 16 or fewer GT repeats were at higher risk of RA compared with patients with 17 or more repeats (OR, 1.46; $P = 0.03$). An association has also been reported between short (< 18 copies) and long (26–43 copies) GT repeats with colorectal cancer patients compared with controls [RR (relative risk), 1.6–2.3 (95 % CI 1.310–1.954); $P \leqslant 0.0001$] [91]. Other reports of TLR2 SNP associations include that of T − 16934A with asthma, lymphoma and infections in ICU (intensive care unit) patients [92–94], and of G2258A (R743Q) with severe dermatitis [95]. The findings from these various studies have not been validated in independent cohorts.

TLR1, TLR6 AND TLR10 POLYMORPHISMS

TLR2 forms a heterodimer with TLR1 or TLR6 [96] to mediate host responses to lipopeptides from several classes of pathogens. We recently described a transmembrane SNP, T1805G (I602S), in TLR1 that regulates lipopeptide-induced signalling [97]. Individuals with the 602SS genotype had a greater than 10-fold reduction in levels of IL-6 after whole blood stimulation with triacylated lipopeptide compared with 602SI and II individuals [97]. Furthermore, I602S was found to regulate lipopeptide NF-κB-mediated signalling in transfected HEK-293 cells. In a separate study, TNF-α production

in lipopeptide-stimulated monocytes from 602SS was impaired in comparison with 602II individuals [98]. In addition, there was diminished cell-surface TLR1 staining of monocytes in 602SS individuals, but normal total cellular levels of TLR1. This finding suggested a defect in TLR1 trafficking to the cell surface in 602SS individuals. The 1805G polymorphism varies in frequency from 1 to 76%, depending on the population [97,98]. In a cohort of leprosy patients from Turkey, the G allele at 1805 (602S) was associated with protection against leprosy [OR, 0.48 (95% CI, 0.29–0.80; $P = 0.004$] [98]. We have independently investigated the association of this SNP with leprosy susceptibility in a separate cohort and found that allele 602S is associated with protection from reversal reaction (E.A. Misch and T.R. Hawn, unpublished work). There is high potential clinical impact of this polymorphism given its frequency and the diverse array of pathogens recognized by TLR1/TLR2 heterodimers.

TLR6 also mediates the recognition of lipopeptides as a heterodimer with TLR2. There have been no functional studies on TLR6 polymorphisms and no association studies with infections. However, there have been several association studies with other diseases. Sun et al. [99] investigated nine TLR6 SNPs, 11 TLR1 SNPs and 12 TLR10 SNPs in a population-based case-control study of prostate cancer in Sweden (CAPS study). A TLR 6 promoter SNP − A1401G was associated with an increased risk of prostate cancer in individuals heterozygous or homozygous for A [OR, 1.38 (95% CI, 1.12–1.70); $P = 0.001$]. Three TLR1 SNPs were associated with an increased risk of prostate cancer. Tantisira et al. [100] reported a protective association of TLR6 C744T with asthma.

TLR10, which resides in a locus close to TLR1 and TLR6, is the only human TLR that has no known ligand. Because of the physical and phylogenetic proximity of TLR10 to TLR6 and TLR1, several authors have looked for disease associations with this receptor. Three coding SNPs in TLR10 have weak associations with prostate cancer risk: TLR10 720C (N241H), 1104C (I369L) and 2322G (I775V) [99]. Zhou and co-workers [101] found a common TLR10 haplotype that was associated with increased risk of nasopharyngeal cancer [OR, 2.66 (95% CI, 1.34–3.82); $P = 0.002$], although adjustments were not made for multiple comparisons [101]. Lazarus et al. [102] have also reported an association between two TLR10 SNPs (TLR10 c.+G1031T and c.+A2322G) and asthma in two separate cohorts.

TLR5 POLYMORPHISMS

TLR5, the receptor for bacterial flagellin, mediates recognition of a number of medically important pathogens, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Proteus* species, *Bacillus* species and *Legionella* species. A common non-synonymous TLR5 polymorphism in the extracellular ligand-binding domain changes an arginine to a stop codon (R392*, base pair C1174T) and abolishes flagellin signalling in transfected cell lines [103]. This polymorphism is present in approx. 10% of the population, and is associated with decreased cytokine production in PBMCs stimulated with flagellin. In addition, the stop codon variant acts in a dominant fashion with respect to the wild-type allele and is associated with increased susceptibility to Legionnaire's disease [392R* frequency of 0.095 in cases and 0.167 in controls; OR, 1.90 (95% CI, 1.06–3.42); $P = 0.03$]. However, this TLR5 polymorphism does not render human carriers universally susceptible to infection with flagellated bacteria, as it had no measurable impact on susceptibility to typhoid fever caused by *Salmonella enterica* serovar typhi [104].

The high prevalence of TLR5 deficiency in the population suggests that there may be an evolutionary explanation for its persistence. Two separate lines of evidence suggest that TLR5 deficiency is associated with protection from non-infectious inflammatory diseases. SLE (systemic lupus erythematosus) is an autoimmune disease with a complex genetic basis that includes susceptibility gene(s) on multiple chromosomes, including 1q41-q4, which is the location of TLR5 [105]. On the basis of transmission disequilibrium testing as well as a case-control study design in a Caucasian cohort containing 199 affected patients and their 75 unaffected siblings and 326 parents, SNP C1174T was associated with protection from SLE [T/NT (transmitted:not transmitted ratio), 19:6; $P = 0.009$; OR, 0.51 (CI, 0.26–0.98); $P = 0.041$]. Although these results indicated that the TLR5 stop codon polymorphism is associated with protection from the development of SLE, a second study in Caucasians did not confirm these findings [106].

Previous studies have demonstrated that flagellins are immunodominant antigens that may trigger autoimmune intestinal pathology in patients with Crohn's disease [107,108]. Activation of TLR5 by flagellin triggers production of pro-inflammatory cytokines, such as IL-6, which in turn can stimulate B-cells to proliferate, differentiate and secrete antibodies. In fact, flagellin is a powerful adjuvant that promotes T-cell responses that stimulate antibody production [109–111]. The TLR5 stop codon was associated with lower levels of flagellin-specific IgG and with protection from Crohn's disease (392R* frequency of 0.009 in cases and 0.065 in controls; $P = 0.037$) [112]. Flagellin could stimulate systemic pathology in SLE and IBD and TLR5 deficiency could protect against this process. Although this speculation is biologically plausible, the current genetic findings from association studies are not statistically robust enough or validated to confirm this hypothesis. Although TLR5 deficiency may protect against pathological pro-inflammatory processes, the prevalence of autoimmune diseases is unlikely to be high

enough to confer sufficient allelic evolutionary pressure for its persistence in the population.

TLR3 POLYMORPHISMS

TLR3 recognizes poly(I:C) (polyinosine:polycytidylic acid), a synthetic dsRNA (double-stranded RNA) analogue, and also recognizes dsRNA from viruses. However, minimal results are available on TLR3 polymorphisms. Two papers have reported signalling defects associated with SNPs in transfected cells [A722T (N284I), C1234T (L412F), and T908C (F303S)] with unknown clinical significance [113,114]. Ueta et al. [115] reported a possible association of two SNPs, TLR3 1378G (259F → F) and an SNP in the 5′ untranslated region, rs3775296 (National Center Biotechnology Information designation), with ocular sequelae of Stevens–Johnson syndrome.

TLR9 POLYMORPHISMS AND INFECTIONS

TLR9 recognizes unmethylated CpG motifs present in bacteria and viruses. Bochud et al. [116] studied a series of TLR variants in a group of Swiss patients with rapid compared with non-rapid progression of HIV disease (65 rapid progressors compared with 363 non-rapid progressors). Two SNPs in TLR9, a SNP in intron I (G1174A) and a synonymous SNP in the coding region [G1635A (P545P)] were associated with rapid progression in HIV. Individuals with genotypes 1174GA and AA at were at increased risk of rapid progression [ORs, 3.64 and 4.22 (95 % CIs, 1.61–8.21 and 1.74–10.2) respectively; $P = 0.002$ and 0.001]. Similarly, individuals with genotypes 1635AG and GG were at increased risk of rapid HIV progression [ORs, 3.92 and 4.73 (95 % CI, 1.67–9.18 and 1.86–12.0) respectively; $P = 0.002$ and 0.001] [116]. Mockenhaupt and co-workers [48] investigated the role of two TLR9 promoter region polymorphisms (T − 1237C and T − 1486C) in susceptibility to and manifestations of malaria in women from Ghana during first pregnancy. Neither variant altered the risk of placental malaria or the parasite burden of the placenta; however, the − 1486C allele was associated with significant differences in birthweight in children born to heterozygous or homozygous mothers.

TLR9 POLYMORPHISMS AND OTHER DISEASES

TLR9 variants have been reported to have associations with asthma, SLE, IBD and atherosclerosis. Lazarus and co-workers [117] explored the association of TLR9 SNPs T − 1237C and G2848A (equivalent to SNP G1635A discussed above) with myocardial infarction, deep vein thrombosis and COPD (chronic obstructive pulmonary disease). The C allele of T − 1237C was associated with an increased risk of asthma among European Americans, although this finding was of marginal significance [OR, 1.85 (95 % CI, 1.05–3.25); $P = 0.042$]. However, Noguchi et al. [118] were unable to find an association between this SNP and asthma in a Japanese cohort. Two further studies found no association of TLR9 SNPs with asthma or with coronary artery restenosis after percutaneous coronary intervention [119,120]. Tao and co-workers [121] investigated TLR9 SNPs G1174A, an intron 1 variant, and T − 1486C, a promoter SNP, in 440 patients with SLE compared with 406 controls. The 1174G allele was more common in lupus patients, with marginal statistical significance (51.6 % of cases compared with 44.0 % of controls; $P = 0.0291$). This allele was frequently co-inherited with allele − 1486C. Functional characterization of the GC haplotype suggested that this variant resulted in reduced transcription of TLR9 compared with the AT haplotype. Three other studies have been unable to find an association between one or both of these TLR9 variants and susceptibility to lupus in patients from Korea, China and the U.K. respectively [122–124].

The TLR9 gene lies close to a susceptibility locus for Crohn's disease and ulcerative colitis, leading several authors to explore possible associations between TLR9 polymorphisms and IBD [125]. Torok et al. [126] reported that − 1237C was associated with Crohn's disease, but not ulcerative colitis, in a study of 174 German patients with Crohn's disease, 138 patients with ulcerative colitis and 265 healthy blood donors. Lammers et al. [127] also reported that TLR9 − 1237C was more frequent in Italian patients with three or more episodes of pouchitis (45.7 %) compared with patients with fewer episodes (20.9 %) [OR, 3.2 (95 % CI, 1.2–8.6); $P = 0.028$]. Kikuchi and co-workers [128] investigated 90 Italian patients with PBC (primary biliary cirrhosis) and 90 controls and found no association between TLR9 SNPs and the risk of PBC [128]. However, B-cells from 2848AA individuals with PBC stimulated with CpG DNA had higher levels of TLR9 expression and higher levels of intracellular IgM compared with B-cells from 2848GG individuals.

TIRAP/Mal

TLRs mediate signalling through homotypic interaction of their TIR domain with adaptor proteins, including TIRAP/Mal. Recent studies of TIRAP have suggested an association with susceptibility to infection. TIRAP has two isoforms (221 and 235 amino acids), and both have a C-terminal TIR domain that mediates signals from TLR2 and TLR4. A TIRAP polymorphism was recently described that changes Ser^{180} to a leucine residue (S180L; C539T) and impairs TLR2-mediated NF-κB signalling in reconstitution experiments [129]. In addition, the 180L variant was less able to bind TLR2 in comparison with the 180S variant. The heterozygous state was associated

with protection from several diseases, including malaria, invasive pneumococcal disease, bacteraemia and TB, with ORs of approx. 0.2 to 0.7. The SNP frequency is low in most populations tested (heterozygote frequency, 0.6–5.9 %), except for the U.K. (up to 29.6 %). The results have been validated in several populations and included case-control and family-based study designs.

We recently examined TIRAP variants in a cohort of patients with TB from Vietnam [130]. Although we did not find an association of S180L with susceptibility to TB, the frequency of this SNP was too low for proper statistical evaluation (2.3 % in cases compared with 1.7 % in controls; $P = 0.61$). We did find that a synonymous SNP (C558T; A186A) was associated with increased susceptibility to TB with a 558T allele frequency of 0.035 in controls compared with 0.074 in cases (OR, 2.25; $P < 0.001$). Subgroup analysis revealed that SNP 558T was more strongly associated with susceptibility to meningeal TB (OR, 3.02; $P < 0.001$) than pulmonary TB (OR, 1.55; $P = 0.22$). In comparison with the 558CC genotype, the 558TT genotype was associated with decreased whole-blood IL-6 production, which suggested that TIRAP influences disease susceptibility by modulating the inflammatory response. We do not currently understand how this SNP alters cytokine protection, but speculate that it may be in linkage disequilibrium with a coding region SNP or one that alters expression levels. These results suggest that the TLR pathway influences susceptibility to meningeal and pulmonary TB by different immune mechanisms.

CONCLUSIONS

Over the past 7 years, genetic analysis of TLR pathway polymorphisms has accelerated and included many seminal observations. There is convincing evidence that common TLR SNPs regulate cellular signalling events and cytokine production. The best evidence includes studies of TLR2 R753Q, TLR5 R392*, TLR1 I602S and TIRAP S180L. Signalling effects from SNP TLR4 D299G have varied, possibly due to the use of different cell types and assays. A number of genetic association studies suggest that TLR polymorphisms may be associated with susceptibility to different diseases; however, very few of these studies have been replicated in a convincing fashion. The most robust genetic association to date has been with TIRAP S180L, which was associated with protection from several different infections. Despite the preliminary status of many of the reported associations, a number of intriguing observations suggest those common TLR pathway polymorphisms are associated with disease susceptibility. Currently, there is not enough evidence available to understand whether specific infections or diseases are more or less likely to be influenced by TLR polymorphisms. Large well-designed studies with precise clinical and microbiological phenotyping will be required to validate these observations.

TLRs play a central role in innate immunity and there is mounting evidence of polymorphisms that regulate immune function. This regulation ranges from control of inflammatory cascades, elaboration of effector molecules and pathogen killing, and interactions with the adaptive immune response. Although initial evidence suggests that TLR polymorphisms influence cellular production of cytokines and chemokines, it is not currently known if other immune functions are affected, particularly at the *in vivo* level. Ongoing investigations over the next several years will provide an important body of data to understand the molecular, cellular and clinical significance of common TLR pathway variation.

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