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REVIEW ARTICLE

The potential of targeting Toll-like receptor 2 in autoimmune and inflammatory diseases

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Abstract The last decade has revealed interesting insights into the initiation and pathophysiology of the innate immune system. Toll-like receptors are of key importance for this process and they are a family of receptors expressed mainly on leukocytes that recognize a variety of microbial products derived from bacteria, viruses, protozoa and fungi. As key players of innate immunity, TLRs and downstream signalling components are important target candidates for drug development. In this review, we focus on TLR2, which recognizes bacterial lipopeptide. TLR2 forms dimers with TLR1 or TLR6. The TLR2/TLR1 dimer recognizes triacylated lipopeptides, whilst the TLR2/TLR6 dimer recognizes diacylated lipopeptides. TLR2 has been implicated in several auto-immune and inflammatory conditions, and its role in disease pathogenesis has been supported by numerous reports of TLR2 polymorphisms in humans linked to disease. Here we discuss the potential of TLR2 as a drug target in autoimmune and inflammatory disease.

Keywords TLR2 · TLR1 · TLR6 · Mal · Inflammation · Polymorphism

Abbreviations

TLR	Toll-like receptor
PAMP	Pathogen associated molecular pattern
DAMP	Danger associated molecular pattern
LRR	Leucine rich repeat
TIR	Toll-IL-1 receptor
MyD88	Myeloid differentiation factor 88
Mal	MyD88 adapter like
Trif	TIR related adapter protein inducing IFNβ
TRAM	Trif related adapter molecule
LPS	Lipopolysaccharide
IBD	Inflammatory bowel disease
RA	Rheumatoid arthritis
OA	Osteoarthritis
T1D	Type I diabetes
UC	Ulcerative colitis
CD	Crohn's disease
SNP	Single nuclear polymorphism

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Introduction

Activation of the innate immune system initiates the host defence response to invading pathogens. Toll like receptors (TLRs) are an important class of receptors in innate immunity [1]. They recognize and bind a range of microbial products [sometimes termed pathogen associated molecular patterns (PAMPs)] derived from viruses, bacteria, fungi and protozoa, as well as endogenous "danger" associated molecular patterns (DAMPs) resulting from tissue injury. The TLRs belong to the IL-1R/TLR receptor super family, and are type I integral membrane glycoproteins comprising an extracellular domain made up from multiple leucine-rich repeats (LRR), a transmembrane domain, and an intracellular signalling domain carrying the defining motif of the IL-1R/TLR superfamily, namely the Toll-IL-1 Receptor (TIR) domain [2, 3]. This domain is a key signalling region of all the TLRs and of IL-1RI, but is also shared by the intracellular signalling adapters Myeloid differentiation factor 88 (MyD88), MyD88 adapter like (Mal), TIR related adapter protein inducing IFN-β (TRIF),

and Trif related adapter molecule (TRAM) [4–7]. Different TLRs recognize different PAMPs. The best characterized is TLR4, which recognizes lipopolysaccharide (LPS) from Gram negative bacteria, a key causative agent of septic shock. TLR3, TLR7, and TLR8 are important anti-viral TLRs, recognizing viral double stranded RNA in the case of TLR3, and single stranded RNA in the case of TLR7 and TLR8. TLR9 recognizes CpG motifs in DNA, which are common in bacterial and viral DNA, whilst TLR5 recognizes bacterial flagellin [1].

TLR2 recognizes various microbial cell wall constituents such as bacterial lipopeptides and lipoteichoic acid, and can either form a homodimer with another TLR2 molecule, or form a heteromeric interaction with TLR1 or TLR6. Triacylated lipopeptides are recognized by TLR2/TLR1 heteromers, and TLR2/TLR6 heteromers recognize diacylated lipopeptides. However, there are diacylated lipopeptides such as Pam_2CSK_4, which signal in a TLR6 independent manner, and it has been proposed that TLR2 when recognizing Pam_2CSK_4 forms a TLR2/TLR2 homodimer [8, 9]. Remarkable molecular detail on ligand recognition by TLR2 has recently emerged from the crystal structure of the TLR1–TLR2 heterodimer. The binding of the triacylated Pam_3CSK_4 induces an "m" shaped heterodimer of TLR1 and TLR2, mediated by the three lipid chains of Pam_3CSK_4, which in turn is further stabilized by numerous hydrogen-bonds and hydrophobic interactions [10]. All of these events, initiated by ligand binding, bring the intracellular TIR domains into closer proximity, and this dimerization of the TIR domains on the intracellular surface of the membrane creates a scaffold which recruits ligand specific signalling components and adapters [11]. Mutagenesis studies have pin-pointed specific amino acids which are critical for a functional TLR2 TIR domain in TLR1/TLR2 signalling. Arg-748, Phe-749, Leu-752 and Arg-753 within the DD loop and part of the αD region of TLR2 TIR are the four amino acids of key importance for signalling [12].

TLR2 (like all TLRs apart from TLR3) signals through Myeloid differentiation factor-88 (MyD88), which was the first adapter described, and another adapter, MyD88-adapter like (Mal) which, working in conjunction with MyD88, gives rise to a complex series of signalling events, ultimately resulting in an increased expression of pro-inflammatory cytokines, chemokines, and effector molecules [4]. TLR3 uses its own adapter Trif, and similarly to TLR2, TLR4 recruits Mal and MyD88, however, TLR4 can also signal via Trif, but requires another adapter TRAM, to recruit Trif [6, 7].

Of all the TLRs, much attention has been paid to TLR2 in terms of disease pathogenesis. In particular, a role for TLR2 in such diseases as rheumatoid arthritis (RA), type I diabetes (T1D), inflammatory bowel disease (IBD), psoriasis, ischemia/reperfusion injury, and atherosclerosis has been indicated (Table 1). Here we summarize the evidence for each and discuss TLR2 and TLR2 signalling as a potential target for drug development.

TLR2 and arthritis

Arthritis is an enormous national and international health problem, affecting nearly 750,000 men, women and children in Ireland alone. Of the 100 types of arthritis described, including osteoarthritis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis and gout, rheumatoid arthritis (RA) is one of the most common and debilitating of them all. The primary symptoms of this systemic disease consist of chronic inflammation, synovial hyperplasia, and destruction of cartilage and bone of numerous joints, and the trigger as well as disease progression is the focus of much research. Activation of synovial fibroblasts has been shown to be a key feature in the disease process, and a role for TLR2 in this activation process has been demonstrated [13]. Also, TLR2 mediates both apoptotic and anti-apoptotic effects, and since a dysregulated apoptotic signalling pathway has been proposed to play a role in the hyperplasia of RA synovium, this may further point to a role for TLR2 in RA. Synovial fibroblasts derived from RA patients exhibit elevated levels of TLR2 predominantly at sites of cartilage and bone destruction, which directly points to an involvement of TLR2 in RA. Synovial cells can be activated by the pro-inflammatory cytokines IL-1β and TNFα, but also by the TLR2 ligand synthetic bacterial lipopeptide (sBLP). These stimuli also result in an increased expression of TLR2 in the synovium [13]. Activating TLR2 in synovial fibroblasts using bacterial peptidoglycan results in an increased expression of integrins, matrix metalloproteinases (MMPs), proinflammatory cytokines, and chemokines [14, 15], and MyD88 deficient mice do not develop a streptococcal cell wall (SCW)-induced arthritis and exhibit a significant amelioration of joint swelling and cartilage degradation [16]. Finally, the presence of a functional microsatellite intronic polymorphism consisting of guanine–thymine repeats in intron II of the human TLR2 gene was reported, and this variant was shown to confer susceptibility to RA in a Korean population [17].

Osteoarthritis (OA) is less of an inflammatory disease, caused mainly by wear of the cartilage within joints, however, articular chondrocytes derived from OA patients show an increased level of TLR2 in response to proinflammatory cytokines and TLR2 ligands are able to induce catabolic responses in these cells. Furthermore, OA lesional cartilage expresses abundant levels of TLR2 compared to non-OA and non-lesional cartilage suggesting a role for TLR2 in OA [18].

Table 1 Evidence for a role for TLR2 in autoimmune and inflammatory diseases

	Disease	Evidence	Polymorphism
TLR2	Arthritis	Increased expression of TLR2 RA simulated by TLR2 ligand	Guanine–Thymine repeats of Intron II
	Type I diabetes	TLR2−/− mice reduced onset of diabetes	
	IBD	Increased expression of TLR2	P631H, R753G, *−196 to 174del*
	Psoriasis	Increased expression of TLR2 TLR-2 neutralizing antibody	
	Ischemia/ reperfusion injury	TLR2−/− protected against ischemia TLR2 antisense protective against ischemia DAMP recognition by TLR2	
	Atherosclerosis	Increased expression of TLR2 TLR2 ligand increased disease burden TLR2−/− reduced disease progression	R753G
	Asthma and allergy		T16934A
TLR6	IBD		S249P
TLR1	IBD		S602I, R80T
Mal	RA	Dominant negative Mal anti-inflammatory in human model of RA	

One of the less common types of arthritis occurs in patients who will or already have developed the skin condition psoriasis (see below), and is hence called psoriatic arthritis. Among 14 people with psoriasis 1 will go on to develop psoriatic arthritis, and as with other types of arthritis, the trigger for the disease is not yet clearly identified, although genetic predisposition appears to be of importance. Evidence for a role for TLRs in psoriatic arthritis is only just starting to emerge. A recent study demonstrates an increased expression of TLR2, but not TLR4, in immature dendritic cells from patients with psoriatic arthritis, providing support for a role for TLR2 and the innate immune system in the pathogenesis of the disease [19].

TLR2 and autoimmune diabetes

Type 1 diabetes (T1D) is an autoimmune disorder resulting from the specific destruction of pancreatic β-cells producing insulin, which may be initiated by an initial increase of physiological β-cell apoptosis, which in turn triggers an anti-islet immune response [20]. Interestingly, a recent study reported that apoptotic cells undergoing secondary necrosis, but not intact apoptotic cells provoked substantial immune responses and that this was mediated through TLR2. TLR2 deficient, but not TLR4 deficient mice, exhibited a marked decline in development of autoimmune diabetes, indicating that TLR2 is central in the onset of this disease. Furthermore, priming of diabetogenic T cells by apoptotic β-cell injury occurred in a TLR2 dependent manner. It was proposed that TLR2 senses β-cell death as an initial event for the stimulation of antigen presenting cells and the development of autoimmune diabetes [21]. Conflicting data, however, demonstrate that a limited degree of β-cell apoptosis can decrease the incident of T1D in non-obese mice [21]. This tolerance phenomena may be dependent on a number of factors including degree of apoptosis, timing of cell death in relation to autoimmune response, and balance of regulatory T cells versus effector T cells [22] where timing and degree of TLR2 engagement may be crucial.

TLR2 and inflammatory bowel disease

The IBDs, ulcerative colitis (UC) and Crohn's disease (CD) are similar but distinct diseases of the gut, characterized by diarrhoea and abdominal pain. Although the exact mechanism of the onset of disease remains unclear, the present model points to a key role for a dysfunctional innate immune response against microbial factors in the gut, in a genetically susceptible host. The intracellular PRR for bacterial peptidoglycan-derived muramyl dipeptide (MDP) nucleotide oligomerization domain 2 (NOD2) was the first susceptibility gene identified for CD.

TLR1, TLR3, TLR4, TLR6 and TLR9 have been implicated in IBD [23–25], and a recent study also points to a role for TLR2 and TLR4 in CD, where variants in these TLRs reduce the titre of IBD marker antibodies [anti-chitobioside (ACCA) antibodies, and outer membrane porin (Omp) of bacteria antibodies] [26]. Antibodies, such as these against self- and microbial epitopes, have long been reported in patients with IBD, and reflect a loss of tolerance

to intestinal bacteria, which causes an elevated adaptive immune response. Henckaerts et al. [26] examined the effect of naturally occurring TLR2 mutants and suggested a correlation of the TLR2 P631H variant with a decrease in Omp antibody prevalence, with a lower median Omp titre (14.5 vs. 16.7 EU, $p = 0.012$). Although this polymorphism points to a role for TLR2 in IBD, further studies are required to exactly identify the mechanism for this TLR2 variant resulting in decreased seroreactivity to microbial antibodies in Crohn's patients.

Pierik et al. [24] also investigated TLR2 polymorphism in the disease extension of IBD. TLR2 R753G polymorphism, although not directly affecting the susceptibility to the disease, affected the disease phenotype, as demonstrated by a clear association with pancolitis in UC. Furthermore, this study also reported on a negative association between two other SNPs; TLR6 S249P and TLR1 S602I and UC, providing more evidence for the role of TLR2 in IBD. Further support of this comes from a −196 to 174 deletion mutant of TLR2 which has been linked to an increased risk of severe steroid dependent ulcerative colitis, which clinically confirms the role of TLR2 in IBD [27].

Finally, Canto et al. [28], who, apart from demonstrating a significant upregulation of TLR2 in monocytes derived from IBD patients, also showed that this increased TLR2 level correlates with an elevated TNFα production in response to the TLR2 ligands lipoteichoic acid and Zymosan.

TLR2 and psoriasis

The exact role of the innate immune response in the chronic inflammatory skin disease, psoriasis, remains to be determined, nor is it fully clear whether psoriasis arises as a systemic disease (since patients with psoriasis are predisposed to developing psoriatic arthritis) or if it originates from a specific molecular defect within the skin. However, the current model includes both genetic and environmental factors as triggers for the disease. The central role of a Th1-type cytokine network in chronic psoriatic plaques is now well established and is known to be mediated through the transcription factor NFκB. Several studies have demonstrated a differential expression of TLR2, and other TLRs in pre-psoriatic skin versus psoriatic plaques [29–31]. The lipophilic yeast *Malassezia furfur* has been implicated in the triggering of scalp lesions in psoriasis, and one recent study demonstrated an increase in TLR2 expression in keratinocytes infected with *M. furfur*. Furthermore, an anti-TLR2 neutralizing antibody inhibited *M. furfur* induced increase in IL-8 and human β-defensin 2 expression supporting the proposed role for TLR2 in skin immunity [32].

TLR2 in ischemic/reperfusion injury

Several studies have demonstrated a role for TLR2 in ischemic/reperfusion renal injury. Since ischemic tissue releases DAMPs, it is no surprise that TLRs (TLR2 in particular), appear to be central in conveying the inflammatory response involved. In a study using TLR2 deficient mice, TLR2 antisense oligonucleotides, and chimeric mice, Leemans et al. [33] demonstrated that tubular epithelial cells needed TLR2 in order to induce significant cytokine and chemokines in an in vitro model of renal ischemia. In addition, TLR2 knock out mice failed to produce cytokines and chemokines, and exhibited a reduced level of renal injury and dysfunction after ischemic/reperfusion injury, suggesting a protective effect of a disrupted TLR2 signalling response. A TLR2 antisense oligonucleotide also had a protective effect on renal dysfunction, neutrophil influx, and tubular apoptosis after ischemic injury, pointing to a central role for TLR2 in the inflammatory responses leading to renal injury. TLR2 is expressed in numerous cell types within the kidney, including the renal tubulis of the outer strip of the medulla, glomeruli, and in the renal vasculature, and this expression pattern is similar in humans and in mice [34]. Since mice deficient in TLR2 are better protected from ischemic injury than MyD88 knock out mice, the question is raised if TLR2 is also able to signal in a MyD88 independent manner [34].

TLR2 also plays a role in ischemia/reperfusion of the heart, especially contributing to endothelial dysfunction after ischemia/reperfusion [35]. This was demonstrated using TLR2 deficient mice which were completely protected against ischemia induced endothelial dysfunction, with reduced infarct size, production of reactive oxygen species and leukocyte infiltration.

What might the TLR2 ligands be in ischemia/reperfusion injury? Apart from recognizing and triggering an immune response to invading pathogens, another unique role of the TLRs is to sense tissue damage by responding to DAMP released from damaged tissues or necrotic cells. Biglycan is a small leucine-rich proteoglycan, which arises as a degradation product of the extracellular matrix, caused by the activation of proteases through injury or inflammation. Biglycan is an endogenous ligand of TLR2 and TLR4, leading to rapid activation of p38 mitogen activated protein kinase (MAPK), p42/p44 MAPK and NFκB, and furthermore, biglycan signalling is significantly impaired in TLR2−/− macrophages. Another degradation product, this time derived from hyaluronan of the extracellular matrix, when occurring in low molecular species after tissue injury or inflammation, has also been shown to signal in a TLR2 dependent manner, and TLR2 has been proposed to have a central role in promoting

recovery from lung injury [36]. The list of proposed endogenous ligands to TLR2 goes on to include, for example: Hsp60, Hsp70, gp96, HMGB1, and minimally modified LDL (reviewed in [37]). If these factors all prove to be acting via TLR2, it is possible that specific co-receptors will exist for each of them.

TLR2 and atherosclerosis

Atherosclerosis is a systemic disease affecting arterial blood vessels. It is a chronic inflammatory response in the walls of arteries, in large part due to the deposition of lipoproteins (cholesterol and triglycerides). The inflammatory response is central in mediating all stages of the disease, including initiation, progression and later thrombotic complications [38]. Growing evidence points to a critical role for TLR2 in atherosclerosis. TLR2 expression in endothelial cells from atherosclerotic lesions is greatly upregulated compared to endothelial cells of normal arteries. Furthermore, TLR2 co-localized with the p65 subunit of NFκB [39]. Intraperitoneal administration of the TLR2/TLR1 ligand Pam_3CSK_4 increased the disease burden in atherosclerosis-prone low-density-lipoprotein-receptor-deficient (*Ldlr−/−*) mice and TLR2 deficient *Ldlr−/−* mice exhibited a marked reduction in Pam_3CSK_4 induced atherosclerosis and plaque formation [40]. Mice deficient in apolipoprotein E (*Apoe−/−*) are also prone to atherosclerosis; however, *Apoe−/−* mice deficient in TLR2 exhibit a significantly reduced level of circulating monocyte chemoattractant protein-1 (MCP-1). Increased serum levels of MCP-1 have been observed in patients with coronary artery atherosclerosis, and have been suggested to play a critical role in atherosclerosis. Hence the reduced levels of MCP-1 in TLR2 deficient mice reflects a reduced progression of atherosclerosis [41]. In addition, this study demonstrated that the role of TLR2 in atherosclerosis is independent of dietary lipids and macrophage LDL uptake. Furthermore, TLR2 plays a role in atherosclerotic lesion development, as atherosclerotic plaques and circulating monocytes exhibit significantly increased expression levels of TLR2 in atherosclerotic *Apoe−/−* mice compared to cells from non-diseased mice [42].

The role for TLR2 in atherosclerosis is further verified by evidence of a link between TLR2 polymorphism and the disease. One recent report suggests that TLR2 Arg753Gln may be associated with arthrosclerosis [43], however, this has recently been disputed as no link was found between TLR2 Arg753Gln and Carotid artery intima–media thickness [44]. Further studies are needed to clearly define the role for functioning TLR2 signalling in atherosclerosis.

TLR2 and asthma and allergy

Asthma and allergies are complex diseases with a strong link to genetic predisposition. The increase in the prevalence of asthma and allergies over the last few decades, however, also suggests a role for environmental factors in triggering the disease. In support of this, children and adults raised on animal farms have been consistently shown to have lower prevalence of asthma, hay fever, and IgE mediated reactivity to local allergens than those living away from farms [45–47], and this has been put down to a high level of exposure to microbial agents such as endotoxins. There is strong evidence for the role of TLR2 polymorphisms in the pathogenesis of asthma, allergic rhinitis, and atopic sensitization. Studying children living in rural areas of Germany and Austria, those carrying a T allele in *TLR2/−16934* (Thr16934Ala) compared with children of the AA genotype were significantly less likely to be diagnosed with asthma, have less symptoms of asthma, less atopic sensitization and lower current hay fever symptoms [48]. This suggests that this genetic variation in TLR2 is a major determinant of susceptibility to asthma and allergies.

TLR1, TLR6 and Mal

As TLR2 signalling requires heterotypic interactions with TLR1 or TLR6, evidence for a role for TLR1 or TLR6 in disease indirectly supports a role for TLR2.

TLR6 S249P was identified as 1 of 22 different SNPs which all occurred with an allele frequency of >5% in a limited cohort study of 24 African Americans, 23 European Americans, and 24 Hispanic Americans [49]. In an exploratory nested case–control disease associated study, the TLR6 S249P was shown to be associated with a decreased risk for asthma, supporting the role of TLR2 in this disease. This finding was subsequently verified in a study where TLR6 S249P was shown to be associated with childhood asthma [50].

Furthermore, polymorphisms of TLR1 and TLR6 have been linked to the disease phenotype of IBD, with a positive association between TLR1 R80T and pancolitis in UC and negative associations between TLR6 S249P and UC with proctitis only [24]. Also, a negative association has been identified between TLR1 S602I and ileal disease in CD, which supports previous data implicating TLR2 in IBD [24].

Analysis of genetic variations in Mal—a key adaptor for TLR2—also supports a role for TLR2 in certain diseases, specifically; Mal polymorphisms have been linked to infectious diseases. The S180L variant has been shown to protect against malaria, tuberculosis, bacteraemia and

pneumococcal pneumonia [51]. The C558T variant of Mal also conveys an increased susceptibility to tuberculosis [52]. Targeting Mal could therefore provide a potential means of attenuating the effects of TLR2 in these diseases. In addition, it has been shown that a dominant negative version of Mal attenuates the spontaneous production of TNF and other inflammatory mediators in a human model of RA. This further supports a role for TLR2 in RA pathogenisis [53].

How might TLR2 be targeted therapeutically?

Central to any drug designed to target TLR2, either as an agonist, or antagonist, is specificity, because all members of the TLR family share a high degree of sequence similarity, and also activate, to a large extent, the same signalling pathways. Structurally, the domain of the TLRs which might be most successfully exploited as a drug target is the LRR ectodomain, which carries the ligand recognition specificity unique to each TLR. In addition, the assembly of distinctive heteromeric receptor complexes may reflect downstream signalling specificity. This remains to be fully mapped and might then provide specific targets unique to a given TLR receptor, minimizing unwanted side effects due to cross reactivity.

Soluble decoy receptors are a naturally occurring means of negatively regulating effects of cytokines and chemokines. A soluble form of human TLR2 has been identified which potentially provides a direct therapy targeted to attenuating the effects of the receptor both in infectious disease such as sepsis and also in chronic autoimmune diseases. LeBouder et al. [54] reported that monocytes constitutively secrete soluble TLR2 (sTLR2), with levels of sTLR2 being further enhanced upon cell activation. Six different types of sTLR2 polypeptides were detected. These are a result of posttranslational modification of TLR2 and were also found as a natural component of plasma and breast milk. Depleting serum of sTLR2 resulted in an exaggerated response of plasma cells to bacterial lipopeptides. Of further interest was the observation that serum taken from tuberculosis patients exhibited a lower titre of sTLR2 [54].

One example of a drug, which targets the regulation of the innate immune system is chaperonin 10, also known as heat shock protein 10 or Xtoll^{TM}. This protein has both anti-inflammatory properties and immunomodulatory properties, targeting TLR2 [55] and TLR4 and inhibiting LPS signalling, and has been shown to be able to reduce both signs and symptoms of RA in a limited human trial with low relative toxicity [56].

Another approach to limit TLR2 signalling would be to block TLR2 (or TLR1 or TLR6) with a neutralizing antibody. As mentioned above, an anti-TLR2 neutralizing antibody was successfully used to inhibit the effects of *M. furfur* in a model of psoriasis. Furthermore, a TLR2-neutralizing antibody has been developed which demonstrates great therapeutic potential for the treatment of sepsis in a murine model. Mice treated with the antibody were protected from a lethal challenge with *Bacillus subtilis* [57]. An antibody like this could potentially be developed into a tool for inhibiting inflammatory effects of an over-active TLR2 (or TLR1/6) response in human disease.

Poor immunogenicity of tumor-associated carbohydrates and glycopeptides and lack of associated high titers of IgG antibodies has been a major hurdle in cancer vaccine development. However, whilst assessing a range of fully synthetic vaccine candidates, a three-component vaccine composed of a TLR2 agonist, together with a peptide T-helper epitope and a tumor-associated glycopeptide was found to elicit exceptionally high titers of IgG antibodies in mice. This promising result may reflect another strategy to influence the efficacy and potency of vaccines developed to target TLR2 signalling [58, 59].

Finally, reducing the expression levels of TLR2 in diseases known to give rise to exaggerated TLR2 levels might provide a means to dampen down the inflammatory effects resulted by TLR2. One possible way of doing this is using TLR2 (or TLR1/6) antisense oligonucleotides, as found protective against renal ischemic injury, which would limit inflammation and disease progression by reducing TLR2 expression [34].

Concluding remarks

In summary, we have described here some of the extensive evidence in the literature pointing to a role for TLR2 in a wide range of autoimmune and inflammatory diseases, caused either by a defect in TLR2 signalling or due to an overactive TLR2 response. TLR signalling in general is a tightly controlled event, with a range of negative regulatory events already described. One significant challenge in drug development involves specificity and great effort is currently underway, mapping differences in the regulation of signalling responses to distinct TLRs. If TLR2 proves to be a critical TLR for specific pathologies, and if specific inhibition of TLR2 can be developed, we can anticipate a novel therapeutic approach to test for a range of diseases, where there is currently an unmet medical need.

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