

Therapeutic Use of Molecules that Mimic Pathogen Danger Signals

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Abstract: Major advances in our understanding of how the mammalian immune system recognises pathogens have evolved from initial observations of fruit-fly developmental mutants. Through this work it has been established that vertebrates possess a specialised 'early warning system' in the form of a panel of detectors to rapidly sense and trigger responses to the presence of microbial invaders through detection of so called pathogen-associated molecular patterns (PAMPs). This discovery has led to the search for new agonists and antagonists that can be used, therapeutically, for rational manipulation of the immune response. These efforts have already yielded several exciting new strategies to treat autoimmune, atopic, malignant and infectious disease. This review article provides an overview of the potential impact of these drugs on human medicine.

INTRODUCTION

Pathogen Associated Molecular Patterns and Host Recognition

Pathogen associated molecular patterns (PAMPs) are a diverse range of molecular structures that are conserved in many microbes but are not found in vertebrate organisms [1-7]. Peptidoglycans, bacterial flagellin, bacterial LPS, bacterial DNA, double stranded RNA and some types of single stranded RNA are all classified as potential PAMPs. In addition, some materials derived from fungi and plants and endogenous molecules produced by the host following tissue damage can act like PAMPs [8-13]. PAMPs are recognized as danger signals by host pattern recognition receptors (PRRs), the best known examples of which are the Toll-like receptors (TLRs). Since identification of the first TLR protein in humans [14], at least eleven others have been identified (Table 1). Several lines of evidence suggest that TLR expression is not uniform across the different cell types involved in mediating immune responses [2, 6, 15-18] and it is apparent that TLR expression can be upregulated by a variety of stimuli [5]. Hence, different cell types participate in the host response to different TLR agonists. Furthermore, there are considerable inter-species differences with respect to the distribution and density of TLR on different cell phenotypes [2, 16, 18-24]. For example, TLR 9 has a much more restricted distribution in humans as compared with mice [25-27]. Conversely TLR 8, is expressed on a wider range of cell types in humans as compared with rodents [28-31]. Hence the magnitude and characteristics of immune responses to some TLR agonists can be quite different in humans as compared with commonly studied laboratory animals. There are further important differences with respect to the cellular location of TLR [28, 32-36]. TLRs 1, 2, 4, 5 and 6 are located on the surface of specific immunological cells; ideally located to sense the presence of PAMPs on the surface of bacterial invaders. By contrast, TLR 3, 7, 8 and 9, seem to specialize in the detection of viral PAMPs, specifically nucleic acid shapes and sequences. These TLR are

found inside specific cells, in endosomal compartments, where the protein envelope or capsid which shields viral nucleic acids can be stripped away by chemicals and enzymes. It is thought that the risk of host nucleic acids triggering potentially damaging autoimmune responses is reduced because TLR 3, 7, 8 and 9 are locked away inside endosomal compartments [30].

TLRs are not the only receptors that play a role in pathogen pattern recognition. Multi-lectin mannose receptors are expressed on macrophages and dendritic cells (DC) and can recognise carbohydrates present on a wide range of microbes [37]. Similarly, it would appear that certain glycolipids, such as α -galactosyl ceramide, can be recognised following presentation to specialised 'natural killer' T-cells in the context of CD1d [38, 39]. Other recently identified PRRs include members of CATERPILLER protein family [39]. Two of the most studied (NOD 1 and 2) are thought to be cytoplasmic sensors for components of bacterial peptidoglycans. NOD 1 binds to tripeptide structures, whereas NOD 2 recognises ligands with muramyl-dipeptidic structures [7, 39]. Consistent with the tenet that these molecules are important in inflammation and infection, polymorphisms or mutations in CATERPILLER proteins are associated with susceptibility to inflammatory disorders. Polymorphisms in NOD2 seem to predispose individuals to Crohn's disease [40]. Mutations in NOD2 are responsible for Muckle-Wells and Blau syndromes and other auto-inflammatory conditions [41, 42].

Innate Response to Pathogen Associated Molecular Patterns

Dependent on the type of cell and receptor stimulated, stimulation of a PRR with its cognate ligand may result in proinflammatory cytokine secretion, antiviral cytokine secretion, antibody secretion, cellular proliferation, cell activation or production of antimicrobial chemicals [2, 21, 23, 30, 35, 43-48]. These 'innate' responses can occur very quickly following PAMP receptor signalling and can result in rapid destruction or elimination of pathogen invaders. Signalling through the MyD88 transduction pathway ultimately leads to activation of nuclear factor- κ B (NF- κ B) and interferon regulatory factor 3 (IRF3) which lead to the production of proinflammatory cytokines and type I interferon production. In contrast to TLRs, NOD1 and NOD2 appear to signal through

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Table 1. Toll Like Receptors and Their Ligands

Toll-like Receptor	Pathogen associated molecular pattern	Source	Reference
1	Tri-acyl lipopeptides	Bacteria	[160]
2	Peptidoglycan	Bacteria	[161]
	Lipoprotein	Bacteria	[162]
	Zymosan	Yeast	[160]
	Glycoinositolphospholipids	Trypanosomes	[163]
	LPS	Bacteria	[164]
3	dsRNA	Viruses	[35]
4	LPS	Bacteria	[165]
	Fusion protein	Respiratory syncytial virus	[166]
	Pneumolysin	Bacteria	[167]
5	Flagellin	Bacteria	[168]
6	Zymosan	Yeast	[160]
	Di-acyl lipopeptides	Bacteria	[160, 169, 170]
7	ssRNA	Viruses	[29, 30]
8	ssRNA	Viruses	[29, 30]
9	CpG DNA	Bacteria, Viruses	[171, 172]
10	Unknown	Unknown	
11	Unknown	Uropathogenic bacteria	[173]

pathways that are independent of the MyD88 family; NOD proteins activate NF- κ B through a pathway that requires the kinase RICK (receptor-interacting serine / threonine kinase).

Influence of Pattern Recognition Receptor Activation on Adaptive Immune Response

Whilst critical for effective host defense, the innate response has only a limited ability to eradicate pathogens. The most effective form of immunity is achieved following activation of appropriate arms of the adaptive immune system. DC are the principal cell type responsible for surveillance of peripheral tissues for microbial invaders and are, by design, richly furnished with PRR [49]. Upon sensing PAMPS and sampling an invading pathogen, DC downregulate chemokine receptor (CCR) 5 and upregulate CCR7, facilitating DC migration to draining lymph nodes [50]. PRR signalling also functions to activate DC, resulting in an increase in their surface expression of MHC and costimulatory molecules (CD80/86) [51, 52]. DC mediated presentation of antigen-MHC complexes (signal 1) to T-cells, with concomitant costimulation (signal 2) *via* CD80/86 is a critical event in the generation of effective adaptive immune responses. Signal 1 in the absence of signal 2 rarely results in T-cell activation and can render T-cells refractive to any subsequent activation events [53]. Furthermore, it is thought that certain cytokines (particularly IL-6) produced by DCs following TLR

activation are important in reducing the activity of regulatory T-cells, which can dampen a developing immune response [54, 55].

PRR signalling also influences the characteristics of antigen specific immune responses. MyD88 deficient mice tend to develop Th2 type antigen specific responses supporting the dogma that TLR signalling directs T-cell differentiation towards a Th1 type response; characterized by the expansion of antigen specific IFN- γ secreting effector T-cells under the influence of IL-12 secreted from DC [23, 49, 56-58]. However, there is also accumulating evidence that low concentrations of some PAMPS can encourage the development of Th2 type responses. Low concentrations of certain TLR2 ligands have been shown to elicit IL-13, IL-5 and IL-10 and aggravate the symptoms of asthma [59, 60]. Similarly, recent data indicate that appropriately formulated single stranded RNA can adjuvant IgG1 isotype dominated humoral responses through TLR 7 / 8 activation [61, 62]. Whether this is related to the strength of MyD88 signalling (single stranded RNA has a very short half-life *in vivo*) or occurs independently of MyD88 is not clear. Hence, not only does PAMP receptor signalling play an important role in influencing the decision to initiate an immune response, it also influences what type of immunological response is generated. Undoubtedly this can impact on the likelihood of an infection being successfully resolved.

USING PATHOGEN ASSOCIATED MOLECULAR PATTERNS AS DRUGS AND VACCINE COMPONENTS

Several molecules based on PAMPs can now be found in licensed medicines [63] and others are being investigated clinically as constituents of novel immunotherapies and vaccines [64-66]. In their natural format, PAMPs tend to be large polymeric molecules and this can have some drawbacks in terms of their pharmacokinetic and pharmacodynamic behaviour *in vivo*. To address this, a number of new PRR agonists have been developed (Table 2). The remaining sections of this review will highlight potential uses of PAMPs and their mimetics in different areas of medicine.

Table 2. TLR Agonist Drugs

Toll-like Receptor	Agonist	Reference
3	Poly I:C	[174]
4	MPL	[151]
4	RC-529	[151]
4	Other LPS analogues	[175]
7	Imiquimod	[63]
7/8	Resiquimod	[63]
7/8	3M-012	[124]
9	CpG	[27]

'Generic' Immunoprotection Against Infectious Agents

Pathogenic viruses have the potential to cause widespread mortality and morbidity. There is growing concern about the threat from epidemics and even pandemics caused by emergent viral pathogens; for example SARS and mutated strains of the influenza virus. Although vaccines are considered to be the most effective countermeasure to these threats, it is feared that vaccines may take too long to develop, produce and distribute; particularly if a new strain has emerged. It has been known for some time that type I interferons (IFN- α and IFN- β) have potent antiviral properties; they limit viral replication and induce death of infected cells [30, 67, 68]. This raises the possibility that they could be used as antiviral drugs [69]. However, their usefulness for prolonged antiviral therapy is limited by their short half-life and potential side-effects [70]. Another approach is to stimulate the body to produce its own antiviral cytokines. Viruses often produce double stranded (ds) RNA during infection of mammalian hosts and it can act as a powerful inducer of type I interferons *via* activation of PAMP receptors [35]. dsRNA is recognised by cytosol located protein kinase R and TLR 3 which is found in endosomal compartments and possibly on the surface of myeloid dendritic cells and some epithelial and endothelial cells. As an alternative to vaccination, certain dsRNA motifs (e.g. the synthetic molecule Poly I:C), appear highly effective in providing rapid protection against a number of viral infections [71], although adverse side effects (fever, leukopenia, nausea) associated with repeated use

of Poly I:C may hinder its development into a licensed antiviral [72-74].

DNA based PAMP mimetics have also been used as immunoprotectants. It has been shown that CpG DNA oligonucleotides can confer short term non-specific immunity to a number of viral pathogens including influenza [75], papillomavirus [76], pox viruses [77] and herpes virus [78]. Through TLR 9 activation, CpG DNA triggers plasmacytoid dendritic cells to secrete type I interferons, and other cytokines, which activate macrophages to engulf and destroy pathogens more effectively. B cells express TLR 9 and are thought to contribute to CpG mediated immunoprotection by secreting polyreactive immunoglobulins [25, 27]. Importantly, in the context of some potential clinical applications, CpG appears to retain potency in individuals with abnormal immune systems: treatment with CpG improves the ability of HIV infected individuals to resist infection through upregulation of innate immunity [79]. Post-exposure therapy with TLR agonists alone is generally ineffective against rapidly progressive acute infectious agents. However, Coley have had clinical success using CpG as a 'stand-alone' therapy to treat chronic hepatitis C virus infection [80, 81].

TLR 7 and 8 are also sensors of viral PAMPs [28]. It was discovered only recently that TLR7 and TLR 8 are activated by guanosine and uridine rich single stranded RNA, commonly found in influenza and other single stranded RNA viruses [28-30, 33, 82]. Prior to that, it was known that the imidazole quinoline family of small molecules could be used to activate immune responses *via* TLR 7 and 8 [82, 83] and these were the first class of PRR agonists to be licensed for clinical use [63]. In humans, TLR 7 agonists activate plasmacytoid dendritic cells and monocytes [31]. TLR 8 agonists activate myeloid dendritic cells and monocytes. Accordingly, TLR 7 agonists are more effective than TLR 8 selective agonists at inducing IFN- α , and TLR 8 agonists are more effective than TLR 7 agonists at stimulating proinflammatory cytokines and chemokines. Topical application of imidazole quinoline based drugs generates a localized immune response that has been used to treat viral infections such as human papillomavirus, herpes simplex virus, mollusca and cancerous lesions including initial squamous cell and basal cell carcinoma in immunocompetent and even immunosuppressed patients.

It is evident that PAMP based drugs can also be used to protect against non-viral pathogens. For a short period, mice pretreated with CpG DNA are able to resist infections caused by a range of pathogenic bacteria [84-87]. CpG can also be used to protect against parasitic infections. Mice can be protected, for a period of several days, against challenge with *Plasmodium yoelii* sporozoites [88] and other parasites [89] using CpG treatment. Encouragingly, from the standpoint of human disease prevention, this protective effect is also seen in non-human primates [90].

Allergen Therapy

The increased incidence of atopic disorders, including allergen induced asthma and rhinoconjunctivitis, in industrialised countries has made development of treatment strategies a key research objective. Allergic reactions result from

the production of Th2 cytokines, such as IL-4, IL-5 and IL-13, in response to innocuous environmental stimuli. Currently, sufferers are treated using a combination of glucocorticoids and bronchodilators administered on a daily basis. Although effective, these drugs have side effects and do nothing to alter the prevailing Th2 responses in hypersensitized individuals. One approach is to redirect the immune response away from a Th2, IgE-mediated allergic hypersensitivity reaction towards a more favourable Th1 type phenotype using PAMP mimetics [91]. Encouragingly, the results of several pre-clinical studies provide evidence that this is viable: Typically, animals are first sensitized by exposure to allergen and then challenged with allergen to elicit clinical manifestations of disease. Experiments with ragweed and house-dust mite have demonstrated that allergic asthma can be treated by administration of CpG during or just after the sensitization phase [92, 93]. Others have shown that resiquimod or the TLR 4 agonist λ -carrageen can be used to inhibit allergen induced Th2 responses [94]. Route of administration appears to be an important factor; consistent with immunological dogma relating to the compartmentalised nature of the immune system, CpG oligo's induce airway allergen tolerance in Th2 sensitised mice more efficiently when delivered directly into the respiratory tract [95].

Immunotherapy can also be achieved with non-TLR based PRR agonists: Chitin is a polymer of N-acetyl-D-glucosamine, which occurs abundantly in nature. It is found in crustaceans, insects, fungi and some microorganisms. Chitosan (poly[β -(1-4)-2-amino-2-deoxy-d-glucopyranose]) is a cationic polysaccharide derived by deacetylation of chitin. It is hydrophilic, biocompatible and biodegradable and can readily be formulated into microparticles and is already approved for use in biomedical implants [96]. Cellular uptake of chitin particles in the 1-10 μ m size bracket occurs *via* mannose receptor mediated phagocytosis [97]. Following take up of chitin microparticles, macrophages become activated (produce nitric oxide) and secrete IL-12, IFN- γ and TNF- α [98]. Using a ragweed-allergic mouse model of airway inflammation, Shibata *et al.* [99] studied the effects of chitin as a substance on the allergic response. IgE production was significantly reduced in ragweed allergic mice following oral administration of empty chitin microparticles. Prophylactic and therapeutic treatment of allergic animals with chitin particles also substantially reduced lung eosinophilia. These data suggest that chitin and its derivatives represent an alternative to the use of TLR agonists for allergen therapy [100]. In light of side effects that can occur following repeated use of the most potent TLR agonists [101] chitin might have some advantages from a safety standpoint.

Vaccines

We are now in an era of 'rational vaccine design' whereby biotechnological advancements have made it possible to create vaccines that contain only the requisite components for protective immunity [102, 103]. By definition, subunit vaccines usually lack the PAMPS present in attenuated and chemically or thermally inactivated vaccines. Without appropriate adjuvantization they are usually weak immunogens. The most commonly found adjuvants in licensed vaccines are the aluminium based compounds commonly referred to as 'Alum'. However, Alum has many shortcomings as an

immune response enhancer; it tends to elicit markedly Th2 biased responses with poor cellular immunity [104-107]. In recent years, several promising alternatives to Alum have emerged, many based on rationally selected PRR agonists: Monophosphoryl lipid A (MPL) is a chemically modified derivative of the lipid A moiety of LPS [108-110] which lacks the toxicity of LPS but retains the ability to activate TLR4. Recently, a Hepatitis vaccine containing MPL has been licensed for human use. CpG is another PAMP based immunostimulant that is being clinically tested as a new vaccine adjuvant [65, 111].

Therapeutic Vaccination

The term 'vaccination' no longer only applies narrowly to disease prophylaxis; considerable resources are being invested into the research and development of 'therapeutic' vaccines to treat cancer and other chronic diseases [103]. Cytotoxic T lymphocyte (CTL) responses play a critical role in fighting chronic intracellular infections [112-114]. Many of these new immunological 'treatments' will need to contain adjuvants which promote CTL. The induction of this type of immunity generally requires antigen access to the cell cytosol so that it can be presented with class I molecules [114]. Recent work has elucidated that 'cross presentation' of endogenously acquired proteins by dendritic cells to CD8 T cells is more effective in the presence of type I interferons [67, 114-118] (Fig. 1). As TLR 3, 7/8 and 9 agonists are known to induce type I interferon production by dendritic cells and thereby encourage cross presentation of endogenously acquired proteins, codelivery of antigen and TLR agonist using a suitable cytosolic delivery system, to facilitate antigen entry into the class I processing pathway, may be the optimal configuration for induction of potent CTL. Recent publications describe formulations, whereby antigen and PAMP are incorporated into particulate delivery vehicles capable of stimulating vigorous CTL responses *in vivo* [119-122]. Alternatively, antigens can be chemically linked to PAMPS, and it has been shown that chemical linkage of antigen to CpG is far more effective than simple admixture [123]. Researchers also highlight the potency of TLR 7/8 agonists conjugated to HIV gag protein for induction of Th1 and CD8 T cell responses [124]. In some cases the CTL response can be comparable in magnitude to the CTL response engendered by live vaccines.

Mounting evidence indicates that immunotherapy can be a beneficial adjunct to surgery, radiotherapy or chemotherapy for treatment of cancer patients [125]. In fact this finding can be traced back to over 100 years ago when William Coley first demonstrated that injection of heat-killed bacteria can lead to tumour regression [126]. The observation that bacterial extracts can have anti-tumour activity can now be explained, at least in part, by PAMP mediated activation of innate immunological responses. In recent years, synthetic PAMP mimetics have been tested as 'stand-alone' immunotherapeutic agents against lymphoma, neuroblastoma, melanoma, glioma, fibrosarcoma, basal-cell carcinoma and lung cancer [81, 127-139]. Therapeutic vaccination against tumors must overcome peripheral tolerance to tumor associated antigens. Because TLR agonists dampen the activity of CD4⁺ CD25⁺ regulatory T-cells, *via* induction of IL-6 production, they can be used to reverse immune tolerance to

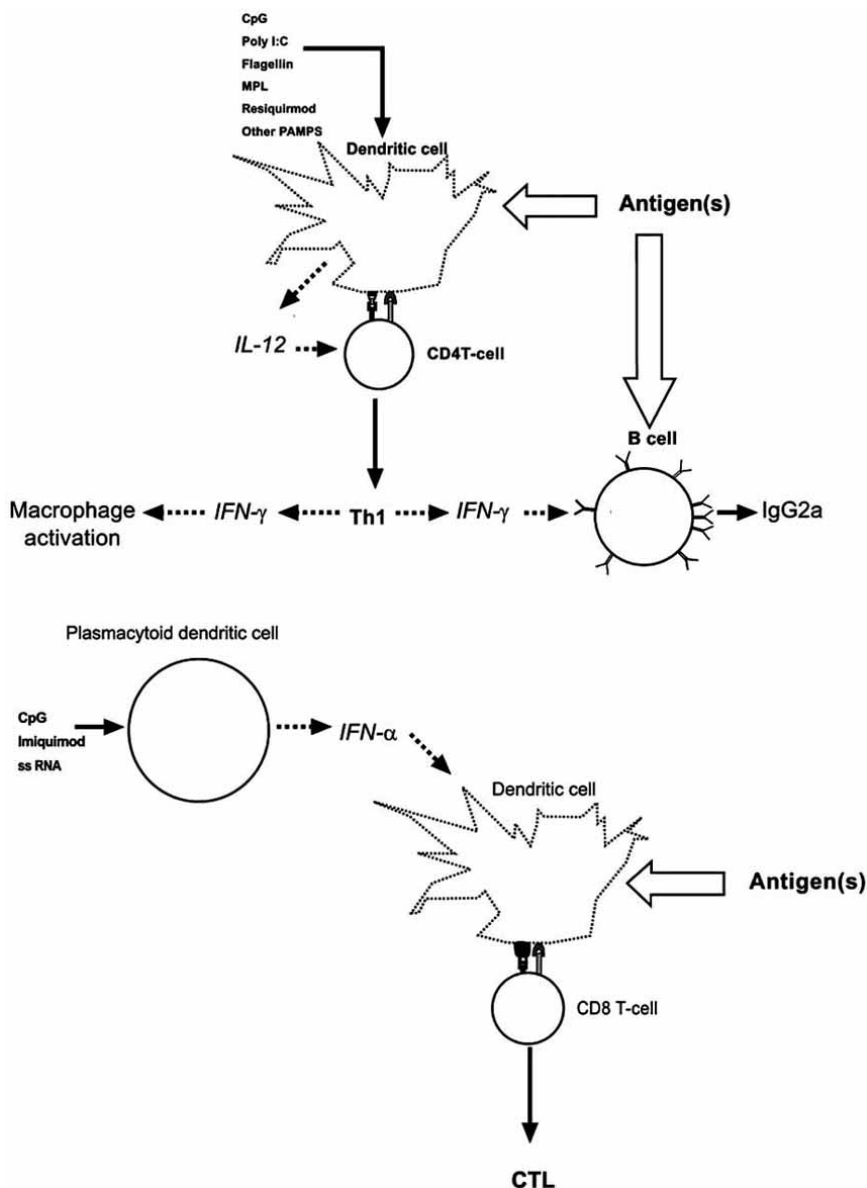


Fig. (1). Schematic representation of mechanism by which PAMPs and their mimetics can influence the development of adaptive immunological responses to vaccine antigens. PAMPs and their mimetics stimulate myeloid dendritic cells to secrete IL-12 which promotes the development of Th1 orientated antigen specific CD4 responses. In mice, a Th1 response will encourage B-cells to develop into plasma cells that secrete IgG2a isotype antibodies. Activation of plasmacytoid dendritic cells by TLR7 and 9 ligands causes IFN- α secretion, which is known to be important for dendritic cell licensing of CD8 responses.

tumor associated antigenic targets [55] (Fig. 2). In addition to inducing IL-6 production, stimulation of TLR 8 on CD4⁺ CD25⁺ regulatory T-cells was recently shown to directly reverse the immunosuppressive function of these cells [140]. Such findings further support the proposition that TLR agonists have utility as components of therapeutic cancer vaccines. A related approach involves the use of PAMP mimetics during *ex-vivo* conditioning of tumour antigen stimulated dendritic cells, which are subsequently injected back into the patient [141, 142]. There are also reports that PAMP mimetics can be used to enhance immunotoxin therapy of chronic lymphocytic leukaemia [143].

SIDE EFFECTS

Although PAMPs and their mimetics have many potential novel applications in human and animal medicine, it is perhaps not entirely surprising that such powerful immunostimulants may also cause undesirable side effects.

It has been known for many years that lipopolysaccharides (LPS) can cause toxic shock by triggering the overproduction of tumour necrosis factor (TNF) from macrophages and dendritic cells. Autoimmunity is another concern with respect to PRR stimulation. Despite a generally good safety profile in non-human primate studies and early phase clinical

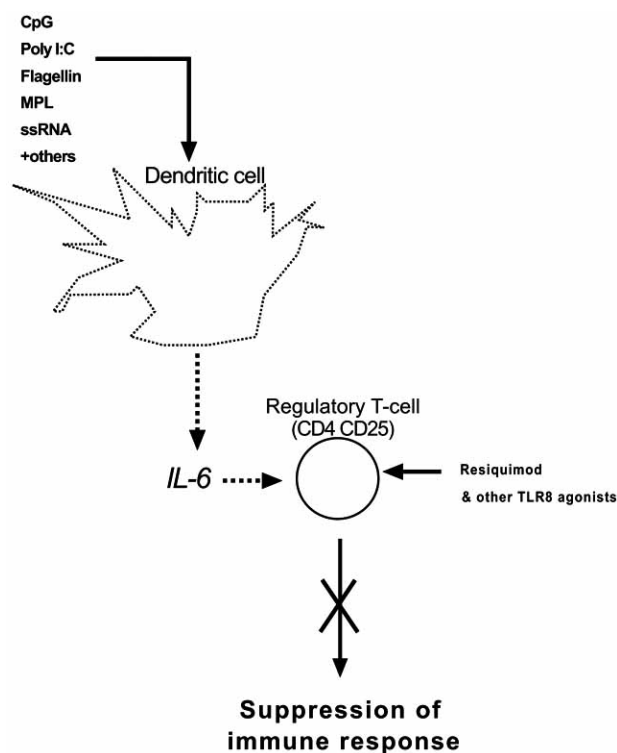


Fig. (2). TLR agonists dampen the activity of CD4 CD25 regulatory T-cells, *via* induction of IL-6 production. Additionally, stimulation of TLR 8 on CD4 CD25 regulatory T-cells was recently shown to directly reverse the immunosuppressive function of these cells.

trials [64, 144, 145], CpG's ability to polyclonally activate B-cells, block lymphocyte apoptosis and stimulate IL-6 production has given rise to concern that it could facilitate induction of dangerous autoimmune responses [146-149] (Table 3). Indeed, animals given daily injections of high doses of CpG can develop abnormalities in the structure and function of their lymphoid organs [101]. Another concern is the potential teratogenic effects of immune response modifiers. Recent studies suggest that high doses of CpG given to pregnant mice can result in markedly increased fetal resorptions and craniofacial limb defects, although lower doses had no such effects [150].

Table 3. Some Reported Side Effects of CpG

Side effect	Cause	Reference
Teratogenesis	Th1 Inflammation	[150]
Splenomegaly	B-cell activation	[101]
Liver / kidney damage	Mononuclear cell-infiltration	[176]
Lupus	IL-6 production	[177]
Multiple sclerosis	activation via CD40	[178]
arthritis	Th1 Inflammation	[179]

One method to reduce the severity of side effects would be to identify new agonists with reduced side-effects. Natu-

ral and synthetic LPS derivatives and synthetic TLR4 agonists have been developed for use as TLR 4 stimuli [151]. Indeed, because recognition of LPS by TLR 4 plays a central role in the development of sepsis during acute bacterial infections, analogues of lipid A are able to act as effective LPS antagonists [152]. Endotoxic shock inhibiting suppressive CpG motifs have also been reported [153].

Splenomegaly is a major side effect when rodents are repeatedly treated with CpGs, especially CpGs which have DNase-resistant phosphorothioate backbones [101]. Recent studies have shown that, unlike high doses of CpG, single stranded RNA based adjuvants do not cause splenomegaly [61]. Researchers have also attempted to reduce the severity of these side effects by more effective targeting of PAMPs to their cognate PRR. Wong *et al.* [71] evaluated the toxicity profiles of free and liposome encapsulated Poly I:C *in vivo*. They found that, as compared with mice treated with equivalent doses of free poly I:C, hypothermia and body weight loss was either completely mitigated or substantially reduced in animals treated with liposomal poly I:C. Storni *et al.* [121] described how CpG toxicity could be significantly reduced by use of virus like particles with no concomitant loss of potency, in-fact quite the reverse. They showed that spleens from mice immunized 12 days earlier with hepatitis core antigen admixed with free CpG weighed significantly more than spleens from animals immunized with hepatitis core antigen and CpG packaged in virus like particles (which had spleen weights the same as un-treated mice). Histological analysis indicated that animals immunized with hepatitis core antigen and naked CpG had abnormalities in their splenic white and red pulp, whereas this was not seen in mice treated with particle packaged CpG. The authors suggested that packaging of CpG into virus like particles reduces side effects by several mechanisms: (1) Particulated CpGs are much more potent, because they are more effectively targeted to endosomal compartments, so can be used at much lower doses. (2) Particles are preferentially taken up by dendritic cells and other phagocytes, so particle packaged CpGs are largely targeted to TLR9 in dendritic cells not B-cells. (3) Because CpGs are protected from nuclease degradation when packaged into virus like particles, unmodified oligonucleotides may be used, which have a more favourable toxicity profile than chemically stabilized CpGs.

CONCLUDING REMARKS

Recent advances in our understanding of pathogen recognition by the immune system have facilitated development of several novel immune-modulators. In animal models it has been shown that these molecules can be used to prevent or treat a wide range of infectious diseases, atopic diseases and even cancer. It is apparent that PRR activation may cause immune dysfunction and clearly this has implications for the safety of new drugs based on PRR agonists [154]. Emerging experimental evidence suggests that more effective targeting of PRR agonists is one method to reduce undesirable side effects [121]. Learning how to block aberrant immune activation *via* PRR stimulation, should also give rise to new opportunities for treatment of bacterial sepsis [152, 153], some viral infections [155] and several of the autoimmune disorders [13, 156-158]. Similarly in some instances, PRR themselves could be used for drug targeting purposes;

as recently shown to be the case with certain tumours [159]. In comparison to the wealth of animal data, there is a comparative paucity of published information available concerning the effectiveness of PRR stimulation in humans. However, this is improving and at least two classes of PRR agonists can already be found in licensed human medicines and vaccines and several others are being tested in clinical trials. All available indication is that other new PRR agonist based drugs will emerge in the near future.

ABBREVIATIONS

DC	=	Dendritic cell
NF- κ B	=	Nuclear factor- κ B
PAMPs	=	Pathogen-associated molecular patterns
IRF3	=	Interferon regulatory factor 3
TLR	=	Toll-like receptor
PRR	=	Pattern recognition receptor
MPL	=	Monophosphoryl lipid A
TNF	=	Tumour necrosis factor
LPS	=	Lipopolysaccharide
dsRNA	=	Double stranded RNA
CCR	=	Chemokine receptor
RICK	=	Receptor-interacting serine / threonine kinase
CTL	=	Cytotoxic T lymphocyte
CD	=	Cluster of differentiation
IFN	=	Interferon
MHC	=	Major histocompatibility complex
IL	=	Interleukin
Ig	=	Immunoglobulin
Th1	=	T-helper 1
Th2	=	T-helper 2

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