Review

Direct and Indirect Role of Toll-Like Receptors in T Cell Mediated Immunity

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Toll-like receptors (TLR) are pathogen-associated molecular patterns (PAMPs) recognition receptors that play an important role in protective immunity against infection and inflammation. They act as central integrators of a wide variety of signals, responding to diverse agonists of microbial products. Stimulation of Toll-like receptors by microbial products leads to signaling pathways that activate not only innate, but also adaptive immunity by APC dependent or independent mechanisms. Recent evidence revealed that TLR signals played a determining role in the skewing of naïve T cells towards either Th1 or Th2 responses. Activation of Toll-like receptors also directly or indirectly influences regulatory T cell functions. Therefore, TLRs are required in both immune activation and immune regulation. Study of TLRs has significantly enhanced our understanding of innate and adaptive immune responses and provides novel therapeutic approaches against infectious and inflammatory diseases. *Cellular & Molecular Immunology*. 2004;1(4):239-246.

Key Words: Toll-like receptor, adaptive immunity, Th1, Th2, regulatory T cell

Introduction

Protective immunity against pathogenic infection in mammals can be divided into innate and adaptive immunity. The innate immune response evolves as a first defence barrier in the host, and mounts an immediate, but non-specific, immune response to rapidly destroy or limit the invaders. Adaptive immunity is a second line defence that includes T (cellular) and B (humoral) cell mediated responses. This is specific, targets only pathogens and not self, and has memory to sustain a long-lasting immunity against reinfection. After antigenic stimulation naïve T cells can differentiate into T helper type 1 (Th1), Th2 or regulatory T cells depending on antigen affinity, costimulation at the immune synapse and cytokine milieu. Th1 cells control intracellular infection but are involved in inflammatory diseases. Th2 cells protect the host against extracellular parasite infection, but are also responsible for allergic responses (1, 2). It is always fascinating to an immunologist what triggers innate and adaptive immunity to a pathogen and what determines T cell differentiation and function.

The subsequent identification of Toll-like receptors (TLRs) has brought fresh answers into this area. Toll-like receptors are a group of evolutionary conserved proteins belonging to the IL-1R superfamily, characterised by an extracellular leucine-rich repeat domain and an intracellular Toll/IL-1 receptor like (TIR) domain (3). Toll was first identified in *Drosophila* as part of the host defence against fungal infection in fruit flies (4). At least 11 TLRs have been identified in humans so far (5), and they are well documented as major initiators of innate immunity (6, 7). However growing evidence has demonstrated that TLRs were also able to directly or indirectly promote adaptive immune responses, especially T cell functions (8). In this review, we will focus on the latest findings of the TLR family and its role in Th1, Th2 and regulatory T cell development and function in immune activation and suppression.

Why do we need so many TLRs?

It has been known for a long time that some non-antigenic microbial components, for instance LPS and mycobacterium compounds in complete Freund's adjuvant (CFA), could trigger immune responses (9, 10). However, the molecular mechanisms involved in these functions remained obscure. By using natural mutant individuals or gene knockout techniques, many functions of TLRs and their definitive ligands have now been identified (11, 12, also Table 1). TLRs are widely expressed on immune cells and act as immune sensors to recognise distinct molecules referred to as pathogen-associated molecular patterns (PAMPs) displayed by microbial components (Table 1) to trigger immunity. They are distinct from each other in ligand

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Abbreviations: TLR, Toll-like receptor; PAMP, pathogen-associated molecular pattern; JNK, C-Jun N terminal kinase; DC, dendritic cell.

Table 1. *Toll-like receptors and their ligands.*

TLR family member	Ligands
TLR1	Tri-acyl lipopeptides (bacteria, mycobacteria); Soluble factors (Neisseria meningitidis); Modulin
TLR2	Lipoprotein/lipopeptides; Peptidoglycan (Gram-positive bacteria) ; Lipoteichoic acid (Gram-positive bacteria); Lipoarabinomannan (mycobacteria); Glycoinositolphospholipids (Trypanosoma Cruzi); Glycolipids (Treponema maltophilum); Porins (Neisseria); Zymosan (fungi); Listeria (Heat-killed bacteria); LPS (Spirochaetae); Modulin
TLR3	Double-stranded RNA (virus); Poly (I:C) (synthetic analog of double stranded RNA)
TLR4	LPS (Gram-negative bacteria); HSP60 (Chlamydia pneumoniae); HSP60 (host); HSP70 (host); Fusion protein (RSV); Taxol (Plant); Envelope proteins (MMTV)
TLR5	Flagellin (bacteria)
TLR6	Di-acyl lipopeptides (mycoplasma); Modulin; soluble tuberculosis factor (STF)
TLR7	GU rich Single-strand RNA (ssRNA), Imidazoquinoline (synthetic compounds); Loxoribine (synthetic compounds); Bropirimine (synthetic compounds)
TLR8	GU rich Single-strand RNA (ssRNA)
TLR9	CpG DNA (bacteria); CpG ODN, (synthetic Oligonucleotides that contain unmethylated CpG dinuleotides)
TLR10	?
TLR11	Uropathogenic strains of *E.coli*

specificities, expression patterns, and signalling pathways, but all act in the initiation and activation of immunity.

TLR4 was the first mammalian TLR identified (13), and is involved in the recognition of lipopolysaccharide (LPS) (14), a major cell wall component of Gram-negative bacteria, which can induce sepsis. Recognition of LPS also requires the association of LPS-binding protein, CD14, a glycosylphosphatidylinositol anchored molecule and MD2 (15). TLR2 is the most powerful receptor and recognizes a wide variety of PAMPs from bacteria, yeast, fungi, parasites and viruses (Table 1). The reason why TLR2 is so versatile is unknown. In some cases, TLR2 needs TLR1 or TLR6 to form a heterodimeric co-receptor to effectively recognize different PAMPs (16, 17). Flagellin is produced by most pathogenic and commensal Gram-positive and Gram-negative bacteria, and is regarded as an agonist for TLR5 (18). TLR9 recognizes unmethylated CpG motifs present in bacterial DNA (19). This recognition may take place in the intracellular compartment, perhaps in endosomes or lysosomes following bacterial lysis (20). TLR3 recognizes double-stranded RNA by a MyD88-independent pathway to induce IFN-β (21). In contrast, TLR7 and 8 recognize single-stranded RNA from viruses that trigger immune response and IFN-α production, suggesting they play a unique role in anti-viral responses (22). In order to respond to all pathogens, TLRs may work together to complement or synergise each other's functions as an immune survival network (23).

Like *Drosophila*, the recognition by mammalian TLRs also triggers innate immune response (6). However, unlike *Drosophila*, mammals have evolved to develop adaptive immunity in which T-lymphocytes play a central role. TLRs are also critical in adaptive immunity especially $CD4^+$ T cell clonal expansion and differentiation.

TLR on Th1 development

Th1 cells play a central role in the host response against intracellular pathogens and in inflammation, and can be triggered by PAMPs through TLR signals. The MyD88 dependent signalling pathway is the main gateway shared by most TLR members, except TLR3, for triggering of innate and adaptive immunity. Interestingly, MyD88 deficient mice developed a profound defect in the antigen-specific Th1 but not Th2 responses, suggesting that TLR signals play an influential role in the immune balance toward to Th1 but not Th2 response (24). The important role of MyD88 in Th1 development has been further confirmed in a *Leishmania* infection model. *Leishmania* infection results in uncontrollable disease in genetically susceptible mice due to a dominant Th2 type immune response and therefore parasite survival. In contrast, in genetically resistant mice, the disease is readily cured due to the development of a Th1 response and parasite clearance (25). Muraille E, et al. have found that MyD88 deficient mice in a genetic resistant background (C57BL/6) developed a Th2 phenotype and completely lost resistance to the infection (26). IL-12 is a major player in Th1 development and the immune balance between Th1 and Th2 responses. However, Jankovic D, et al. have argued that MyD88 play a more critical role than IL-12 in determining pathogen induced $CD4^+$ T cell differentiation (27). *Toxoplasma gondii,* a protozoan parasite triggers an IL-12 dependent Th1 response required for protecting the host against the infection. By infecting either IL-12 or MyD88 deficient mice with the parasites, they found that IL-12 knockout mice developed a reduced Th1 response, but failed to default to a Th2 pattern. In contrast, MyD88 deficient animals developed a pure Th2 response and uncontrolled disease, indicating that the TLR mediated MyD88 signalling pathway is a major determinant in Th1 and Th2 balance.

Therefore, theoretically, any TLR that uses the MyD88 signalling pathway for its action should be capable of mediating a Th1 response. Indeed, activation of TLR2 on dendritic cells (DCs) selectively induced IL-12 but not IL-10 (28). Bacterial lipopeptides stimulated human PBMCs

to produce IFN-γ but not IL-4, in a TLR2 dependent manner (29). The TLR4 agonist LPS, from *E.coli*, promotes the production of the Th1 inducing cytokine IL-12p70 and is associated with Th1 responses (30). CpG containing bacterial DNAs initiates a strong Th1 biased response by up-regulating costimulatory molecule p40 and induction of IL-12 through TLR9 (18, 31). This indicates the therapeutic potential of CpG in the treatment or prevention the Th2-type dominated diseases, such as allergies (32). The agonists of TLR 5, 7 and 8 also induced IL-12 or IFN-α, β production from antigen presenting cells (APCs) through a MyD88 dependent pathway, suggesting they may also have a role in Th1 development (18, 21). Interestingly, double-stranded RNA interacting with TLR3 signals through IRF3 also supports Th1 development, probably by the induction of IL-12 and type 1 IFN by DC (33, 34). More recently, TLR11 was found to be highly expressed in kidneys and responded to uropathogenic bacteria, suggesting a unique role in the urogenital system. However, its potential in Th1 or Th2 function still needs to be examined (35).

How the MyD88 pathway drives the Th1 response is not entirely clear. One explanation may be that MyD88 signalling induces IL-12 and IFN-α production from APCs that are potential Th1 inducers (30, 34). MyD88 signalling also leads to the translocation of NF-κB that is required for Th1, but not Th2 development, perhaps through induction of IL-12 and IFN-γ production (36). TLRs also induce IL-12 transcription by APCs through an NF-κB independent pathway. The nucleosome remodelling at the IL-12 p40 promoter induced by LPS and bacterial lipoproteins through the TLR dependent pathway but NF-κB independent pathway, resulted in IL-12 production and promoted Th1 development (37). Furthermore, the caspase recruitment domain (CARD)-containing serine/threonine kinase Rip2 that is recruited to the TLR2 signalling complex may also contribute to TLR mediated Th1 development (38). Rip2 deficient T cells display severely impaired NF-κB activation, proliferation and IFN-γ, but not IL-4 production, indicating Rip2 is required for optimal Th1 response. However, the relationship between MyD88 and Rip2 is unclear. Given that MyD88 is more capable of driving Th1 responses than IL-12, its ability may be beyond IL-12 induction. This needs to be investigated in IL-12 deficient mice.

TLR in Th2 development

Despite the current belief that TLR signalling favours a Th1 development, there is accumulating evidence that TLRs are also important for Th2 skewing by MyD88 dependent and independent mechanisms. Eisenbarth, et al. reported that low dose, but not high dose, inhaled LPS lead to Th2 response to inhaled antigens and severe pulmonary inflammation in a murine allergic model (39). In parallel, Dabbagh, et al. have shown that TLR4 defective mice developed reduced Th2 cytokine production, allergen-specific IgE, eosinophils and airway inflammation compared to wild-type mice in an asthma model, suggesting that LPS and TLR4 are required for optimal Th2 responses (40).

TLR2 also plays a role in Th2 instruction. The interaction of TLR2 with its synthetic ligands, Pam3Cys, induced a predominant Th2 biased immune response with high levels of IL-13 and IgG1 and aggravation of asthma (41). Stimulation of bone marrow derived DCs with Pam3Cys upregulated B7RP-1, which supports Th2 responses and preferentially induces Th2 cytokines such as IL-13, GM-CSF. Interestingly, TLR2 stimulation failed to induce IL-12p70 and IP-10 but resulted in the release of the IL-12 inhibitory p40 homodimer, which would favour Th2 development (42). This may be also due to Pam3cys and TLR signalling induced ERK and c-fos that selectively suppressed IL-12 but enhanced IL-10 production (43). Moreover, recent results showed that bacterial flagellin also drives MyD88-dependent Th2 type response (44). Flagellin promotes the secretion of IL-4 and IL-13 by antigen specific $CD4^+$ T cells as well as IgG1 *in vivo*. The failure of induction of IL-12 p70 and TNF secretion by DCs may be responsible for this Th2 instruction.

However, the molecular mechanism that drives Th2 development by TLRs is still unknown. Given that the MyD88 dependent pathway is essential for Th1 polarisation, the MyD88 independent signals induced by TLR may be more favourable to Th2 development (45). Since LPS use both MyD88 dependent and independent pathways this might explain its capacity to drive both Th1 and Th2 responses. However, this hypothesis needs to be further confirmed using Myd88 knockout mice. Moreover, TLR3 that uses IRF3/Trif, but not MyD88 dependent signalling pathway can induce IL-4 expression in human lymphocytes *in vitro,* suggesting its potential role in Th2 responses (46). C-Jun N terminal kinase (JNK) signalling is essential for ST2L, an IL-1R like receptor belonging to the TLR super family, to induce Th2 cytokine production in Th2 cells (47). It is interesting that this signalling pathway is also shared by TLRs, but whether this is a response to TLR mediated Th2 development is still unclear.

Toll-like receptor and regulatory T cells

The immune response is highly controlled to ensure only targeting of foreign invaders and not self-tissues. Regulatory T cells play a central part in the immune regulation network. At least three types of regulatory T cells have been identified with different functions (48, 49). $CD4^+CD25^+$ regulatory T cells are naturally generated in the thymus and are necessary for the controlling of autoimmune and Th1 and Th2 mediated diseases (50, 51). IL-10 producing T cells (Tr1), and TGFβ producing T cells (Th3) are induced from peripheral tissues and also contribute to the immune regulation network through the IL-10 or TGF-β they produce. Interestingly, there is growing evidence from human and animals that TLR signalling also influences the function of regulatory T cells either directly or indirectly.

TLR2 plays an important role in the function of $CD4^+CD25^+$ regulatory T cells. *Candida albicans* causes a severe infection in an immunocompromised host, and contains a PAMP for TLR2 (52). TLR2 deficient mice developed a 50% reduction in the $CD4^+CD25^+$ regulatory population and were more resistant to disseminated *Candida* infection, suggesting that TLR2 signalling is required for the development or homeostasis of regulatory

T cells. *In vitro* experiments also supported this, in that regulatory T cells showed enhanced survival with a TLR2 ligand but not a TLR4 agonist. This result is also confirmed in that $CD4^+$ T cells respond to TLR2, but not TLR4 ligand despite expressing both TLR2 and TLR4 at the surface (53). The resistance to *Candida* infection is associated with decreased release of IL-10 and enhanced proinflammatory cytokines TNF and IL-1, suggesting that control of IL-10 producing regulatory T cell may favour protective immunity. However the underlying mechanism of TLR2 signalling leading to regulatory T cell development is unknown, but indicates that TLR2 mediated signals are crucial for their homeostasis and function.

TLR4 also affects regulatory T cell functions. $CD45RB^{low}CD25^+$ regulatory T cells selectively express TLR4, 5, 7 and 8 messages. Exposure of the cells to LPS from *Salmonella typhimurium* upregulated several activation markers including MHC Class I, CD69 and B7.1 and enhanced their survival/proliferation (54). Moreover, LPS treatment increased $CD4^+CD25^+$ cell mediated suppressive efficiency. *In vivo,* LPS-activated regulatory T cell controlled naive $CD4^+$ T cell induced wasting disease. Although it is contradictory to the current belief that $CD4^+$ T cells do not respond to LPS directly (55, 56), the results suggest that murine $CD4^+CD25^+$ regulatory T cells might respond directly to bacterial products for survival and function. The molecular mechanism involved in the effect of LPS on regulatory T cells is still unknown.

TLR4 signal is also critical for the generation and function of IL-10 producing Tr1 regulatory T cells in *Bordetella pertussis* infection, perhaps through a DC mediated indirect pathway (57). DCs from TLR4 mutant C3H/Hej mice are less mature and produce decreased IL-10 after infection with *Bordetella pertussis*. The infection was more severe in the mutant mice than control C3H/HeN mice, accompanied by reduced IL-10 producing T cells but enhanced inflammatory cytokines and severe lung pathology.

TLR signals as immune adjuvant can enhance DC mediated adaptive immunity by helping DC maturation and antigen presentation. It is now recognised that the adjuvant function of TLR stimulated APCs is not only due to effective priming of effector cells but also overcoming the suppressive functions of regulatory T cells (58). Pasare C, et al. found that LPS or CpG stimulated DC and reversed $CD4^+CD25^+$ regulatory T cell mediated suppression. The blockage of suppression is not dependent on cell-cell contact but is dependent on the MyD88 mediated signalling pathway, suggesting TLRs are required. Furthermore, IL-6 is partially responsible for overcoming regulatory T cell mediated suppression. However other soluble factors may be also involved. IL-6 deficient mice were severely compromised in T cell responses and IL-2 production. LPS stimulated DC from the mice lost the ability to block the suppression. All the results indicated IL-6, a pro-inflammatory cytokine induced by TLR signalling, is required for overcoming regulatory T cell function by DC. How IL-6 works in this system and whether it directly abrogates regulatory T cell function or enhances the resistance of effector T cells to the suppression needs to be further investigated.

It is also reported that virus provided TLR signals that could bypass regulatory T cell-mediated $CD8^+$ tolerance (59). Viral vaccines broke $CD8^+$ tolerance in the presence of $CD4^+CD25^+$ regulatory T cells. However, reversal of CD8 tolerance by the dendritic cell-based vaccines was dependent on removal of Treg cells or coadministration of the TLR ligands, LPS or CpG *in vivo*, suggesting that TLRs and regulatory cells are required in $CD8^+$ tolerance. The mechanism underlying this apparent dichotomy is yet to be unravelled.

Taken together, TLR signals can manipulate regulatory T cell functions either by modulating DC function or directly acting on Treg cells. The delivery of TLR signals is necessary for immune regulation and tolerance.

TLR on DCs determines the diversity of T cell differentiation

It appears that signalling through TLRs can direct T cell differentiation towards Th1, Th2 or Treg cells. What determines the outcome of this functional diversity of TLR in a pathogenic infection is still unknown. Dendritic cells are the most effective professional antigen presenting cells for T cell priming and they play a critical role in directing T cell differentiation. DCs consist of heterogeneous subsets, as determined by their location, surface markers and cytokine profiles (60). It is noted that TLRs are differentially expressed on DC subsets. Human blood contains at least two types of DCs, $CD11c^+$ and plasmacytoid DC (PDC). $CD11c^+$DC selectively expresses most TLRs but not TLR9. In contrast, PDCs strongly express TLR9 but lack TLR3, 4 and 8 (61, 62). In accordance with their TLR expression profiles, $CD11c^+$DC do not respond to the TLR9 ligand CpG DNA but do respond to TLR2 ligands to produce TNF-α, but not IL-12 (63). In contrast, PDC failed to respond to lipoteichoic acid, poly I:C and LPS, but responded to CpG and induced strong Th1 differentiation (61, 62). This selective expression of TLRs and the differential response to microbial products by DC subsets may give rise to distinct guiding of Th cell development.

Different TLR agonist signals on the same DC induce disparate Th responses (64). Thus, TLR4 and TLR5 ligands, *E.coli* LPS and flagellin respectively stimulate $CD11c^+$ monocyte-derived DCs to produce IL-12 and instruct Th1 responses. However, TLR2 agonist, Pam3cys barely induces IL-12, but strongly induces IL-10 and yields a Th2 type response. This suggests that differentiation towards Th1 or Th2 responses may be manipulated by selective usage of different microbial products by the same type of DC. Moreover, different loading of an agonist on the same TLR could lead to selective Th1 or Th2 response (38). They showed that low levels of inhaled LPS signalling through TLR4 induced a Th2 response to inhaled antigen, but high levels resulted in a Th1 response.

It is notable that the utilisation of TLR by immature DCs may result in the generation of DC subsets capable of polarising T cells with regulatory capacity. Human immature monocyte-derived DC, when cultured with a TLR2 ligand, phosphatidylserine from *schistosome* eggs, released low level of IL-12 but gained the ability to induce the development of IL-10 producing regulatory T cells (65).

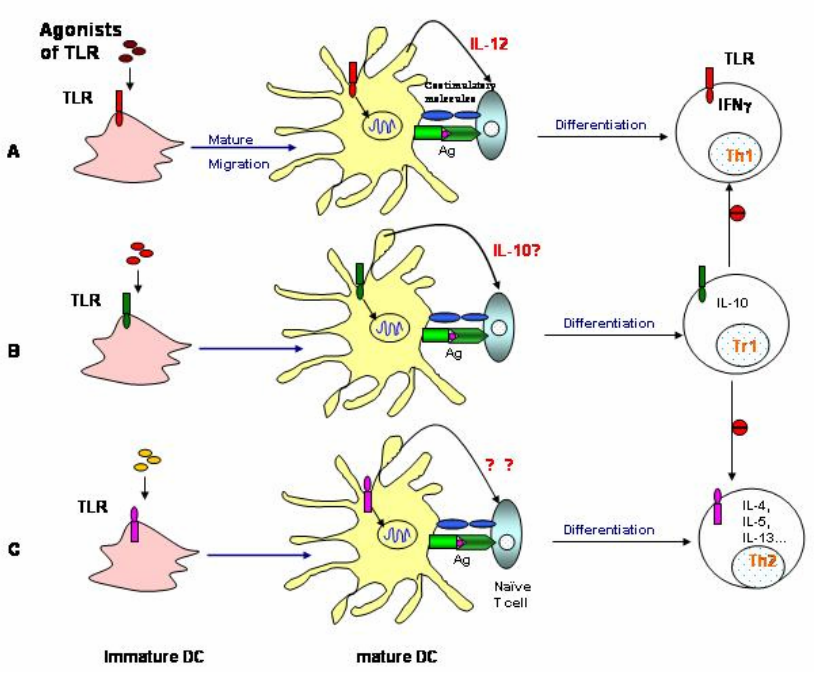

Figure 1. The functional diversity of TLRs on DC subsets determines distinct T cell differentiation.

In addition to the lack of IL-12 production, secretion of IL-10 may also be a feature of these regulatory T cell polarising DCs. LPS from *Bordetella pertussis* acting through TLR4 can stimulate DC maturation and production of IL-10 that directly or indirectly promotes IL-10 –secreting type 1 regulatory T cells (57). Interaction between TLR and TCR signalling to microbes might also contribute to the balance of Th cells but the possibility has not been explored.

Toll-like receptors directly act on T cell function

TLRs can prime adaptive immunity through acting on APCs. Can TLRs also directly engage with T cells and what role might they play on T cells? This is fundamentally important, but a technically difficult question to answer because highly purified T cells are needed to avoid contamination by APCs.

By using highly purified T cell subsets it has been reported that human and mouse $CD4^+$ and $CD8^+$ T cells do express detectable levels of TLR messages (66-68). T cells also express MyD88, MD2 and CD14 messages (68). These molecules are important as associated receptors in TLR2 and 4 signalling, suggesting TLR ligand may act directly on T cells.

More recently, results from our laboratory demonstrated that naïve human $CD4^+$ and $CD8^+$ T cells do not express detectable TLR2 and 4 proteins. Once activated through the TCR high levels of cell-surface TLR2 and 4 can be induced. The expression of TLR can be co-localised with the presence of CD3 at the single cell level. Activated T cells produced elevated levels of Th1 cytokines in response to the TLR2 ligand, bacterial lipopeptide (Pam3Cys-SK4), through a TLR2 dependent mechanism. In contrast, the activated $CD4^+$ T cells failed to respond to LPS. Furthermore, $CD4^+CD45RO^+$ memory T cells from peripheral blood constitutively expressed TLR2 and produced significantly higher levels of IFN-γ and IL-2 than activated $CD4^+CD45RA^+$ naïve T cells in response to TLR2 ligands. The memory T cells also had markedly enhanced proliferation and IFN-γ production compared to naïve cells in bystander culture conditions with IL-2 or IL-15 and TLR2 ligand but without TCR activation, suggesting that TLR2 might play a unique role in memory T cell function. Thus, the results were the first to demonstrate that TLR2 directly serves as a co-stimulatory receptor for human antigen-specific T cell development and might participate in the maintenance of T cell memory (53). The direct role of TLRs on mouse $CD4^+$ T cells was also confirmed by Gelman and colleagues (69). They have shown that mouse naïve $CD4^+$ T cells expressed TLR3 and TLR9 messages that could be up-regulated by TCR ligation. Treatment of activated $CD4^+$ T cells with the dsRNA synthetic analogue poly I:C and CpG DNA, ligands respectively for TLR3 and TLR9, directly enhanced their survival without augmenting proliferation. The enhanced T cell survival was dependent on NF-κB activation and was probably due to upregulation of the survive signal Bcl-xL but not Bcl-2 or 3. These results suggest that the adjuvant function of TLR3 and 9 is not only through the activation of APCs but also directly by the augmented survival of T cells. It is intriguing that TLR signalling which induced apoptosis in macrophages, but promotes survival in T cells, thus suggesting that TLR signalling may have a different

role in T cells (70, 71). Controversially, the paper also indicated that activated mouse $CD4^+$ T cells did not express TLR2 and TLR4 messages and did not respond to TLR2 and 4 ligands for survival. The reason for the discrepancy is unclear. It may be that different T cells and a different assay system have been applied in the two papers. It will be interesting to confirm whether TLRs perform differently in human and murine T cells, and whether other TLRs are also directly involved in T cell activation and function. Nevertheless, both results suggest that T cells express functional TLRs on their cell surface. TLR signalling can directly modulate T cell function either as co-stimulatory or survival signalling. These findings provide a novel role for TLRs in T cell activation and functions. It may also help to explain how activated/memory T cells are sustained in an immune competent host.

Microbial signals from invading pathogens can be recognised as mitogen or antigen by immature DC subsets (Figure 1). The interaction of microbial products with TLRs leads to DC maturation characterized by the production of innate cytokines such as IL-12, TNF-α or IL-10, upregulation of costimulatory molecules such as CD40, CD80, CD86 and MHC class II, and the expression of chemokine receptors. Differential expression and ligation of TLRs on distinct DC subsets result in the generation of DCs with different phenotypes of cytokine production, costimulatory molecule expression and antigen presentation capacity, and therefore the ability to polarise different T cell subsets. These differentially matured DC subsets migrate from non-lymphoid tissues to the nearest draining lymph nodes where they meet and prime naïve T cells into antigen specific Th1, Th2 or Treg cells that can then mediate immune activation or suppression. On the other hand, effector cells express TLRs on the cell surface that allows T cells to directly respond to microbial signals for activation, survival or immune regulation. Therefore, TLR signalling is required for the differentiation and clonal expansion of $CD4^+$ T cell subsets.

Immature dendritic cells are located in the peripheral tissues. Interaction of microbial products with TLR causes the upregulation of the expression of costimulatory, major histocompatibility complex (MHC) and the secreting innate cytokine by DCs. Differential expression and ligation of TLRs on DCs generate DC subsets with distinct capacity to polarise different T cell subsets. The differently matured DC subsets migrate to the draining lymph nodes where they meet and present antigen signal to naïve T cells together with innate cytokine that results in the differentiation of Th1, Th2 or Treg cells.

Perspectives

The discovery and functional identification of TLRs has significantly increased our understanding in T cell mediated immunity, especially in T cell differentiation and functions. Data accumulating suggests that differential expression and activation of TLRs on DC subsets play a determining role in selective polarisation of T cell subsets. However, the mechanism involved in the determinations, especially in Th2 and Treg development, remains obscure.

A direct role of TLR on T cells has led to novel pathways that involves T cell activation and homeostasis. However, the physiological functions that are mediated by direct function of TLR on T cells *in vivo* remain to be investigated.

Understanding of these new immunological pathways will not only open new avenues for immunological manipulation against infectious disease, may also lead to the identification of new targets for the intervention in a range of autoimmune diseases.

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