**MINIREVIEW**

Recent insights into microbial triggers of interleukin-10 production in the host and the impact on infectious disease pathogenesis

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**Abstract**

Since its initial description as a Th2-cytokine antagonistic to interferon-alpha and granulocyte-macrophage colony-stimulating factor, many studies have shown various anti-inflammatory actions of interleukin-10 (IL-10), and its role in infection as a key regulator of innate immunity. Studies have shown that IL-10 induced in response to microorganisms and their products plays a central role in shaping pathogenesis. IL-10 appears to function as both sword and shield in the response to varied groups of microorganisms in its capacity to mediate protective immunity against some organisms but increase susceptibility to other infections. The nature of IL-10 as a pleiotropic modulator of host responses to microorganisms is explained, in part, by its potent and varied effects on different immune effector cells which influence antimicrobial activity. A new understanding of how microorganisms trigger IL-10 responses is emerging, along with recent discoveries of how IL-10 produced during disease might be harnessed for better protective or therapeutic strategies. In this review, we summarize studies from the past 5 years that have reported the induction of IL-10 by different classes of pathogenic microorganisms, including protozoa, nematodes, fungi, viruses and bacteria and discuss the impact of this induction on the persistence and/or clearance of microorganisms in the host.

**Introduction: IL-10 in infection**

Fulminating microbial infection involves severe tissue pathology that typically stems from excessive host signalling pro-inflammatory cascades such as those described by the so-called ‘cytokine-storm’ model (Bisno et al., 2003; Stanford et al., 2007; Schreiner & Liesenfeld, 2009). Excessive immune responses, which, in the case of bacterial pathogens are triggered by unique structures such as lipopolysaccharide (LPS) (Ianaro et al., 2009), can lead to organ-specific inflammation to such a degree that irreversible septic shock ensues (Latifi et al., 2002). Uncontrolled immunopathology influences the pathogenesis and progression of colitis during enteric infections (Kullberg et al., 2002), in the inflammation of infected airways (Demangel et al., 2002) and in disseminated intravascular coagulation leading to sepsis (van der Poll & Opal, 2008). Infection-induced inflammation and immunopathology resulting from it is often associated with deregulated haematopoiesis, and, in addition to cytokine ‘storms’ usually comprises abnormal proliferation of cells that mediate innate and adaptive immune responses such as natural killer (NK) cells, cytotoxic T lymphocytes (CTLs) and other lymphocyte subsets (Couper et al., 2008a, b; Moreira et al., 2008). Interleukin-10 (IL-10) is a central player that moderates these potentially excessive immune responses during infection (Mege et al., 2006).

Much of the current knowledge of IL-10 function in infection is derived from the investigations of immune defence mechanisms that function at first-contact, mucosal sites of colonization such as the gastrointestinal and respiratory tracts [as reviewed in (O’Garra et al., 2008)], and more recently, the urinary tract (Duell et al., 2012). In acute infections, high microbial loads that may develop on the surface of the mucosa often induce severe inflammatory responses but such responses are moderated by...
the balance between T Helper (Th)1 and Th2 effector mechanisms (Fiorentino et al., 1989). On the one hand, Th1 responses promote cell-mediated immunity (CMI) enabling phagocytosis, degranulation of cells such as neutrophils, and the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS) to kill invading pathogens (Couper et al., 2008a, b). In contrast, Th2 responses favour humoral immunity by promoting B lymphocyte clonal selection and production of pathogen-specific immunoglobulins (Ig) such as secretory IgA (sIgA) at the mucosa (Couper et al., 2008a, b). An inappropriate balance between Th1, Th2 and antigen (Ag)-specific responses thwarts effective antimicrobial responses and enables invading microorganisms to survive, which can lead to immunopathology caused by chronic inflammation and persistent infection (Fleming et al., 1999). Cytokines from both Th1 and Th2 responses are involved in intimate cross-regulation of homeostasis and pathology, which has been described in various infection models that have dissected the balance between pro- and anti-inflammatory responses (O’Garra et al., 2004). In bacterial, parasitic, viral and fungal infections IL-10 functions as a moderator of these responses (Mege et al., 2006; Couper et al., 2008a, b) where it works to achieve balance between Th1 and Th2 responses within the dynamic host environment during infection. Recent reports of IL-10 in protozoan, fungal, nematode and viral, in addition to bacterial infections are outlined in Table 1. Thus, as an anti-inflammatory that inhibits the production of various pro-inflammatory factors (Moore et al., 2001), IL-10 can moderate infection-associated immunopathology linked with strong Th1 responses (Maloy et al., 2003). IL-10 also drives secretion of microorganism-specific IgA and B lymphocyte activation (Defrance et al., 1988, 1992; Fernandez-Botran et al., 1989; Moore et al., 1990; Rousset et al., 1991, 1992; Vieira et al., 1991).

**Cellular sources of IL-10 and mechanisms of action**

Interleukin-10 is a 37-kDa protein that exists as a homodimer of two 18.5-kDa parts (Fiorentino et al., 1989; Vieira et al., 1991). Five paralogues of IL-10, namely IL-19, IL-20, IL-22, IL-24 and IL-26 (Mege et al., 2006), along with IL-28 and IL-29 comprise the ‘IL-10 Family’ of which IL-10 is the founding member (Moore et al., 2001; Mosser & Zhang, 2008). IL-10 is derived from a number of cellular sources relating to the type of infection, the type of host cell that the microorganism or foreign epitope comes into contact with, and the signal transduction pathway(s) initiated (Moore et al., 2001; O’Garra et al., 2004). It is sourced principally from monocytes/macrophages, dendritic cells, CD4(+) and T-reg lymphocytes during or shortly after antigen presentation (Ettinger et al., 1995; Bourreau et al., 2007; Bozza et al., 2007; De Witte et al., 2007; Ferreira et al., 2007; Goldmann et al., 2007; Kurokawa et al., 2007; McNally et al., 2007; Obonyo et al., 2007; Patrone & Stein, 2007; Setiawan et al., 2007; Xin et al., 2007; Yang et al., 2007; Couper et al., 2008a, b; Jongyota et al., 2008; Lazarus et al., 2008; Rocha-Ramirez et al., 2008; Souza et al., 2008; Bogaert et al., 2009; Fang et al., 2009; Srle et al., 2009; Sinimeri et al., 2010; Vargas-Inchaustegui et al., 2010; Groseth et al., 2011; McCoy-Simandle et al., 2011; Ota et al., 2011; Stabel & Robbe-Austerman, 2011).

Mechanistically, IL-10 promotes B lymphocyte proliferation by altering the Th cell environment and suppresses inflammation and macrophage activity by inhibiting the production of interferon (IFN)-gamma, IL-2, IL-12, IL-18 and tumour necrosis factor (TNF)-alpha as well as other cytokines (Moore et al., 2001; Couper et al., 2008a, b). Thus, the cytokines action towards pathogenesis during infection are believed to hinge on microorganism clearance by stimulating adaptive immune effector mechanisms involving clonal proliferation and maturation of Th2 lymphocytes as recently reviewed elsewhere (Ouyang et al., 2011). The suppressive influence of IL-10 towards macrophages and Th1 responses enables Th2 responses, characterized by IL-4, IL-5, IL-6 and IL-13 (Couper et al., 2008a, b). This effect on humoral effector mechanisms related to B lymphocytes, antibody production and alternately activated macrophages (Couper et al., 2008a, b) is important in the resolution of some infections such as helminth and protozoan infections, excluding malaria (Bate et al., 1992; Stijlemans et al., 2007). IL-10 may also work in concert with transforming growth factor (TGF)-β to suppress Th1 and Th2 responses through a Th3 response (Cools et al., 2008). While TGF-β maintains T lymphocyte tolerance to antigens via its direct effects on the differentiation of T effector lymphocytes (T-eft) and T regulatory (T-reg) lymphocytes, IL-10 operates as a feedback inhibitor of T lymphocyte responses. Together, both activities appear to control inflammatory responses triggered by microbial insult (Li & Flavell, 2008). The mechanisms of action of IL-10 was also described recently in terms of its effects on T-reg and Th0 cells, leading to the down-regulation or destruction of T-eft lymphocytes (Fuchs et al., 2009). While T-reg lymphocytes such as natural T-reg cells are critical in some infections such as helminth infections, a subset of T-reg cells, Type 1 regulatory T (Tr1) lymphocytes, are produced in response to bacterial infection of dendritic cells (McGuirk et al., 2002). Tr1 lymphocytes suppresses Th1 responses triggered by pathogen stimulation (Groux et al., 1997) along with other T-reg lymphocytes through the T cell receptor (TCR) (Roncarolo et al., 2006). This causes IL-10 and TGF-β
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<th>Type of microbe and pathogen</th>
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H, Human; M, Mouse; C, Cow; Ha, Hamster.
synthesis that down-regulates pro-inflammatory cytokines and CD8+ T lymphocyte proliferation. In turn, this down-regulates CTLs, NK cells and large granular lymphocytes, which comprise the T-eff lymphocyte group (Wu et al., 2007).

In terms of timing, the early phase of infection is the key stage at which an inflammatory, regulatory and/or memory response is preferentially induced (Moreira et al., 2008) and recent studies have shown that this is when IL-10 can radically influence ensuing responses (Xin et al., 2007; Zheng et al., 2009). Challenge with microorganisms or microbial extracts can up-regulate both pro-inflammatory cytokines (TNF-alpha and IL-12) and IL-10, demonstrating that concurrent induction of conflicting responses early in the response to microorganisms can occur (De Witte et al., 2007; Rocha-Ramirez et al., 2008). IL-10 at the early stages of infection can drive the developing immune response from a CMI pro-inflammatory one, to a pro-regulatory, humoral response useful for orchestrating antibody-driven resolution of infection. As a result of the early regulatory role of IL-10 in host responses to infection inappropriate timing or degrees of production can lead to ineffective pathogen clearance and, as a result, persistent infection. In other words, the nature of IL-10 on a sliding scale of pro-inflammatory and pro-memory responses means that poorly timed or poorly controlled degrees of synthesis can hamper disease resolution. IL-10 produced too early prompts an inappropriately timed change from CMI to humoral responses, and too much IL-10 can cause persistent or chronic infection (McGuirk et al., 2002). In such cases, less inflammation fails to promote microbial clearance because the stage of the infection is too early for effective B lymphocyte-mediated Ag-specific responses (McGuirk et al., 2002). Examples of deregulated IL-10 early during infection that leads to poor antimicrobial effector mechanisms, increased disease severity and chronicity include Pseudomonas aeruginosa lung infection (Chmiel et al., 1999), colitis (Kullberg et al., 2002) and malaria (Plebanski et al., 1999; Couper et al., 2008a, b). A contrasting, defensive role for early IL-10 produced immediately after infection with uropathogenic Escherichia coli was shown in a recent study on cystitis (Duell et al., 2012) underscoring the complexity of early IL-10 effects on host defence in the first few hours after acute bacterial infection.

At the signalling level, IL-10 inhibits transcription of pro-inflammatory cytokines, and post-transcriptional events associated with their actions via mechanisms such as mRNA degradation (Bogdan et al., 1992; Wang et al., 1994; Aste-Amezaga et al., 1998; Kishore et al., 1999; Kontoyiannis et al., 2001; Zhou et al., 2004). This has been shown in studies using LPS (Wang et al., 1994; Niero et al., 1995; Brown et al., 1996; Dokter et al., 1996; Lentsch et al., 1997; Song et al., 1997; Zhou et al., 2004). IL-10 induces suppressor of cytokine signalling (Socs)-1 and Socs-3, and roles for janus kinase 1, tyrosine kinase 2, signal transducers and activators of transcription (Stat)-1, Stat-3 and Stat-5 in downstream signalling events are beyond the scope of this review and described elsewhere (Grutz, 2005). In terms of signal transduction, IL-10 effects phosphoinositide 3-kinase and Akt (Murphy et al., 1994; Bhattacharyya et al., 2004) but there remains debate on the influence of IL-10 on p39 mitogen activated protein kinase and nuclear factor-KappaB (NF-kB) (Wang et al., 1995; Dokter et al., 1996; Song et al., 1997; Clarke et al., 1998; Denys et al., 2002). Regarding NF-kB activity, IL-10 appears to alter the composition of NF-kB from transactivating p65/p50 heterodimers to inhibitory p50/p50 homodimers (Driessler et al., 2004). Overall, however, the molecular mechanisms underlying the signalling events that lead to IL-10’s anti-inflammatory actions are not entirely clear.

**Newly discovered microbial triggers of IL-10 in the host**

Certain pathogens can trigger selected cytokine production pathways in a manner that favours their survival within the host and IL-10 is increasingly associated with such virulence strategies (Mege et al., 2006; Rahman & McFadden, 2006). Antigen-presenting cells (APCs) such as macrophages, monocytes and dendritic cells use Fc and other receptors to detect microorganisms and secrete IL-10 in response to organisms, including salmonella, yersinia, neisseria, helicobacter, leishmania and mycobacteria as well as nematodes, fungi, viruses and pathogenic protozoa (Table 1). The IL-10 that is produced by these APCs and other cells during infection influences cell activation and differentiation (Edwards et al., 2006) and can alter cell population responses to infection (Katakura et al., 2004). A number of studies on Gram-positive and Gram-negative bacteria and Chlamydia in the last few years in particular have shed new light onto how IL-10 is induced in response to these pathogens and what its production means for pathogenesis.

IL-10 induced by Gram-positive bacteria, including streptococci and staphylococci, has major implications for the hosts’ ability to control these organisms at mucosal sites of infection. Type-II activated macrophages, defined elsewhere (Edwards et al., 2006; Gordon & Martinez, 2010), produce IL-10 in response to streptococci. This leads to anti-inflammatory effects via Th2 lymphocytes in a response that mediates tissue repair and regeneration in infection rather than phagocytosis, which may prolong microorganism clearance. IL-10 from macrophages is
secreted into serum in response to Streptococcus pyogenes M protein (Price et al., 2005). The M protein, which may impact host cell apoptosis, as reviewed elsewhere (Ulett & Adderson, 2006), binds to CD46 and the TCR and binding to naïve CD4+ T lymphocytes initiates induction of Tr1 cells. This causes IL-10 synthesis (Price et al., 2005). Here, the IL-10 may promote a delayed immune response and enable the bacteria to colonize the host more effectively, thus increasing the magnitude of infection (Price et al., 2005). Streptococcus pneumoniae also triggers IL-10 in macrophages and T lymphocytes (Table 1), which is associated with impaired innate and acquired cellular responses to this organism in neonatal and infant mice (Ota et al., 2011). However, early IL-10 triggered by Streptococcus agalactiae was recently shown to play a role in shaping protective immune responses against this organism through effects on neutrophil trafficking (Madureira et al., 2011). Other defence mechanisms related to streptococci at the mucosa encompass complement/CD46-induced T-reg cells (ct-reg), which are capable of promoting antibody production via IL-10 signalling and cell–cell contact (Fuchs et al., 2009). CD25 and CD137 may provide a switch for such responses as their expression coincides with fewer T-eff cells and B lymphocyte activation via CD46 stimulation/high IL-10 levels (Fuchs et al., 2009).

Aside from streptococcal M protein being a significant epitope for IL-10 stimulation, recent evidence has highlighted a role for staphylococcal peptidoglycan as a modulator of T lymphocyte-mediated toxic shock syndrome (Chau et al., 2009; Frodermann et al., 2011). Staphylococcus aureus induces IL-10 in monocytes and macrophages (but not dendritic cells) after recognition of peptidoglycan-embedded lipopeptides and glycopolymers in the bacterial cell wall (Table 1) (Frodermann et al., 2011). Toll-like Receptor (TLR)2 signalling stimulates the IL-10 production, however, when the same interaction occurs with dendritic cells, an IL-12 pro-inflammatory response is initiated (Frodermann et al., 2011). Thus, this response is dependent upon the type of APC-peptidoglycan interaction. In this case, peptidoglycan-rich Gram-positive species may down-regulate inflammation when present in large quantities, to counteract the effect of other pro-inflammatory antigens (Gjertsson et al., 2002; Chau et al., 2009). This, as a result, may influence pathogen clearance. It is therefore reasonable to assume that such differential APC responses in terms of IL-10 production may account for divergent staphylococcal disease outcomes in different tissues and infection sites (Chau et al., 2009; Frodermann et al., 2011). A recent suggestion of IL-10-centric suppressive effects mediated by mass Gram-positive peptidoglycan/cell wall components at the enteric mucosa (Chau et al., 2009) parallels the biology of host responses to LPS in this way, wherein IL-10 modulates overactive immune responses and limits inflammation triggered by Gram-negative organisms (Donnelly et al., 1999; Moore et al., 2001). Together, these data also highlight the function of IL-10 in maintaining the balance of normal flora within mucosal sites, such as the gastrointestinal and genitourinary tracts. Genetic evidence of this function is seen in IL-10-deficient mice that exhibit colitis because of immune dysregulation, altered normal flora, and complex IL-10-related colitogenic effects (Mahler et al., 2002).

For Gram-negative pathogens, microorganism load can influence IL-10 responses during certain infections, where higher bacterial burdens promote IL-10 production, in contrast to lower burdens that appear to induce IL-12 pro-inflammatory responses. For Helicobacter pylori, this occurs in a partially MyD88/TLR4-dependent fashion (Obonyo et al., 2007). These findings support the concept that variable conditions of APC activation play a role in regulating the type of inflammatory response involving IL-10 during infection, as discussed for staphylococcal peptidoglycan. For Salmonella and Yersinia, subcomponents of the organisms’ flagella, displayed on the cell surface and used for motility, have been shown to influence IL-10 production in the host under distinct conditions. On the one hand, live flagellated Salmonella induce Th1 activity, but non-native, soluble FlIC flagellar protein (the major component of the flagella apparatus) induces a Th2 type host response (Cunningham et al., 2004). This example underscores the divergent APC polarization responses that can occur for inflammatory or suppressive effects depending on the nature of the foreign antigen encounter. Other studies have demonstrated that Salmonella flagella trigger IL-10 secretion in spleenocytes (Sbrogio-Almeida et al., 2004), monocytes (Giacci-Woolwine et al., 1997; Wyant et al., 1999) and in serum of infected mice (Eaves-Pyles et al., 2001). In contrast, when expressed in a Paracoccidioides brasiliensis vaccine antigen, Salmonella enterica FlIC appears to dampen IL-10 production in the lungs of immunized mice (Braga et al., 2009) (Table 1). Flagella produced by Yersinia enterocolitica were also recently associated with IL-10 induction in human macrophages (McNally et al., 2007). Mechanistically, the immune modulatory effects of Gram-negative bacterial flagella towards IL-10 synthesis presumably occur through TLRI5, as demonstrated for other cytokines such as IL-6 (Hayashi et al., 2001; Andersen-Nissen et al., 2005) although this has not yet been demonstrated.

There are a number of chlamydial antigens associated with the production of IL-10 in macrophages and T lymphocytes, the most studied being the major outer membrane protein (MOMP) (Vats et al., 2002; Azenabor et al., 2011; Bermudez-Fajardo et al., 2011). IL-10 secretion can have both positive and detrimental effects on
chlamydial persistence during infection (Thiel et al., 2000; Bandholtz et al., 2002). The negative effects of IL-10 production stem from its immune modulatory effect of suppressing the production of IFN-γ, a cytokine required for effective clearance of Chlamydia from tissues. Contrasting positive effects also stem from the anti-inflammatory influences of IL-10, because of reduced severe pathological sequelae associated with infection. An effect related to both consequences, however, is that IL-10 also reduces the chances of IFN-γ-mediated chlamydial persistence during infection, which is an interaction largely related to tryptophan, although RNS may play a role as well, as discussed below (Rottenberg et al., 2002).

At the cellular level, IL-10 may inhibit several antimicrobial activities in APCs such as fusion of vacuoles with lysosomes and IFN-γ-mediated intracellular tryptophan depletion, which could provide an opportunity for chlamydial persistence in host cells. IL-10 is known to effect both of these pathways in other systems (MacKenzie et al., 2003; Weiss et al., 2005); firstly, by restricting phagolysosomal maturation (Coutinho-Silva et al., 2003; O’Leary et al., 2011), and secondly, by suppressing the production of IFN-γ, which inhibits bacterial acquisition of host cell tryptophan via the activation of indoleamine 2,3-dioxygenase (Ibana et al., 2011). Intracellular Chlamydia are also killed in APCs by nitric oxide (NO) under certain circumstances (Gold et al., 2004), and NO (Rottenberg et al., 1999; Carratelli et al., 2005; Jayarapu et al., 2010) and iNOS (Ramsey et al., 2001; Rothfuchs et al., 2001; Shimada et al., 2011) induction has been associated with anti-Chlamydophila pneumoniae, as well as pathological (Huang et al., 2002) effects. The influence that IL-10 might exert over these mechanisms of intracellular killing of Chlamydia, however, is unclear. IL-10 down-regulates NO induced by other pathogens including P. brasiliensis (Moreira et al., 2010) and parasites (Gazzinelli et al., 1992), and macrophages deficient in IL-10 kill C. pneumoniae better than the wild-type macrophages, which appears to be related to iNOS (Rothfuchs et al., 2001). In addition, mechanisms of host cell death, which are effected by NO in other infections (Ulett & Adderson, 2005), are modulated by Chlamydia in various cell types including epithelial cells, T lymphocytes, and macrophages (Yaraei et al., 2005; Huston et al., 2011; Olivares-Zavaleta et al., 2011). Modulation of host cell death (including inhibition of) by Chlamydia has also been linked to altered redox (Sessa et al., 2009) and ROS (Vardhan et al., 2010), among other mechanisms as reviewed elsewhere (Sharma & Rudel, 2009). To date, however, there are few studies that have explored the regulation of cell death responses in relation to NO or IL-10 during chlamydial infection.

Also in terms of chlamydial persistence, conditions relating to monocytes, T lymphocytes and a combination of high IL-10 and low TNF-α levels are themes among several studies (Holland et al., 1996; Yin et al., 1997; Braun et al., 1999; Giraldo et al., 1999; Kinnunen et al., 2003; Appel et al., 2004). In one infection model, IL-10-deficient mice demonstrated accelerated clearance of Chlamydia trachomatis infection, which correlated with a lack of a fibrotic tissue. This study suggested that IL-10 might have interfered with T lymphocyte-driven Th1 responses, leading to an increased susceptibility to re-infection (Yang et al., 1999). In addition to MOMP, chlamydial recurrence has also been linked to Heat Shock Protein-60 (HSP-60) (Kinnunen et al., 2003). Another study showed that CD4+ T lymphocytes help control persistent infection during the later stages of disease (Morrison & Morrison, 2000), and, more recently, Tr1-mediated IL-10 pathways were implicated in persistence (Appel et al., 2004). Finally, steroid hormones including β-estradiol may also influence the role of IL-10-mediated immune responses in chlamydial persistence because these correlate with IL-10 levels during C. trachomatis infection and fertility disorders (Kaushic et al., 2000; Agrawal et al., 2007, 2009a, b). Thus, in addition to effects on intracellular killing mechanisms as discussed earlier, IL-10 may contribute to chlamydial survival in the host by suppressing Th1 responses, mediating Tr1 pathways, and may be affected by hormonal mechanisms within the reproductive cycle that are important in C. trachomatis persistence.

Both monocytes and T lymphocytes generate IL-10 in response to C. pneumoniae (Mamata et al., 2007) but fail to do so when stimulated with a single chlamydial antigen such as MOMP. The lack of response to such an immunogenic antigen in single-lineage monocyte or T lymphocyte exposure models may indicate cell-specific actions of MOMP (Vats et al., 2007; Azenabor et al., 2011) or may reflect inherent intercellular communication effects. Here, it is important to highlight the role of intercellular interactions in studies of responses to infection because such cellular communications are often essential to drive host-pathogen dynamics. This has been shown for optimal cytokine production, microorganism transfer between host cells (Vanham et al., 2000), bacterial killing (Ulett et al., 1998) and apoptosis during infection (Sharma et al., 2009), as recently reviewed elsewhere (Duell et al., 2011). Further to the divergent effects of whole C. pneumoniae and MOMP towards monocyte and T lymphocyte-derived IL-10 are varied effects of viable and killed C. pneumoniae. While stronger Th1 responses are associated with live C. pneumoniae (Mamata et al., 2007), killed bacteria cause directed Th2 responses. This is probably related to the unique developmental life cycles of
Chlamydia, where extracellular and intracellular forms exist and require two different types of immune responses to be initiated for eradication. Thus, seemingly conflicting chlamydial triggers of IL-10 synthesis based on pathogen form reflect the essential plasticity of host responses towards this organism at different stages of infection.

In addition to macrophages, dendritic cells produce IL-10 in response to Chlamydia. A plasmacytoid dendritic cell subset is especially predisposed to IL-10 production stemming from Chlamydia muridarum elementary body infection (Moniz et al., 2009). Classical dendritic cells, in contrast, fail to make IL-10 during equivalent infection and instead generate Th1-centric responses in vivo. This suggests that the early stimulatory events of dendritic cell activation during C. muridarum infection drive different facets of pathogenesis (Moniz et al., 2009). For example, the shaping of IL-10 suppressive effects by plasmacytoid dendritic cells may influence the role of IL-17 during infection (Bai et al., 2009), which modulates the Th1 developmental activities of dendritic cells when in co-culture with T lymphocytes. Altered dendritic cell populations and subsequent effects on IL-10 may also relate to locational bias in host tissues during chlamydial infection. In this regard, recent findings of divergent Th1 and Th2 responses in distinct areas of the genital tract during chlamydial infection, for example, may reflect local dendritic cell activities and IL-10 effects (Marks et al., 2010).

Notably, NK cells also play a role in the balance of Th cell responses when co-cultured with dendritic cells during C. muridarum infection and exhibit robust responses that could influence pathogenesis (Jiao et al., 2011). In these systems, the triggers of IL-10 may not denote simple bacterial–host receptor interactions but rather, intercellular synergies between host cells that may indirectly modify signalling in defence pathways. Finally, C. pneumoniae was also reported to stimulate IL-10 in a recent study on gingival fibroblasts (Table 1), which has implications for the pathogenesis of chlamydial oral disease.

In terms of protozoan factors that stimulate IL-10 production, numerous recent studies have demonstrated that IL-10 is triggered by Leishmania spp., Plasmodium spp., Schistosoma japonicum, Toxoplasma gondii and Trypanosoma spp. (Table 1). The specific protozoan components that induce the IL-10 in monocytes, macrophages, T lymphocytes and plasma in the host response to these pathogens, however, is not clear. Recent studies on cytokine stimulation in response to Leishmania spp. have focused on candidate vaccines and prophylactic measures to generate Th1-centric inflammatory responses (Bacellar et al., 2000; Murphy et al., 2001). Findings on the immunogenicity of whole cell extracts or protein fractions have indicated induction of IL-10 in macrophages and dendritic cells by Leishmania Eukaryotic Initiation Factor (LeiF) (Skeiky et al., 1995; Probst et al., 1997; Barhoumi et al., 2011) in conjunction with IL-12/Th1 responses. Leishmania infantum LeiF induces variable levels and ratios of IL-10, IL-12 and TNF-α dependent upon the specific antigenic peptide fragment used for stimulation (Barhoumi et al., 2011). Here, the ability of the one protein (i.e. LeiF) to generate opposing cytokine responses may reflect distinct conditions of APC activation, or may indicate limitations of the in vitro testing approach used for these studies. In vivo testing of different peptide fragments would be valuable to investigate these results and provide new insight into the effects of single proteins and peptides on the strength of IL-10 feedback loops within broader Th1 and Th2 cytokine responses. Finally, Th1/Th2 switching through up-regulation of IL-10 was recently shown in Heligmosomoides polygyrus infection in which anti-IL-10R antibody reversed the response and up-regulated inflammation in the intestinal mucosa (Setiawan et al., 2007).

Numerous human viral pathogens have been shown to induce IL-10 in various in vivo studies reported during the past 5 years (Table 1). For viral infections in particular, an intriguing facet of IL-10 mediated immune suppression has become evident from recent observations of cytokine patterns induced by closely related members of the same viral family. Monocytes and macrophages infected with different species of Arenaviridae, for example, exhibit different inflammatory effects dependent upon the viral species traits (Grosseth et al., 2011). This illustrates that, even for viruses that are similar in structure and genome organization, the synthesis of IL-10 occurs distinctly and probably hinges on the conditions of APC activation and T-reg lymphocyte activity. In most cases of viral infection, the suppressive effect of the IL-10 produced during infection towards T lymphocyte and pro-inflammatory cytokine activity is not clearly understood.

Finally, as aforementioned, dendritic cells produce IL-10 in response to a number of microorganisms and microbial components, including Leishmania spp., P. brasiliensis and Human Papilloma Virus (Table 1). One particular class of dendritic cells that secretes abundant IL-10 after exposure to LPS is the so-called tolerogenic CD11c (low)CD45RB(high) subset of naturally occurring dendritic cells (Fujita et al., 2006). These IL-10 responses in dendritic cells, similar to those induced in macrophages after Fc receptor binding to LPS (Pengal et al., 2006), probably help to moderate endotoxaemia and peritonitis during disseminated Gram-negative infections. In terms of the response triggered in dendritic cells specifically, TLRs initiate anti-inflammatory responses via IL-10, which promotes IL-10 production by T-reg lymphocytes and this can down-regulate Th1 responses and suppress
inflammation (Higgins et al., 2003). IL-10 produced from dendritic cells as a result of bacterial binding to CD46, CD47 or CD61 induces T-reg cells to differentiate into Tr1 cells (Groux et al., 1997), which subsequently secrete IL-10 (McGuirk et al., 2002). This causes a down-regulation of T-eff lymphocytes and CMI responses (Price et al., 2005). Responses such as these could therefore prolong infection in circumstances where CMI responses are unable to effectively reduce pathogen numbers during periods of clonal selection and proliferation.

**IL-10 effects on mucosal sIgA**

The pathogenesis of infectious disease at mucosal sites involves sIgA, which forms a key defence mechanism in various infections to protect tissue barriers against microbial invasion (Tsujii et al., 2008). IL-10 has a major regulatory role in the development of sIgA responses. Functionally, sIgA, along with T-reg cells, allows mutualism with normal flora at mucosal sites and mediates Ig-dependent defence in these tissues (Brandtzæg, 2009), which contain most (~70%) of the Ig-producing cells in the body (Mestecky & Russell, 2000). sIgA-producing plasma cells originate from Gut-associated lymphoid tissues (GALT), bronchus-associated lymphoid tissue (BALT) and the nasopharynx-associated lymphoid tissues (NALT) (Mestecky & Russell, 2000). While IgA is predominantly monomeric, in secretions, IgA exists as polymeric or dimers, formed through a receptor-mediated mechanism (Woof & Kerr, 2006). Secretion of dimeric IgA occurs via polymeric immunoglobulin receptors (pIgR) that line mucosal epithelial cells and aid in the delivery of polymeric sIgA to the extracellular milieu. CD4+ T lymphocytes help induce IgA by activating B lymphocytes to proliferate and mature in response to T lymphocyte-derived cytokines including IL-10 and others, namely TGF-β, IL-2, IL-5 and IL-6 (Mega et al., 1992; Salvi & Holgate, 1999). sIgA contributes to antimicrobial defence at the mucosa through various mechanisms, as discussed elsewhere (Woof & Kerr, 2006). sIgA binds to Fc alpha receptors on phagocytes to potentiate microbial uptake, and mediates immune exclusion by inhibiting microbial adherence to mucosal epithelium. It also neutralizes viruses, activates alternative complement, and synergizes with nonspecific antimicrobial effectors in airway secretions to kill pathogenic microorganisms (Salvi & Holgate, 1999).

IL-10 is a potent growth factor for B lymphocytes; when these cells are activated through their antigen receptor or CD40, IL-10, together with IL-2 and IL-4, is the key factor that drives secretion of IgA (and also IgM and IgG) (Defrance et al., 1988; Rousset et al., 1991, 1992). IL-10 up-regulates the expression of IL-2 receptors on B lymphocytes and, when derived from Th2 lymphocytes, stimulates early B lymphocyte activation. In this way, IL-10 affects the proliferation and differentiation of B lymphocytes into plasma cells (Fernandez-Botran et al., 1989; Moore et al., 1990; Vieira et al., 1991; Defrance et al., 1992; Rousset et al., 1992) and stimulates terminal differentiation of IgA-producing plasma cells. IL-10 also complements IL-5-driven developmental effects in B1 (CD5+/Ly-1+) lymphocytes (Noelle et al., 1984; Roehm et al., 1984; Go et al., 1990; Ishida et al., 1992; Flückiger et al., 1993) and, together with TGF-β, stimulates CD40-activated naïve B lymphocytes into isotype switching towards IgA1 and IgA2 production (Salvi & Holgate, 1999).

However, IL-10 displays pleiotropic, suppressive effects towards B lymphocytes and IgA under certain conditions. For example, whereas IL-10 and TGF-β enhance IgA induction in slgD+ B lymphocytes, IL-10 suppresses IgA production in slgD+ B lymphocytes (Defrance et al., 1992). IL-10 has been shown to suppress late B lymphocyte differentiation into Ig-secretory cells (Fiorentini et al., 1989; Go et al., 1990; Moore et al., 1990; Vieira et al., 1991). Activated B lymphocytes that secrete IL-10 may also act to suppress bystander-mediated B lymphocyte activation (Pecanha et al., 1992). This has some similarity to the suppressive effects of IL-10 towards Th1 immune responses where the cytokine alters the environment in which lymphocytes are activated (Fiorentino et al., 1989; Go et al., 1990; Moore et al., 1990; Vieira et al., 1991). Thus, these effects of IL-10 show its complex pleiotropic role in influencing sIgA responses and the related Ig-dependent mechanisms of microbial clearance at mucosal sites. Finally, sIgA may also influence the role of IL-10 itself in antimicrobial defence; in a recent study, mice immunized with recombinant sIgA displayed heightened IL-10 responses in mesenteric lymph nodes and spleen, suggesting that oral immunization promotes IgA switching and increases the production of cytokines systemically that promote the induction of T-eff lymphocytes (Favre et al., 2005).

**Insights into IL-10 function in infection from recent probiotic studies**

Several clinical and experimental studies conducted over the past 5 years have provided vital insight into the role of IL-10 at mucosal surfaces in the context of microbial probiotics. Probiotics comprise live microorganisms, and, taken as dietary nutrition supplements, can enhance anti-inflammatory responses. This has implications for local and systemic immunity against a multitude of mucosal pathogens. Recently, for example, probiotics have been associated with increased resistance to various infections (Reid et al., 2003; Isolauri & Salminen, 2005), inflammatory bowel
delivery of probiotics enhanced protection at mucosal surfaces with up-regulated IL-10 production and CD4+ Foxp3+ T-reg populations. Inhibition of effector T lymphocyte development and down-regulation of IL-12 was noted in this model (Mengheri, 2008; Villena et al., 2009; D’Inca et al., 2011). In another study, probiotics provided therapeutic effects in an experimental inflammatory bowel disease model (Kwon et al., 2010). Results consistent with these findings were more recently reported in human studies (Gad et al., 2011; Rutten et al., 2011). Collectively, data from the probiotic field suggest a critical role of IL-10 in maintaining a balance between immune suppression and pro-inflammatory protective immunity in situations of microbial challenge.

Conclusions

Recent insights into newly discovered microbial triggers of IL-10 have important meaning for antimicrobial defence in the early to mid-stages of various infections because of diverse classes of microorganisms, including protozoa, nematodes, fungi, viruses and bacteria. For future studies, it will be essential to tease apart the mechanisms of production, cellular sources and functional impact of microorganism-triggered IL-10 in these infections. Considering the impact of IL-10 on Ag-specific immunity and the importance of its timing of production at the early stages of infection, the temporal kinetics of IL-10 production will also be useful to measure in appropriately characterized models of infection or in clinical studies. A better understanding of these facets of IL-10 in response to its microbial triggers in the near term will aid in further defining the intriguing nature of this key regulator of immune defence in infectious disease.

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Conflict of interest

All authors have no conflict of interest.

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