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BRIEF REVIEWS

IL-10: The Master Regulator of Immunity to Infection

Kevin N. Couper, Daniel G. Blount,¹ and Eleanor M. Riley²

IL-10 is an anti-inflammatory cytokine. During infection it inhibits the activity of Th1 cells, NK cells, and macrophages, all of which are required for optimal pathogen clearance but also contribute to tissue damage. In consequence, IL-10 can both impede pathogen clearance and ameliorate immunopathology. Many different types of cells can produce IL-10, with the major source of IL-10 varying in different tissues or during acute or chronic stages of the same infection. The priming of these various IL-10-producing populations during infections is not well understood and it is not clear whether the cellular source of IL-10 during infection dictates its cellular target and thus its outcome. In this article we review the biology of IL-10, its cellular sources, and its role in viral, bacterial, and protozoal infections. The Journal of Immunology, 2008, 180: 5771–5777.

It is widely appreciated that many of the severe complications of infection result from excessive immune activation. Therapeutic and preventive strategies to augment immune-mediated clearance of pathogens and infected host cells have, on occasion, directly exacerbated tissue damage and increased mortality (1–3). These studies demonstrate that maximal pathogen control does not necessarily lead to minimal disease and highlight the essential role for immunoregulatory components of the immune response in limiting pathology.

First described as a product of Th2 cells that inhibited cytokine synthesis in Th1 cells (4), IL-10 is now known to be produced by macrophages, dendritic cells (DC),³ B cells, and various subsets of CD4⁺ and CD8⁺ T cells (5, 6). Initially shown to regulate T cell responses, many of the effects of IL-10 on T cell and NK cell function are now known to be indirect, being mediated via a direct effect of IL-10 on monocyte-macrophages. Thus, IL-10 inhibits MHC class II and costimulatory molecule B7-1/B7-2 expression on monocytes and macrophages and limits the production of proinflammatory cytokines (including IL-1 α and β , IL-6, IL-12, IL-18, and TNF- α) and chemokines (MCP1, MCP5, RANTES, IL-8, IP-10, and MIP-2) (reviewed in Ref. 5). Importantly, autocrine IL-10 signaling in DC can inhibit chemokine production and prevent

their trafficking to lymph nodes as shown in mycobacterial infection, leading to the failure to recruit and induce Th1 differentiation of naive T cells (7). Nevertheless, IL-10 can act directly on CD4⁺ T cells, inhibiting proliferation and production of IL-2, IFN- γ , IL-4, IL-5 and TNF- α (5, 8, 9). Thus, IL-10 can directly regulate innate and adaptive Th1 and Th2 responses by limiting T cell activation and differentiation in the lymph nodes as well as suppressing proinflammatory responses in tissues, leading to impaired pathogen control and/or reduced immunopathology.

The role of IL-10 during infection

IL-10 has emerged as a key immunoregulator during infection with viruses, bacteria, fungi, protozoa, and helminths (Table I), ameliorating the excessive Th1 and CD8⁺ T cell responses (typified by overproduction of IFN- γ and TNF- α) that are responsible for much of the immunopathology associated with infections including *Toxoplasma gondii* (1, 10), *Trypanosoma* spp. (2, 11), *Plasmodium* spp. (12, 13), *Mycobacterium* spp. (14), and HSV (15). Thus, as summarized in Table I, ablation of IL-10 signaling results in the onset of severe, often fatal immunopathology in a number of infections including *T. gondii* (1, 10), malaria (3, 16, 17), and *Trypanosoma cruzi* (2). IL-10 by itself and through cooperation with Th1 cytokines (such as IL-12) also regulates Th2 responses (8, 9, 18–20) to prevent the overproduction of IL-4, IL-5 and IL-13, cytokines that can lead to severe fibrosis in, for example, *Schistosoma mansoni* (reviewed in Ref. 21), hepatitis C virus (22), and mycobacterial (23) infections. Amelioration of the allergic Th2 responses that can accompany helminth infections also depends on the induction of IL-10 (24). Nevertheless, excessive or mistimed IL-10 production can inhibit the proinflammatory response to *Plasmodium* spp. (25, 26), *Leishmania* spp. (27–29), *T. cruzi* (30), *Mycobacterium* spp. (31), and lymphocytic choriomeningitis virus (32, 33) to the extent that pathogens escape immune control, resulting in either fulminant and rapidly fatal or chronic non-healing infections. For example, during *Mycobacterium avium* infection very early IL-10 production in BALB/c but not C57BL/6 mice is correlated with the failure of BALB/c mice to control the infection; ablation of IL-10 signaling led to enhanced pathogen control in BALB/c but not C57BL/6 mice, demonstrating the causal relationship between IL-10 and the

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³ Abbreviations used in this paper: DC, dendritic cell; Foxp3, Forkhead box transcription factor 3; Treg, regulatory T cell; nTreg, natural Treg.

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Table I. Immunoregulatory roles of IL-10 during infection^a

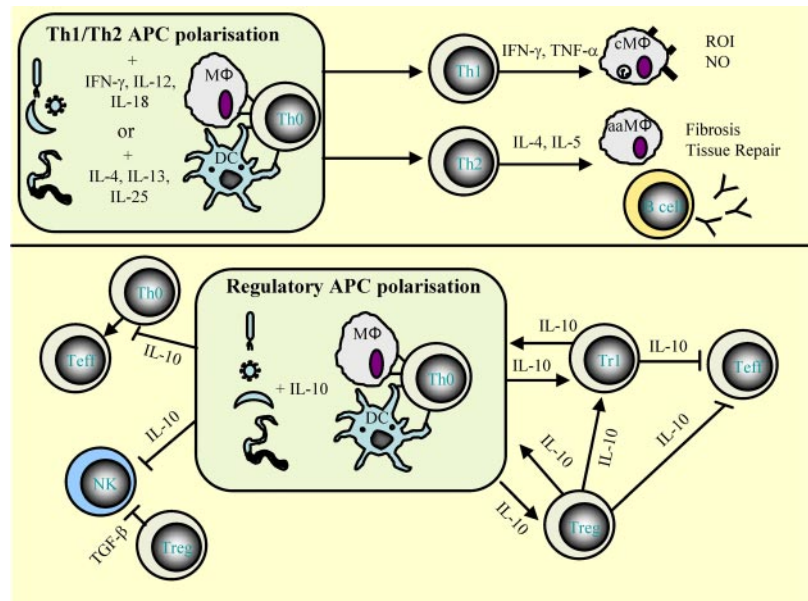
Pathogen	Source of IL-10	Role of IL-10	Effect of Neutralization/Absence	References
Protozoa				
<i>Toxoplasma gondii</i>	Th1, DC, MΦ	Th1, APC suppression; inhibits IL-12, TNF-α, IFN-γ	↑ Immunopathology; ↑ TNF-α, IFN-γ	1, 10, 68, 79
<i>Leishmania</i> spp.	nTreg, Tr-1 Th1, DC, MΦ	Th1 suppression, parasite persistence, memory development; reduced IL-2 and IFN-γ	↑ IFN-γ; ↑ parasite clearance; ↓ memory responses	28, 37, 52, 64, 80, 81
<i>Plasmodium</i> spp.	nTreg, Th1/Tr1, DC, MΦ	Th1 suppression; reduced IL-12 and IFN-γ	↑ TNF-α, IFN-γ; ↑ parasite clearance; ↑ mortality; ↑ immune pathology/CM	3, 16, 17, 26, 82, 83
<i>Trypanosoma cruzi</i>	CD4 T cells, MΦ	Inhibits NO, TNF-α, IL-12 and IFN-γ; reduces pathology; inhibits parasite killing	Severe pathology; ↑ TNF-α, IFN-γ; ↑ parasite clearance	2, 30, 84
Bacteria				
<i>Mycobacteria</i> spp.	T cell, DC	Suppresses MΦ and DC IL-12, NO, TNF-α production	↑ Airway inflammation; ↑ IFN-γ; ↓ bacterial load	7, 31, 85
<i>Listeria monocytogenes</i>	MΦ	Inhibits MΦ bacteria killing	↓ Bacterial load; ↓ Ag specific T cells and memory	86
<i>Helicobacter</i> spp.	nTreg, Tr1	Suppresses Th1 IFN-γ	↓ bacterial load, ↑ colitis	63
<i>Bordetella</i> spp.	DC, Tr-1	Suppresses IL-12 from APC	↑ T cell proliferation; ↑ IFN-γ in vitro	77, 87
<i>Streptococcus pyogenes</i>	Tr1	Suppresses IL-12; induces granzyme B	ND	78
Nematode				
<i>Schistosoma mansoni</i>	nTreg, innate cells	Th2 suppression; Th1 cytokine (IFN-γ) and proliferation suppression; increased CCR8 expression on CD4	↑ Immunopathology (granuloma) and mortality	34, 88
<i>Heligmosomoides polygyrus</i>	DC, T cell (non-Treg)	Suppresses IFN-γ; increases IL-4	↑ IFN-γ; ↓ IL-4; no suppression of <i>Citrobacter rodentium</i> -induced colitis	89, 90
Virus				
HIV	MΦ, CD8 T cell	Suppresses cytolysis and IL-2	↑ Monocyte IL-6, TNF-α and IFN-γ	91, 92
Hepatitis	MΦ, nTreg	Suppresses PBMC IFN-γ and mononuclear IL-12	↑ IFN-γ in vitro; ↓ lesion severity	22, 93
HSV-1	nTreg	Suppresses IFN-γ and IL-2, T cell migration, and Ag-specific T cell numbers	ND	15
LCMV	aTreg, DC	Suppresses TNF-α, IL-2, CTL activity	↓ Lymphopenia; ↑ IFN-γ; ↑ CD8 ⁺ T cells; ↑ viral clearance; ↑ memory	32, 33
MCMV	Th1	Th1 suppression, down-regulation of MHC II	↓ Viral load; ↑ MHCII expression	94, 95
Fungus				
<i>Candida albicans</i>	DC, nTreg	DC induce nTreg; control immunopathology and develop memory	↓ nTreg activation and expansion	53, 96

^a Abbreviations: aTreg, adaptive Treg; CM, cerebral malaria; LCMV, lymphocytic choriomeningitis virus; MΦ, macrophage; MCMV, murine cytomegalovirus; ↑, increase; ↓, decrease.

lack of pathogen control (31). Similarly, in other infections where production of IL-10 correlates with poor pathogen control, experimental ablation of IL-10 or inhibition of IL-10 signaling restores pathogen control and reduces the severity of disease, thereby establishing a direct correlation between inappropriate IL-10 production and disease severity. Conversely, ablation of IL-10 signaling during normally benign infections may augment proinflammatory responses, enhancing pathogen control at the considerable cost of more severe immunopathology (1–3, 17, 34). However, it is often not clear whether high concentrations of IL-10 during virulent infections are a cause or a consequence of high pathogen burdens. In the former case, IL-10 would directly inhibit pathogen clearance (and may be induced by the pathogen to promote its

own survival). Thus, transgenic overexpression of IL-10 (under control of the MHC II promoter) in APC leads to uncontrolled pathogen growth in *Leishmania major*, *Listeria monocytogenes*, and *M. avium* infections (35, 36). In the latter case for example, where the pathogen is able to resist clearance by normally effective mechanisms, IL-10 may be produced to reduce inflammation and thereby minimize pathology. For instance, during virulent infection with the SD strain of *L. major*, high pathogen loads drive excessive Th1 responses (27) and these, in turn, promote the development of self-limiting adaptive IL-10-producing T cells that dampen down Th1 responses, (28, 37), establishing a positive feedback loop whereby T cell-derived IL-10 further inhibits anti-microbial immune responses, allowing fulminant

FIGURE 1. The sources and targets of IL-10 during infection. Interactions between pathogens and APC direct the development of Th1, Th2, or Treg populations depending on the cytokine environment and the level of costimulation. APC promoting regulatory responses are induced by priming under regulatory conditions (often involving IL-10 signaling) or as a result of direct modulation of their functions by the pathogen. IL-10 may act in an autocrine manner to suppress APC proinflammatory responses, may act directly on effector T cells to limit their proliferation and function, or may promote the differentiation of naive T cells into regulatory populations. Adaptive and natural regulatory T cells may then directly influence macrophage (MΦ), DC, and effector T cell differentiation and effector functions via IL-10-dependent mechanisms. aaMΦ, Alternatively activated macrophage; cMΦ, classical macrophage; ROI, reactive oxygen intermediate.



and inevitably fatal infections to develop. In such cases, IL-10 concentrations often “track” pathogen burdens and systemic IFN- γ concentrations (25, 27, 38).

Taken together, these studies indicate that resolution of infection requires a coordinated response in which initial proinflammatory mechanisms clear the pathogen and are then downmodulated by IL-10 before pathology occurs. Thus, the timing as well as the relative amounts of proinflammatory and anti-inflammatory cytokine production are critical for safe resolution of infection.

Sources of IL-10 during infection

It is evident that IL-10 can be produced by many different myeloid and lymphoid cells and that more than one population of IL-10-producing cells may be induced during a single infection (Table I and Fig. 1). The complexity of IL-10 responses, together with inconsistencies in the nomenclature for regulatory T cell (Treg) populations (natural Treg (nTreg), Tr1, Th3, adaptive Treg, IL-10-producing T cells) and the paucity of markers to differentiate them, has resulted in considerable confusion in the published literature regarding the role of particular cell populations during specific infections. Hopefully, new tools such as IL-10-GFP reporter mice (6) will allow many of these inconsistencies to be resolved.

Dendritic cells

Ligation by pathogens of pattern recognition receptors on DC typically causes activation of the DC and cytokine release, leading to the development of Th1 or Th2 effector cells. However, under certain conditions (typically following exposure to IL-10 or TGF- β) DC can initiate the development of Treg that limit these effector responses (39, 40). Myeloid DC are a particularly potent source of IL-10 after TLR-9 ligation (41), and a naturally occurring population of tolerogenic CD11c^{low}CD45RB^{high} DC has been identified that produces copious amounts of IL-10 in response to LPS stimulation and can prevent experimental endotoxemia and bacterial peritonitis (42). Thus, the specific DC populations driven to IL-10 production likely depend on the precise na-

ture of the pathogen-associated ligand and the patterns of expression of its receptors among DC.

Although IL-10 from DC may protect hosts from immunopathology, for example during *Chlamydia* spp. infections in which CD8⁺ DC inhibit Th2 cell activation through ICOS- and IL-10-dependent mechanisms, thereby preventing allergic responses (43), and during *Bordetella pertussis* infection where TLR-4 signaling on DC promotes the development of IL-10 producing Treg cells that limit lung pathology (44), the modification of DC (and macrophage) signaling pathways to minimize the induction of antimicrobial effector mechanisms is an immune-avoidance strategy that has been exploited by all classes of pathogens. For instance, CD8⁺ DC are a potent source of IL-10 during lymphocytic choriomeningitis virus infection, directly inhibiting viral control (33). Similarly, modulation of TLR-2 signaling by *S. mansoni* lysophosphatidylserine and by *Mycobacterium tuberculosis* can lead to DC production of IL-10 and the induction of IL-10-secreting Treg that inhibit effector T cell activity and reduce parasite control (45, 46). In the case of *M. tuberculosis*, IL-10 production can be blocked (without reducing protective IL-12 responses) by inhibiting TLR-2 function (46). During malaria infection, however, IL-10 provides a sensitive, protective homeostatic mechanism; interactions between parasitized cells and CD8⁺ DC drive a coordinated switch from Th1 to Th2 and IL-10 responses (47, 48) that allow timely control of infection, amelioration of pathology, and secretion of Abs that protect against reinfection. Sustained triggering of TLR-4 or TLR-9 leads to TLR tolerance (47) and, as with repeated administration of LPS, IL-10 appears to induce the differentiation of adaptive Treg (49, 50).

Macrophages

Macrophages are potent antimicrobial effector cells that can participate in both proinflammatory (classical) and fibrotic (alternatively activated) responses (51). Consequently, it is not surprising that pathogens have evolved mechanisms to subvert macrophage function or that macrophages are a major source of IL-10 during infection. A population of “regulatory” macrophages has been identified, at least in vitro, characterized by the

production of IL-10 following Fc receptor ligation by immune complexes or IgG-coated *Leishmania* amastigotes (51, 52). IL-10 is also induced in macrophages in vitro following either CD40 ligation or CpG stimulation (41), and modulation of macrophage TLR-2 signaling during *Candida albicans* (53) infection or following exposure to *Yersinia* spp. V protein (54) has been shown to drive IL-10 production, leading to the induction of Treg (53) and impaired pathogen control. Importantly, macrophage-derived IL-10 can inhibit differentiation of neighboring cells into classically activated macrophages, allowing the macrophage population to be self-regulating (55).

The power of the macrophage IL-10/STAT-3 pathway to facilitate pathogen survival and, thus, the evolutionary advantage conferred by being able to exploit it, is clearly illustrated in toxoplasmosis and mycobacterial infection. Macrophage-derived IL-10 inhibits the apoptosis of *M. avium*-infected cells, facilitating pathogen survival by maintaining the reservoir of infected cells (56). More remarkably, *T. gondii* can directly activate STAT-3, bypassing any need to induce IL-10 (57); the downstream effects, i.e., inhibition of IL-12 and TNF- α production, are however identical with those of IL-10, and this subversion of macrophage function likely leads directly to enhanced parasite survival and replication.

Regulatory T cells

Natural Treg are constitutively produced in the thymus and express very high levels of CD25. They require IL-2 for both their maintenance in the periphery and for the production of IL-10 (58, 59); their suppressive function is linked to the expression of Forkhead box transcription factor 3 (Foxp3) (60). First described for their role in preventing autoimmune disorders, nTreg can prevent immunopathology in all types of infections (reviewed in Refs. 61 and 62). Although the means by which nTreg regulate inflammation appears to vary between infections (reviewed in Ref. 62), their ability to secrete IL-10 has been implicated in numerous diseases (Table I). IL-10-producing nTreg have been implicated in maintaining the balance between pathogen elimination and immunopathology in viral infections, including HSV-induced stromal keratitis (15), helminth (e.g., *S. mansoni*; Ref. 34), bacterial (e.g., *H. hepaticus*; Ref. 63), and fungal (e.g., *C. albicans*; Ref. 53) infections. During *L. major* infection the ability of nTreg to limit antiparasitic effector responses (leading to persistent low level infection) is in part IL-10 dependent (64), and ablation of IL-10 is required to fully eliminate the parasites. Interestingly, these all tend, in immunocompetent individuals, to be rather slowly developing but persistent infections.

By contrast it is becoming apparent that, in the rapidly reproducing, virulent infections associated with highly proinflammatory immune responses, nTreg may be unable to effectively regulate the immune response and adaptive Treg, which are generated in the periphery during an immune response, tend to act in an Ag-specific manner (reviewed in Ref. 65), and do not necessarily express Foxp3 or CD25, may be more important in preventing immune-mediated pathology. Several populations of adaptive Treg have been defined: IL-10-producing Tr1 cells (66), TGF- β -producing Th3 cells (67), a number of populations of regulatory CD8⁺ T cells (defined by surface expression of CCR7, CD122, or lack of CD28) that produce IL-10 and/or TGF- β (reviewed Ref. 65), and Th1 cells that coproduce IL-10 and IFN- γ (28, 37, 68). Tr1 cells do not make

IL-4, differentiating them from Th2 cells that produce both IL-4 and IL-10 (66). TGF- β , but not IL-10, is required for the development of Foxp3-negative Tr1 cells (69). Recent studies have begun to unravel the pathways leading to IL-10 production by different T cell populations and it is becoming clear that some proinflammatory cytokines directly induce IL-10, allowing immune responses to be inherently self-regulating. Thus, IL-27 and IL-6 (both amplified by TGF- β) promote IL-10 production by Tr1, Th1, Th2, Th17, and CD8⁺ T cells in a STAT3- and STAT1-dependant mechanism (70–73), and IL-12 and IL-23 prime CD4⁺ and CD8⁺ T cells for IL-10 production (74–76), suggesting that the IL-12 family of cytokines (IL-12, IL-23, and IL-27) is indeed self-regulating.

One of the first descriptions of Tr1 cells was in *B. pertussis* infection in which bacterial filamentous hemagglutinin (binding to CD61 (integrin β_3) and CD47 (integrin-associated protein) on myeloid DC caused them to produce IL-10 that, in turn, induced differentiation of adaptive Treg (77). Tr1 cells are also induced during *Streptococcus pyogenes* infection; in this case the bacterial virulence proteins M5 and M22 interact with CD46 on the CD4⁺ T cell, inducing secretion of IL-10 and bystander suppression of effector T cells (78). IL-10-producing Th1 cells have been identified during *T. gondii* and virulent *L. major* infections, which are characterized by particularly strong inflammatory responses and high parasite burdens (37, 68), suggesting that development of IL-10-producing Th1 cells may be correlated with the extent of Th1 cell activation and/or the concentration of proinflammatory cytokines. The finding that IL-12 and IL-23 promote IL-10 production by T cells in a dose-dependent manner (75, 76) offers a mechanism by which this might occur.

Concluding remarks

Irrespective of the source of IL-10, its effects are similar in all of the infections that have been studied: IL-10 suppresses macrophage and DC function, thereby limiting Th1 and Th2 effector responses (Table I). Nevertheless, the impact of IL-10 is clearly determined by the timing and site of its production, and these are both likely to be affected by which cells are making IL-10. Moreover, because IL-10 production by one cell population can affect the ability of other cells to make IL-10, there is the potential for IL-10-producing cells to regulate each other. The picture that is emerging is that in infections of low to moderate virulence, i.e., inducing commensurately low to moderate inflammatory responses, IL-10 from DC or macrophages drives the production of IL-10 by nTreg, preventing pathology but allowing long-term escape of pathogens from immune control and giving rise to persistent (typically asymptomatic) infections; examples include *C. albicans* and mycobacterial infections. Alternatively, in highly virulent infections giving rise to strong proinflammatory responses, IL-10 production from larger populations of induced (adaptive) Treg seems to be required to minimize pathology during the resolution phase of the infection; the ability of Th1 cells to coproduce IL-10 and IFN- γ may favor simultaneous pathogen clearance and suppression of downstream pathologies; examples include *T. gondii*, malaria, and leishmaniasis (17, 37, 64, 68). We postulate that the strength of the regulatory IL-10 response reflects the strength of the preceding inflammatory response (i.e., IL-6, IL-12, IL-23, and/or IL-27 levels) and that IL-10 from nTreg

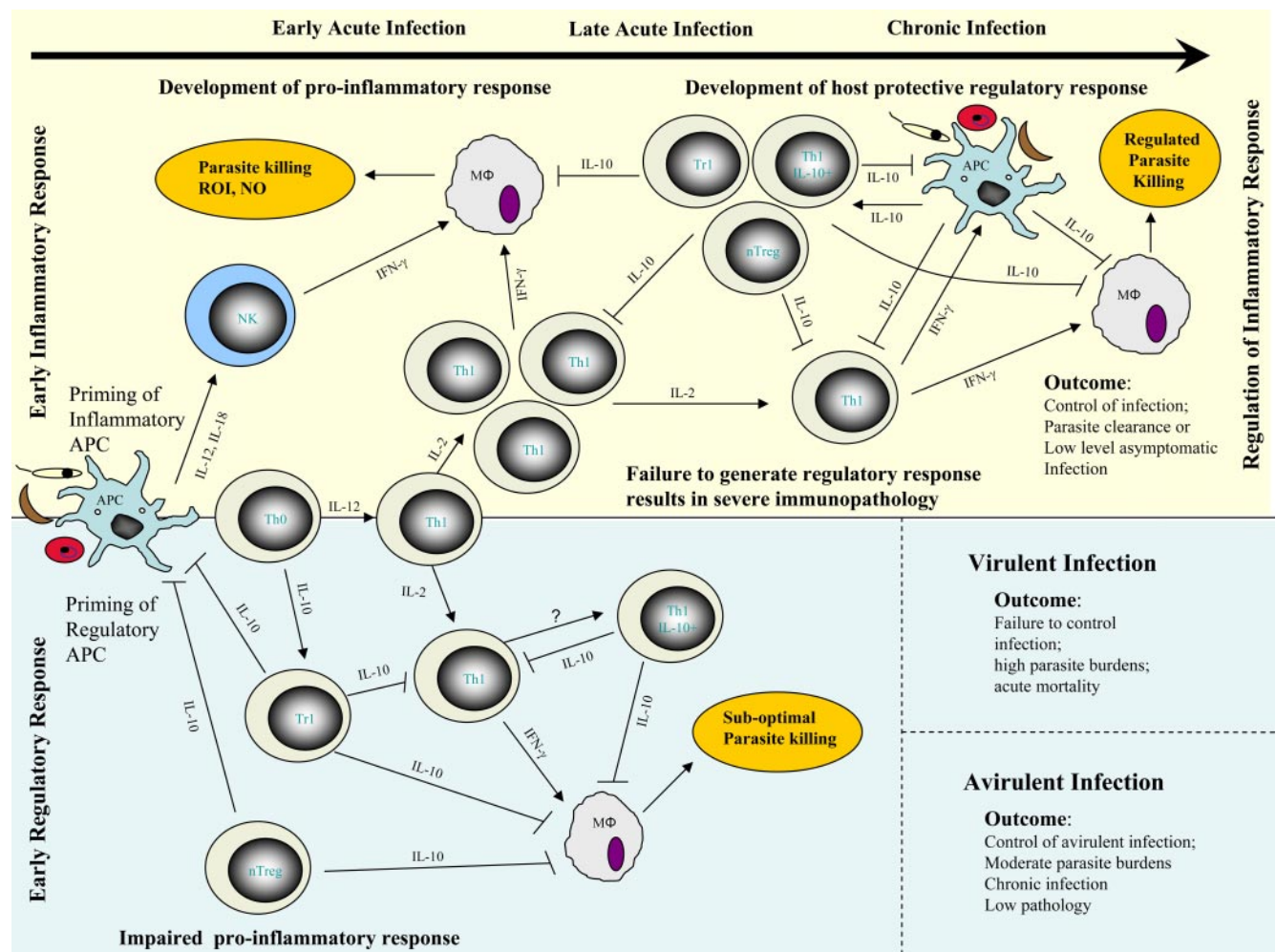


FIGURE 2. The source, timing, and magnitude of IL-10 production determines the outcome of protozoan infections. Early priming and polarization of proinflammatory immune responses are crucial for the effective control of protozoal infection. Proinflammatory cytokine production by APC after interaction with pathogens and the subsequent activation of NK cells and Th1 cells are required to activate macrophages (MΦ) to eliminate microbes. Regulatory DC and macrophages and/or regulatory T cells (Tr1, IL-10-Th1, and nTreg) must then control inflammation to prevent immune-mediated pathology. By contrast, early polarization toward regulatory, IL-10-producing APC populations inhibits inflammation. In the case of avirulent infections, this will allow the pathogen to persist in the absence of tissue damage. In the case of virulent infections, this leads to uncontrolled pathogen dissemination and death. ROI, Reactive oxygen intermediate.

alone is insufficient to counter the very high levels of inflammation associated with virulent infections. Irrespective of the source of IL-10 (nTreg or Tr1), its production is of potential benefit to both the host (limiting pathology) and the pathogen (allowing persistent infection and thereby favoring onward transmission). However, if the source and thus the timing of IL-10 secretion are inappropriate, i.e., produced too early during a virulent infection or too late during an avirulent infection, overwhelming infection or severe tissue damage, respectively, will result (Fig. 2).

The Th1:Th2 paradigm of immunity to infection in which Th1 cells were regarded as proinflammatory and Th2 cells were regarded as anti-inflammatory has undergone a major realignment in the last 10 years and, as in the development of the original paradigm, studies of infection have been crucial to this process. Depending on the nature of the infectious agent, both Th1 and Th2 cells are now known to mediate inflammation and tissue damage as well as pathogen killing. Anti-inflammatory functions, in contrast, are now known to rest with populations of regulatory cells that may be myeloid or lymphoid in origin and can include fully mature, classical Th1 or Th2 cells that

produce IL-10 as a negative feedback mechanism to limit their own response. More than any other cytokine, IL-10 is an essential component of this regulatory response in almost all infections. Therapeutic strategies augmenting IL-10 to reduce host injury during infection must therefore be combined with effective antimicrobials to ensure that the underlying problem, the pathogen, is eliminated. Similarly, adjuvant therapies designed to block IL-10 or components of its signaling pathway in order to augment the effects of antimicrobial drugs or vaccines need to be applied with care, because they may have unintended side effects.

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Disclosures

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