THE LANCET INFECTIOUS DISEASES

Review

The two faces of interleukin 10 in human infectious diseases

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Resolution of infections depends on the host's ability to mount a protective immune response. However, an exacerbated response to infections may result in deleterious lesions. Consequently, immunoregulatory mechanisms are needed to control immune response and prevent infection-associated lesions. Interleukin 10 may be a major regulator of innate and adaptive immunity in vitro and in animals, but its role in human infections is still unclear. Review of the published work reveals wide involvement of interleukin 10 in two major features of infectious diseases. On one hand, interleukin 10 prevents the development of immunopathological lesions that result from exacerbated protective immune response to acute and chronic infections. On the other hand, it is critically involved in persistence of bacteria and viruses by interfering with innate and adaptive protective immunity. Moreover, infections induce the expansion of interleukin-10-producing regulatory cells that are involved in protection against allergic diseases.

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Introduction

Resolution of infections depends on the host's ability to mount a protective immune response mainly based on the recruitment of immunocompetent effectors and the establishment of immune memory. When immune response is impaired, as exemplified by primary and secondary immunodeficiencies, infections are no longer controlled. However, exacerbated responses to infectious diseases induce tissue or systemic lesions, which may be deleterious to the patient. In other words, immunoregulatory mechanisms are necessary to shape the amplitude of immune response and to prevent infection-associated lesions. Interleukin 10 is a critical immunoregulatory molecule. It is a member of an expanding family consisting of cellular and viral cytokines. Its cellular version is produced by myeloid cells, B cells, and as more recently reported, by regulatory cells. Many bacteria, viruses, parasites, or their products are able to stimulate production of interleukin 10 by host cells. Viral versions of the molecule are believed to act as a molecular decoy leading to immune evasion. Interleukin 10 acts as a multifunctional cytokine in human infectious diseases. By disarming innate as well as adaptive responses, it creates favourable conditions for the persistence of microbes and chronic infectious diseases. However, controlling the immune response is also important because it prevents reactivity to self-antigens and attenuates exaggerated immune response that can lead to deleterious tissue lesions. Although much research has described the regulatory effects of interleukin 10 in vitro and in animal models of infection, its role in clinical situations has yet to be elucidated. Our purpose is to provide new insight into the role of interleukin 10 in primary and secondary infections through analysis of clinical situations.

Structure, production, and functions

Interleukin 10 belongs to the class II family of α-helical cytokines that is composed of the type I interferons, interferon γ, and interleukin 10. The main structural feature is a left-handed anti-parallel four-helix bundle.[1,2] The cellular subfamily of the molecule includes interleukin 10, initially described as cytokine synthesis inhibitory factor, and five paralogues named interleukins 19, 20, 22 (interleukin-10-related T cell derived inducible factor), 24 (melanoma differentiation-associated antigen 7), and 26 (AK155).[1,3] The viral interleukin 10 subfamily includes interleukin 10 found in the Epstein-Barr virus genome,[4] and seven members present in large DNA viruses (herpesvirus and poxvirus).[3] Classification of the interleukin 10 family is based on sequence analysis and three-dimensional structure of human interleukin 10 and Epstein-Barr viral interleukin 10. Members of this family have sequence identities with human interleukin 10 ranging from 80% (Epstein-Barr viral homologues, equine herpesvirus 2, and ovine parapoxvirus) to 20% (cytomegalovirus viral homologues, Yaba-like disease virus, and human cellular paralogues).[3]

Human interleukin 10 is a protein of 160 aminoacids with a molecular weight of 18·5 kDa that exists as a 37 kDa homodimer. It is produced by alternatively activated macrophages,[5] dendritic cells, and B lymphocytes. Naturally occurring CD4+ regulatory T cells (Tregs), which express membrane CD25 and the transcriptional repressor FOXP3 (forkhead box P3),[6,7] and antigen-specific inducible Tregs, which do not express CD25 until they are activated through the T-cell receptor, are an important source of interleukin 10.[7,8] Production of interleukin 10 is regulated at translational and transcriptional levels.[9] Different polymorphisms have been found in the 5′ region of the human interleukin 10 gene. They include two repeat microsatellite polymorphisms (1·2 kb and 4 kb upstream of the transcriptional start site) and three point mutations (at –1082 [G/A], –819 [C/T], and –592 [C/A]).[9] The interleukin 10 genotype and functional response are related. Indeed, the –1082 [G] point mutation is associated with increased production of interleukin 10 in T cells and monocytes.[10] The receptors of α-helical cytokines are composed of an extracellular binding module, a membrane spanning helix, and an intracellular domain. Two subunits are needed to generate a functional receptor complex. It is interesting to note that the interleukin 10 receptor (10R) complex is structurally analogous to the interferon-γ-receptor complex. Moreover, the receptor and ligand complexes of interleukin 10 and interferon γ, respectively, have similar quaternary structures.[2] The

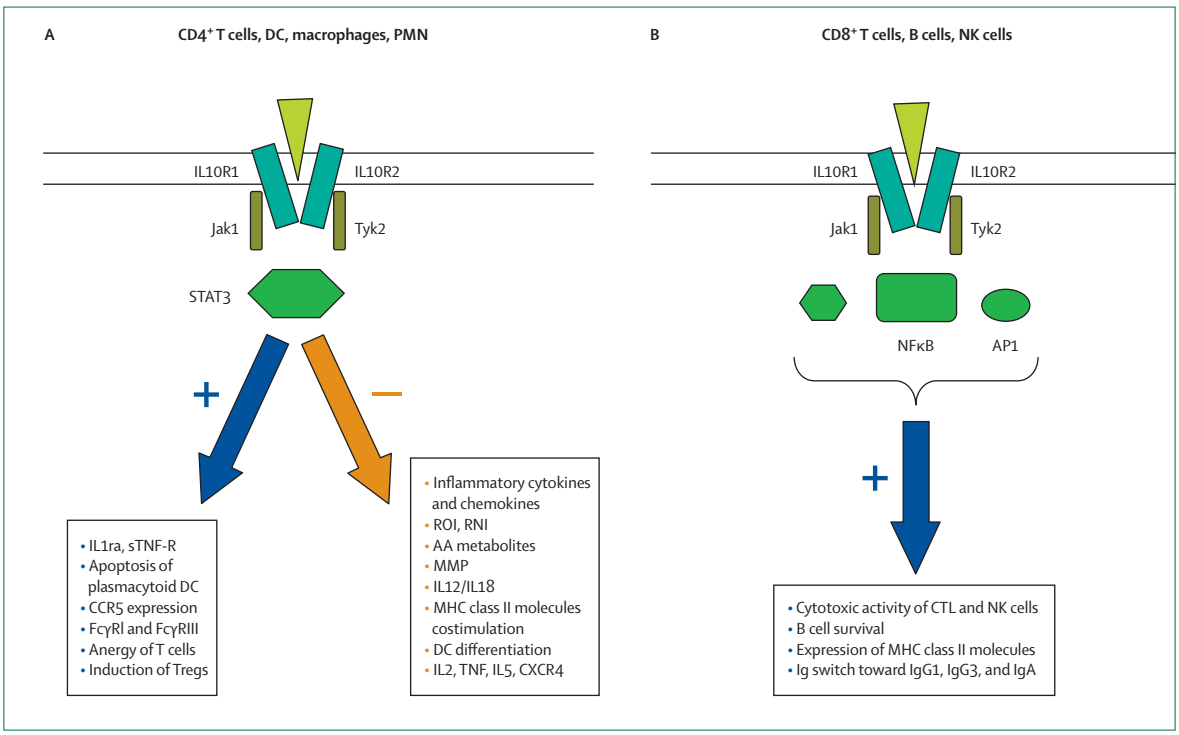

Figure 1: **Immunoregulatory and stimulatory effects of interleukin 10**
(A) Viral and mammalian interleukin 10 interacts with interleukin 10R (IL10R) expressed on monocytes, macrophages, dendritic cells, CD4+ T cells, and polymorphonuclear neutrophils (PMN). STAT3 is the transcriptional factor largely involved in the inhibitory action of interleukin 10 including the inhibition of NFκB. Interleukin 10 inhibits numerous inflammatory and antigen-presenting functions and stimulates other responses in immune cells. (B) Viral and mammalian interleukin 10 interact with CD8+ T cells, B cells and NK cells, in which they stimulate NFκB and AP-1. This leads to cytotoxic activity of CD8+ T cells and NK cells, and to B cell activation. AA=arachidonic acid. DC=dendritic cell. MMP=matrix metalloproteinases. RNI=reactive nitrogen intermediates. ROI=reactive oxygen intermediates.

molecules of the interleukin 10 family interact with the interleukin 10R, which consists of interleukin 10R1 (ligand-binding subunit) and interleukin 10R2 (accessory subunit for signalling).[3] The interaction of interleukin 10 with its receptor engages Jak1 and Tyk2, which mainly activate STAT3, the common transcription factor downstream of interleukin 10–interleukin 10R that mediates most inhibitory actions of interleukin 10 upon innate and adaptive immune responses.[1,3]

Interleukin 10 is a major regulator of innate immunity (figure 1). It interferes with the production of inflammatory mediators by polymorphonuclear neutrophils, monocytes, and macrophages as well as upregulating the expression of molecules that amplify the anti-inflammatory effect of interleukin 10.[9] This anti-inflammatory role is illustrated by interleukin-10-deficient mice that develop chronic inflammatory bowel disease owing to an inappropriate innate immune response to intestinal bacterial antigens.[11] Interleukin 10 regulates adaptive immune responses through its effects on antigen-presenting cells and T cells. In antigen-presenting cells, interleukin 10 inhibits production of interleukin 12 and interleukin 18, as well as reducing expression of MHC class II molecules and co-stimulatory molecules.[9] Additionally, interleukin 10 impairs differentiation of monocyte-derived dendritic cells, induction of apoptosis in plasmacytoid dendritic cells, and alters the migration of dendritic cells by modulating surface expression of chemokine receptors.[9] Interleukin 10 directly affects the function of CD4+ T cells by inhibiting the expression of interleukin 2, tumour necrosis factor (TNF), interleukin 5, chemokine receptor CXCR4, and the response to stromal cell-derived factor-1. Activation of T cells in the presence of interleukin 10 can induce non-responsiveness or anergy that cannot be reversed by interleukin 2 stimulation.[12] Microarray experiments show that interleukin 10 is a potent stimulator of natural killer (NK) cells as well as CD8+ cytotoxic T cells (CTL).[13] It is interesting to note that interleukin 10 activates NFκB and AP-1 in CD8+ T cells but inhibits them in monocytes and CD4+ T cells.[9] Interleukin 10 also stimulates murine and human B cells by enhancing the expression of MHC class II molecules and increasing survival. Interleukin 10 is a switch factor for IgG1 and IgG3, whereas transforming growth factor β is a switch factor for IgA1 and IgA2. Interleukin 10 restores IgA production by B cells from patients with IgA deficiency activated by anti-CD40 antibodies.[9] The effect of interleukin 10 is probably mediated by dendritic cells and macrophages via the expression of CXCL-13, which recruits and activates B cells, and SLAM (signalling lymphocytic activation molecule), a B cell activator.[14] This effect on B cells may account for the presence of high

circulating levels of antibodies including IgA associated with overproduction of interleukin 10 in clinical situations.

Susceptibility to primary infections

Interleukin 10 increases host susceptibility to numerous intracellular microorganisms such as *Mycobacterium bovis* (Calmette-Guérin bacillus) and environmental mycobacteria (*Mycobacterium avium*) in animal models because reducing the amount of interleukin 10 improves resistance to infection and increasing it impairs resistance to infection. These findings have been exhaustively reviewed (table 1).[9] Interleukin 10 increases host susceptibility to extracellular bacteria such as *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* in models of primary infections.[38,39] It has a complementary role to interleukin 4, another macrophage-deactivating cytokine, in the increased susceptibility of mice to murine leishmaniasis. By contrast, interleukin 10 decreases the susceptibility to prion diseases probably through downmodulation of inflammatory cytokines that seems to be essential for initiating disease.[65]

	Infectious disease	Human beings (with key approach)	Mouse model (with key approach)
M bovis	Mycobacterial infection	..	KO mice[15,17,18] mAb to interleukin 10R[16]
M avium	Opportunistic infections	Circulating interleukin 10, interleukin 10 production[19]	mAb to interleukin 10[20,21] Human interleukin 10 overexpression[22]
Mycobacterium tuberculosis	Tuberculosis	Interleukin 10 production in lesions[23] Interleukin 10 production and SLC11A1 gene polymorphism[25] Polymorphism of interleukin 10 gene[27–29] Interleukin 10 production[30,32] Circulating interleukin 10[31]	*KO mice[24,26]
Mycobacterium leprae	Leprosy	Interleukin 10 production in lesions[33] Interleukin 10 production[34] Polymorphism of interleukin 10 gene[35,36]	..
Mycobacterium ulcerans	Buruli ulcer disease	Interleukin 10 production in lesions[37]	
Klebsiella pneumoniae, *Streptococcis pneumoniae*, *Pseudomonas aeruginosa*	Pneumonia	..	mAb to interleukin 10[38] mAb to interleukin 10[39] mAb to interleukin 10[40]
Neisseria meningitidis	Meningococcal disease	Polymorphism of interleukin 10 gene[41,42]	
Listeria monocytogenes	Listeriosis	..	mAb to interleukin 10[43] Interleukin 10 administration[44] KO mice[45,46]
Chlamydia trachomatis	Venereal lymphogranulomatis, trachoma	Polymorphism of interleukin 10 gene[47]	KO mice[48]
Leishmania major, *Leishmania mexicana* *Leishmania aethipica*	Cutaneous leishmaniasis	Interleukin 10 production[49] Interleukin 10 production in lesions[51]	KO mice[50] KO mice[52] Treg transfer[53] Tregs[54] KO mice, anti-interleukin 10 mAb[55] KO mice[56] Tregs (review)[57] KO mice[58]
Leishmania donovani	Visceral leishmaniasis	Interleukin 10 production[59,60]	Treg cells (review)[57]
Toxoplasma gondii	Toxoplasmosis	..	KO mice[61]
Aspergillus fumigatus	Aspergillosis	..	KO mice[62]
Cryptococcus neoformans	Cryptococcosis	..	KO mice[63]
Candida albicans	Candidosis	..	KO mice[62]
Epstein-Barr virus	Infectious mononucleosis, lymphoma	Polymorphism of interleukin 10 gene[64]	..
Prion	Prion disease	..	KO mice[65]

*Susceptibility of mice to *M tuberculosis* does not depend on interleukin 10. mAb=monoclonal antibodies. KO=knockout.

Table 1: **Role of interleukin 10 in susceptibility to primary infections**

Besides oversimplification of animal studies, the role of interleukin 10 in susceptibility to infectious diseases is questionable, especially in mycobacterial infections (table 1). It seems to be associated with increased susceptibility to infections caused by fast growing mycobacteria. Production of interleukin 10 is increased in monocytes stimulated by *M avium* from patients infected with HIV and the highest production is in patients with advanced AIDS.[19] In Buruli ulcer disease, caused by *M ulcerans*, production of interleukin 10 is increased and levels are higher in patients with ulcers than in patients with nodules.[37] In infections caused by slow growing mycobacteria, interleukin 10 is one factor in the increased susceptibility to disease. Interleukin 10 production is higher in patients with active tuberculosis than in tuberculin skin test responders. It is higher in tissues from patients with lepromatous leprosy than in patients with tuberculoid leprosy, reflecting Th2 polarisation.[33] However, interleukin 10 production is also increased in pleural fluid cells from patients with tuberculous pleuritis where prognosis is favourable and the immune response is skewed toward a Th1 response.[23] Genetic studies show that in the general population, tuberculosis and leprosy are associated with genetic polymorphisms (HLA-DR2; SLC11A.1, formerly NRAMP-1) and with susceptible loci.[66] In patients with pulmonary tuberculosis who carry allele 2 of SLC11A.1, interleukin 10 production is increased.[25] An association between tuberculosis susceptibility and polymorphisms at position –1082 in the interleukin 10 gene has been reported in Cambodian patients, but not in Spanish or Gambian patients.[27–29] Interleukin 10 is one candidate for the increased susceptibility to leishmania. Interleukin 10 is not expressed in the skin of patients with cutaneous leishmaniasis that exhibit self-healing lesions, but is expressed in dermis and epidermis from patients with

	Infectious disease	Human beings	Animal model
M tuberculosis	Tuberculosis	Interleukin 10 production (review)[67] Interleukin 10 production[68,70]	KO mice (review)[67] Interleukin 10 overexpression[69] Interleukin 10 production[71]
M leprae	Leprosy	Interleukin 10 production in lesions[33]	..
Coxiella burnetii	Q fever	Interleukin 10 production[72,73,75] In-vitro model[74]	..
Bartonella quintana	Bacteraemia	Interleukin 10 production[76]	..
Helicobacter pylori	Gastritis, ulcer, carcinoma	Polymorphism of interleukin 10 gene[77,78]	..
L major *Leishmania amazonensis* *Leishmania braziliensis* *Leishmania guyanensis* *L mexicana*	Cutaneous leishmaniasis	Interleukin 10 production[79,82] Interleukin 10 production in lesions[80]	KO mice[58,81,83] Tregs, mAb to anti-interleukin 10R[84]
L donovani	Visceral leishmaniasis	..	Treg cells[53] KO mice, interleukin 10 overexpression[85] Viral interleukin 10 administration[86]
Schistosoma mansoni	Schistosomiasis	Interleukin 10 production[87]	Interleukin 10 production[88]
Onchocercas volvulus	Onchocerciasis (river blindness)	Interleukin 10 production[89] Tregs[90]	..
Epstein-Barr virus	Mononucleosis syndrome	Tregs[91] Interleukin 10 production[92]	..
Epstein-Barr virus	Lymphomas	mAb to interleukin 10[93] Interleukin 10 production[95,96]	Interleukin 10 production[94]
Cytomegalovirus	Cytomegalovirus infection	Interleukin 10 production, viral interleukin 10[97] Viral interleukin 10[98,99]	..
Hepatitis C virus	Viral hepatitis	Polymorphism of interleukin 10 gene[100–103]	..
Hepatitis B virus	Viral hepatitis	Interleukin 10 production[104,105]	..
Friend retrovirus	Retroviral infection	..	Tregs[106]
HIV	AIDS	Polymorphism of interleukin 10 gene[107] Circulating interleukin 10[108] Interleukin 10 production[109,110]	..
HIV	Lymphomas	Circulating interleukin 10[111] Polymorphism of interleukin 10 gene[112]	..

Table 2: **Role of interleukin 10 in microbial persistence**

non-healing leishmaniasis.[49,51] Visceral leishmaniasis, the most severe clinical form of the disease, is associated with parasite replication in peripheral tissues, defective delayed-type hypersensitivity, and increased amounts of interleukin 10 transcripts in bone marrow.[59,60]

By contrast with mycobacterial and leishmanial infections, the role of interleukin 10 in meningococcal disease, in which inflammatory response is crucial for the prognosis, is unambiguous. The poor prognosis is associated with high amounts of interleukin 10. Families with high interleukin 10 production have increased risk for fatal meningococcal disease, which is potentiated by low TNF production.[41] The outcome of meningococcal disease is associated with interleukin 10 gene polymorphisms at position –1082.[42] In conclusion, if the role of interleukin 10 seems to be critical in susceptibility or resistance in animal models of infection, the analysis of clinical situations reveals a dispensable role of the molecule. It is likely that polarisation of the immune response is more critical than immunomodulation of committed immune effectors.

Microbial persistence and evolution of infectious diseases

Interleukin 10 is clearly involved in the persistence of bacteria in hosts via the induction of an anergic state and, consequently, in the evolution of infectious diseases. By contrast with its role in susceptibility, numerous clinical reports support the role of interleukin 10 in the evolution of infectious diseases (table 2). One example is Q fever, an infectious disease due to *Coxiella burnetii*. Q fever is characterised by a primary infection that is often asymptomatic and may become chronic in patients with valvulopathy or immune disorders.[113,114] We have provided evidence that the development of the disease depends on interleukin 10. Indeed, interleukin 10 is overproduced by monocytes from patients with Q fever endocarditis and those from patients with acute Q fever and valvulopathy.[72] The risk associated with developing Q fever endocarditis, the major manifestation of chronic Q fever, is related to interleukin 10 overproduction.[73] Interleukin 10 interferes with macrophage activation by specifically stimulating replication of *C burnetii* by decreasing the production of TNF[74] and blocking phagosomal maturation. Phagosomes that contain *C burnetii* fuse with lysosomes in monocytes from patients with acute Q fever; however, these phagosomes are unable to fuse with lysosomes in monocytes from patients with Q fever endocarditis. Neutralising interleukin 10 corrects defective phagosome-lysosome.[75] Furthermore, interleukin 10 probably interferes with granuloma formation, which is essential for protection against *C burnetii* by altering leucocyte trafficking. Indeed, transendothelial migration of leucocytes is defective in Q fever endocarditis and is related to overproduction of interleukin 10 (unpublished data).

Interleukin 10 is involved in persistence of *M tuberculosis*. In most cases after primary infection, the immune system is able to contain the infection, but the development of latency can be broken down, resulting in reactivation of tuberculosis.[67] Reactivation is associated with excessive production of interleukin 10 and the emergence of interleukin-10-producing Tregs, which is illustrated by animal models overexpressing interleukin 10.[69]

The third example of bacterial infections involving interleukin 10 is *Bartonella quintana*, which causes chronic asymptomatic bacteraemia that constitutes a model of bacterial persistence in homeless people.[115] By contrast with homeless people without this infection who have an inflammatory profile, those with *B quintana* bacteraemia have an attenuated inflammatory profile and a marked increase in interleukin 10 secretion by mononuclear cells.[76] Interleukin 10 is associated with the persistence of *Bartonella henselae*, the causative agent of cat scratch disease.[116]

Viral persistence may result from exploitation of viral interleukin 10 properties. Viral interleukin 10 is probably involved in viral immunosuppression.[97,98] However, the properties of cytomegalovirus interleukin 10 are distinct from those of Epstein-Barr viral interleukin 10,[117] suggesting that viruses have developed independent but convergent methods for escaping the immune system. Indeed, Epstein-Barr viral interleukin 10 is expressed during the lytic phase of infection and facilitates latent infection by suppressing antiviral immune responses. It has lost many immunostimulatory properties of mammalian interleukin 10[9] but interferes with the development of specific Th1 responses.[91,99] By contrast, cytomegalovirus interleukin 10 is produced during both productive and latent cytomegalovirus infection of permissive cells.[99] Persistence of viruses such as HIV and hepatitis viruses B and C may result from immunosuppression secondary to inappropriate production of interleukin 10 by mammalian cells[118] (table 2). Patients with AIDS progression have more interleukin 10 than non-progressing patients. Individuals carrying the allele –592 [A/A] of the interleukin 10 gene are at high risk of HIV-1 infection and, once infected, rapidly progress to AIDS. By contrast, the allele –592 [C/C] is associated with long-term non-progressors.[107] Interleukin 10 and HIV persistence are believed to be related because highly active antiretroviral therapy that induces partial HIV clearance induces partial decrease in interleukin 10 production.[108] It is likely that interleukin 10 is also involved in the persistence of hepatitis viruses in humans. Specific interleukin 10 polymorphisms, haplotypes, and microsatellites seem to be associated with outcome of infection, but this matter is still debated.[100,119] The expansion of interleukin-10-producing Tregs is probably essential for viral persistence as reported for patients infected with hepatitis C virus,[120] chronic hepatitis B,[104] and HIV patients with disease progression or viral replication.[109] The functional consequence of expanding interleukin-10-producing Tregs in HIV infection may be the impairment of

interferon-γ production by $CD8^+$ T cells as described in Friend virus infection.[106]

The virus persistence mediated by interleukin 10 may also favour infection-triggered diseases. Concentrations of interleukin 10 are higher in HIV-infected patients with rather than without hypergammaglobulinaemia. Increased production of interleukin 10 and IgG in patients receiving a single bolus of intravenous immunoglobulins suggests there may be an amplification loop.[121] Interleukin 10 may be also involved in the development of non-Hodgkin B cell lymphomas. Indeed, serum interleukin 10 is higher in HIV-infected patients with lymphomas than in those without. Moreover, the time course of interleukin 10 production is related to the occurrence of lymphomas.[111,112] Multicentric Castelman disease is associated with human herpes virus 8, viral load, and concentrations of interleukin 10 in plasma with respect to HIV infection.[122]

Protection in infection-mediated tissue injuries

In the preceding sections, we have shown that interleukin 10 is involved in the evolution of infectious diseases and consequently compromises health through host immunosuppression. However, like the two-faced Roman god Janus, interleukin 10 may protect hosts from exaggerated inflammatory and immune reactions and tissue injuries secondary to acute or chronic infections. This is illustrated by interleukin-10-deficient mice that develop colitis triggered by commensal flora.[123] Interleukin 10 also protects hosts from anaphylaxis and some parasitic infections. The hygiene hypothesis states the occurrence of infections may modulate the mechanisms leading to atopy and autoimmunity. We will specifically review the role of interleukin 10 in the relationship between atopy and helminthiasis.

Interleukin 10 limits the development of lesions caused by exacerbated inflammatory response induced during acute infections. Its protective effect is illustrated in different animal models of acute infections (table 3). Interleukin 10 is protective in human sepsis and its effect is probably genetically determined. The –592 [C/C] genotype of interleukin 10 is associated with high production of the molecule and high survival rates, whereas the [A/A] or [A/C] genotypes are associated with low production and high patient death.[124] However, the effect of interleukin 10 in patients with sepsis is complex.[163] Indeed, some studies have reported that non-survivors have increased persistent amounts of interleukin 10.[164,165] One can suppose that interleukin 10 is necessary to overcome an exaggerated inflammatory reaction but higher amounts are deleterious because they abolish the inflammatory reaction.

Interleukin 10 also prevents complications of acute parasitic infections such as malaria. The amount of interleukin 10 in plasma is high in patients with uncomplicated malaria,[134] decreased in patients with severe anaemia,[135] and lowest in patients with cerebral malaria.[129] An interleukin 10/TNF ratio lower than 1 is a

	Infections disease	Human beings	Animal model
Escherichia coli	Endotoxinaemia, septic syndromes	Polymorphism of interleukin 10 gene[124] Interleukin 10 administration[126]	KO mice[125] Human interleukin 10 administration[127]
S pneumoniae	Pneumonia	..	Interleukin 10 administration[128]
Plasmodium falciparum	Cerebral malaria	Circulating interleukin 10[129,131,133]	Interleukin 10 production (review)[130] KO mice[132]
P falciparum	Anaemia	Circulating interleukin 10[134,135]	..
Borrelia burgdorferi	Lyme disease (arthritis)	Interleukin 10 production[136,140] Interleukin-10 production in lesions[138,139]	Interleukin 10 production, KO mice[137]
Staphylococcus aureus	Arthritis	..	KO mice[141]
H pylori	Gastritis, ulcer, carcinoma	Interleukin 10 in lesions[142] Polymorphism of interleukin 10 gene[77,78]	Tregs[143] KO mice[144,145]
Schistosoma spp	Schistosomiasis (fibrosis)	Interleukin 10 production[146,148]	KO mice[147,149] Review[150]
	Allergy	Interleukin 10 production[151]	
Trypanosoma cruzi	Chagas disease	..	KO mice[152]
Herpes virus*	Stromal keratitis	..	Interleukin 10 administration[153,154]
Hepatitis C virus	Hepatitis	Interleukin-10 administration1[155-157] Polymorphism of interleukin 10 gene[101]	..
Hepatitis B virus	Hepatitis	Circulating interleukin 10[158]	..
Respiratory syncytial virus	Bronchiolitis	Polymorphism of interleukin 10 gene[60,160] Circulating interleukin 10[161]	KO mice[159]
Dengue virus	Dengue	Circulating interleukin 10[162]	..

*Intracorneal administration of interleukin 10 or DNA-encoding interleukin 10 allows complete resolution of infected animals and decreases local inflammation without compromising immune response to viral antigen. This is an example of anti-inflammatory use of interleukin 10.

Table 3: **Role of interleukin 10 in limiting or prevention of infection-mediated tissue injuries**

risk factor for cerebral malaria and severe anaemia, whereas a ratio higher than 1 is common in uncomplicated hyperparasitaemic patients.[131] However, the cytokine network may be modulated in malaria, reflecting a complex relation between cytokine production and disease manifestations. In a large cohort of patients from Mali,[133] circulating amounts of interleukin 10 and inflammatory cytokines were higher in patients with complicated malaria than in those without complications.

The severity of bronchiolitis caused by respiratory syncytial virus is linked to host response and specifically to interleukin 10. A recent study has reported the association of two single nucleotide polymorphisms, *IL-10-1117G* and *IL-10-3585A*, with this form of bronchiolitis necessitating mechanical ventilation. Although *IL-10-3585A* is associated with low production of interleukin 10, *IL-10-1117G* is associated with increased secretion.[166] On the other hand, respiratory syncitial virus may exacerbate asthma and increase expression of the interleukin 10 gene present locally in these patients.[167]

In addition to controlling lesions due to acute infections, interleukin 10 limits lesions associated with chronic infectious diseases (table 3). Lyme disease, caused by *Borrelia burgdorferi*, causes lesions such as erythema migrans and arthritis associated with an inappropriate Th1 immune response.[136,168] Interleukin 10 produced by synovial cells inhibits antigen-mediated lymphoproliferation, production of TNF and interferon γ,[138] and reduces transendothelial migration of monocytes and lymphocytes, thus leading to prevention of tissue lesions.[169] It is likely that the production of interleukin 10 is associated with inflammatory responses as reported for T cells in chronic borreliosis.[139,140]

Helicobacter pylori causes inflammatory gastritis and duodenal and gastric ulcers probably via induction of inflammatory and Th1-mediated host cell responses. Both responses are controlled by interleukin 10, which is produced by mononuclear cells of lamina propria from *H pylori*-positive patients with gastritis[142] and by interleukin-10-producing Tregs.[143] Hence, interleukin 10 has a protective role against gastritis and ulcers. By contrast, it may be associated with a risk of carcinoma in patients infected with *H pylori*. The –819 [T/T] genotype of interleukin 10 is associated with intestinal metaplasia and non-cardia gastric cancer,[77,78] which may be owing to colonisation by highly virulent strains of *H pylori* since carriers of the GCC haplotype have higher mucosal mRNA amounts than carriers of the ATA haplotype and are infected by more virulent strains of the bacteria.[170]

Schistosomiasis is an example of an infectious disease in which Th2-mediated responses are a source of complications. The resolution of liver granulomas leaves fibrotic plaques, which lead to hepatic fibrosis and dysfunction of portal circulation.[171] As described above for Th1-mediated responses, interleukin 10 may prevent schistosomiasis complications. In children from endemic areas in Uganda, fibrosis is mainly associated with low production of interleukin 10.[146] Low interleukin 10 production in response to *Schistosoma haematobium* is also associated with bladder morbidity.[172] However, analysis of children infected with *S haematobium* shows that high levels of interleukin 10 are a risk factor for reinfection.[148]

The role of interleukin 10 in hepatic fibrosis due to hepatitis C virus offers new therapeutic possibilities. Daily treatment of patients with interleukin 10 returns alanine aminotransferase values to normal in half of patients including interferon-naive and interferon-non-responder patients.[155] Another study confirms that interleukin 10 treatment reduces fibrosis in a large proportion of interferon-non-responder patients with chronic hepatitis.[156] However, long-term treatment has side-effects.[157] Patients with decreased fibrosis have increased hepatitis C virus burden and decreased numbers of CD4+ and CD8+ interferon-γ-secreting cells specific for hepatitis C virus, thus reorienting the immune response toward a Th2 response. Hence, the use of interleukin 10 to prevent immunopathological lesions remains questionable.

Infections and atopy

The hygiene hypothesis states that improved hygiene and public health measures along with the use of vaccines and antibiotics have reduced the incidence of infections but have also increased the number of inflammatory diseases including asthma, atopy, inflammatory bowel disease, and multiple sclerosis in developed countries.[173,174] There is an inverse relationship between bacterial (*M tuberculosis, H pylori*), viral (measles, hepatitis A), and protozoan

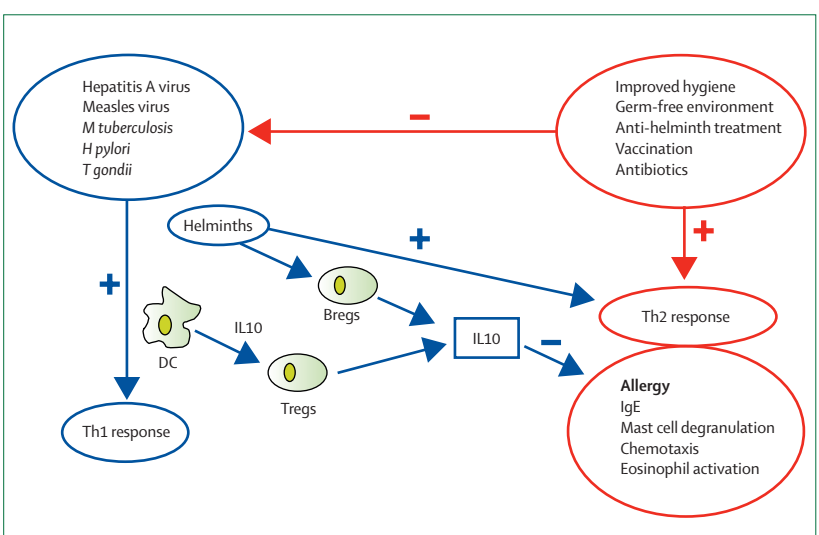

Figure 2: **Infections, atopy, and interleukin 10**
In developed countries, bacterial, viral, and protozoan infections induce Th1-mediated responses and protect from allergy through the induction of T cell tolerance mediated by interleukin-10-producing Tregs. Conversely, clearing microbial environment through improved hygiene or medical treatment reduces the incidence of infections but increases the risk of allergy that is based on Th2-type responses. In developing countries, helminth infections and allergic diseases are also inversely related although both are dependent on Th2-dependent mechanisms. Protection against allergic diseases is shared by interleukin 10 and interleukin-10-producing regulatory B cells (Bregs).

Infectious agent	Effectors	Human beings	Mouse model
HIV	Natural Tregs	177–179	..
Cytomegalovirus	Natural Tregs	177	..
Herpes virus	Natural Tregs	..	180, 181
Hepatitis C virus	Natural Tregs Inducible Tregs (Tr1) CD8 Tregs	182 118, 120 183	..
Epstein-Barr virus	Inducible Tregs (Tr1) CD8 Tregs	91 184	..
Friend virus	Inducible Tregs (Tr1)	..	106
Murine leukaemia virus	Inducible Tregs (Tr1)	..	7
Helicobacter hepaticus	Natural Tregs Inducible Tregs	..	143 185
H pylori	Natural Tregs	186, 187	7
Bordetella pertussis	Inducible Tregs (Tr1)	..	188
M tuberculosis	Inducible Tregs (Tr1)	68, 70	..
Listeria monocytogenes	Natural Tregs	..	189
S mansoni	Natural Tregs	..	190, 191
O volvulus	Inducible Tregs	89	7, 90
L major	Natural Tregs	..	53, 192
P falciparum	Natural Tregs	193	..
Plasmodium berghei, Plasmodium yoelii	Natural Tregs	..	7
Pneumocystis carinii	Natural Tregs	..	194
C albicans	Natural Tregs	..	195

Naturally occurring (natural) and antigen-driven (inducible) Tregs induce immunosuppression by preventing Th1-type and Th2-type immune responses through secretion of interleukin 10. Consequently, interleukin-10-producing Tregs increase host susceptibility to infections, chronic evolution of infectious diseases, and viral persistence in mice and in human beings. Tr1=type 1 regulatory T cells.

Table 4: **References to role of Tregs in infectious diseases**

(*Toxoplasma gondii*) infections that induce Th1-mediated immune responses and atopy that induces a Th2-mediated immune response[175,176] (figure 2). Protection against allergy does not result from the Th2/Th1 conversion but rather from the induction of T-cell tolerance mediated by Tregs (table 4). Indeed, patients with mutations in the *FOXP3* gene, which is required for the development of Tregs, show systemic autoimmune reactions, eczema, and high amounts of serum IgE.[196] Additionally, commensal bacteria at mucosal surfaces in the gastrointestinal tract and in the upper respiratory tract probably control immune tolerance and the expansion of Tregs.[197]

In developing countries with high prevalence of helminth infections, the risk of developing an allergic disease is lower in infected populations than in uninfected populations.[151] In South America, children whose infections have been cleared with anti-helminth treatment develop heightened skin reactivity to house dust mites, whereas untreated patients exhibit decreased skin reactivity when parasite load is increased. In Gabonese children chronically infected and treated with anti-helminth drugs, the rate of developing skin sensitivity to house dust mites is increased.[198] These findings seem to be paradoxical since allergy and helminth infections share Th2-dependent mechanisms. Interleukin 10 is actually critical for protection associated with helminth infection. In Gabonese schoolchildren with urinary schistosomiasis, the prevalence of positive skin tests to house dust mites is lower and interleukin 10 production is higher than in children without infection.[151] The interleukin-10-mediated protective mechanisms induced by infections in developed countries and by helminth infections in developing countries are probably distinct. In a murine model combining schistosomiasis and anaphylaxis, *S mansoni* elicits protection from allergen-induced anaphylaxis or IgE-mediated passive systemic anaphylaxis. This protection is mediated by interleukin 10 and interleukin-10-producing regulatory B cells known to have a protective role in experimental encephalomyelitis and collagen-induced arthritis.[199,200] Interleukin 10 mediates protection by impairing the activity of anaphylaxis effectors. It has also been shown that interleukin-10-producing regulatory B cells are able to transfer the protection against anaphylaxis to uninfected animals.[201]

Conclusions

Our review reveals a major role for interleukin 10 in two features of infectious diseases. First, although interleukin 10 is dispensable for human susceptibility to intracellular pathogens, it is closely associated with microbial persistence by interfering with innate and adaptive protective immunity. Blocking systemic interleukin 10 may be an attractive therapeutic approach but using antibodies to interleukin 10 increases the risk of autoimmunity or inflammatory disorders. Second, interleukin 10 prevents the development of immunopathological lesions owing to exacerbated protective immune response. Studies of interleukin-10-producing viruses show its role in immune evasion. These viruses provide potential pharmacological tools for

Search strategy and selection criteria

We did an extensive Medline search of publications from 1985 until January, 2005. Only English language papers were considered. Search terms included "IL-10", "IL-10 and hepatitis B virus", "IL-10 and hepatitis C virus", "IL-10 and Epstein Barr virus", "IL-10 and cytomegalovirus", "IL-10 and human immunodeficiency virus", "IL-10 and tuberculosis", "IL-10 and *Mycobacterium*", "IL-10 and Leishmaniasis", "IL-10 and Helminths", "IL-10 and *Coxiella burnetii*", and "IL-10 and *Bartonella*". We also searched using the names of prominent scientists in the field, and used PubMed. A third search was done by listing relevant reviews and chapters of major textbooks on this topic and the references cited. The manuscript was further updated in October, 2005, by searching Medline using "IL-10" in the same combinations as above.

controlling immune response. This possibility is strengthened by gene therapy with interleukin 10 and induction of tolerance to cardiac transplant. Finally, converging reports suggest that the effects of interleukin 10 are genetically controlled. Further genetic analysis of infectious diseases will allow discrimination between genetically controlled factors and factors related to pathogen-stimulated interleukin 10 production.

Conflicts of interest

We declare that we have no conflicts of interest.

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