

INTERLEUKIN-10 AND THE INTERLEUKIN-10 RECEPTOR

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■ **Abstract** Interleukin-10 (IL-10), first recognized for its ability to inhibit activation and effector function of T cells, monocytes, and macrophages, is a multifunctional cytokine with diverse effects on most hemopoietic cell types. The principal routine function of IL-10 appears to be to limit and ultimately terminate inflammatory responses. In addition to these activities, IL-10 regulates growth and/or differentiation of B cells, NK cells, cytotoxic and helper T cells, mast cells, granulocytes, dendritic cells, keratinocytes, and endothelial cells. IL-10 plays a key role in differentiation and function of a newly appreciated type of T cell, the T regulatory cell, which may figure prominently in control of immune responses and tolerance in vivo. Uniquely among hemopoietic cytokines, IL-10 has closely related homologs in several virus genomes, which testify to its crucial role in regulating immune and inflammatory responses. This review highlights findings that have advanced our understanding of IL-10 and its receptor, as well as its in vivo function in health and disease.

INTRODUCTION

Interleukin-10 (IL-10) was first described as cytokine synthesis inhibitory factor (CSIF) (1), an activity produced by mouse Th2 cells that inhibited activation of and cytokine production by Th1 cells. Mouse and human IL-10 (mIL-10, hIL-10) cDNAs were reported a short while later, along with the discovery of IL-10's counterpart Epstein-Barr virus gene, BCRF1 (viral IL-10, vIL-10) (2-4). The ability of IL-10 to inhibit cytokine production by both T cells and NK cells was found to be indirect, via inhibition of accessory cell (macrophage/monocyte) function (5-8). These studies were soon extended to show that IL-10 profoundly inhibited a broad spectrum of activated macrophage/monocyte functions, including

monokine synthesis, NO production, and expression of class II MHC and costimulatory molecules such as IL-12 and CD80/CD86 (9–16).

In vitro and in vivo studies with recombinant cytokine and neutralizing antibodies revealed pleiotropic activities of IL-10 on B, T, and mast cells (17–22) and provided evidence for in vivo significance of several of IL-10s in vitro activities (23–25). Inflammatory bowel disease and other exaggerated inflammatory responses exhibited by IL-10 deficient (IL-10^{-/-}) mice (26–28) indicated that a critical in vivo function of IL-10 is to limit inflammatory responses. Clinical studies of IL-10 in normal subjects and several human inflammatory and autoimmune settings are well underway (29).

This is being written at the tenth anniversary of IL-10's discovery. Our database searches reveal nearly 4200 reports of research involving IL-10. This chapter emphasizes more recent developments illuminating the role of IL-10 in normal and pathological immune responses in vivo, as well as IL-10 and IL-10 receptor (IL-10R) structure and signalling.

IL-10 PROTEIN, GENE, AND EXPRESSION

Protein

IL-10 amino acid sequences have been derived from cloned cDNAs. The Genbank database contains entries for the human (4), pig-tailed macaque, mangabey, rhesus, and owl monkeys, lemur, mouse (2), rat (30), guinea pig, Syrian hamster, rabbit, woodchuck, gerbil, opossum, cat, dog, cow, sheep, red deer, pig, horse, and killer whale cytokines. The open reading frames (ORF) encode secreted proteins of ~178 amino acids with rather well conserved sequences—mIL-10 and hIL-10 are ~73% identical—consistent with an α -helical bundle structure similar to interferons and hemopoietic cytokines (31).

Recombinant hIL-10 and vIL-10 are 17–18 kDa polypeptides that are not N-glycosylated. Both recombinant and T cell-derived mIL-10 appear to be heterogeneously N-glycosylated at a site near the N-terminus (2, 32); glycosylation of mIL-10 has no known influence on biological activity. At least one rat monoclonal antibody (Mab) cross-reacts with m- and hIL-10 (33). hIL-10 is active on both mouse and human cells, whereas mIL-10 is effective only on mouse cells.

Early studies suggested that IL-10 is dimeric (1, 34, 35). Biochemical (36) and X-ray crystallographic analyses of hIL-10 (37–39) and vIL-10 (40) demonstrated that IL-10 is an acid-sensitive, noncovalent homodimer of two interpenetrating polypeptide chains, similar to interferon- γ (IFN γ) (41). An engineered hIL-10 altered to favor monomer formation bound to the IL-10 receptor (IL-10R) and retained biological activity, although with reduced (60-fold) affinity and 10-fold lower specific activity in a biological assay compared to the wild-type cytokine (42).

Synthetic peptides derived from the IL-10 amino acid sequence were described that appear to mimic certain IL-10 activities *in vitro* and *in vivo* (43,44). A peptide consisting of the 9 C-terminal amino acids of hIL-10 was reported to inhibit IL-8 production and HLA-DR expression by human monocytes and TNF production by CD8⁺ T cells, enhance IL-1RA production by monocytes, chemoattract CD8⁺ T cells, and enhance proliferation of a murine mast cell line (MC/9) in response to IL-4. A second peptide corresponding to hIL-10 amino acids #8–#16 also stimulated MC/9 cells but did not exhibit any other IL-10-like activities (43). Administration of the former peptide in a rabbit model of acute lung injury reportedly reduced mortality and inhibited development of acute lung injury (44). These results imply provocatively that IL-10 actions can be mimicked by small fragments of the cytokine. As no information is yet available regarding direct interaction of such peptides with IL-10R or induction of IL-10R-dependent signaling pathways, it remains to be determined whether they act as genuine IL-10 mimics or function indirectly, for example by facilitating endogenous IL-10 expression or release.

The IL-10 Gene and Its Expression

The mIL-10 and hIL-10 genes are encoded by five exons on the respective chromosomes 1 (45,46). Activation of IL-10 gene expression results in ~2 kb (hIL-10) and ~1.4 kb (mIL-10) mRNAs; a ~1 kb mRNA was also seen in a mouse Th2 clone (2,4). IL-10 can be expressed by a variety of cells, usually in response to an activation stimulus; clearly its expression is regulated by different mechanisms in different cell types, such as T cells and monocytes/macrophages (reviewed in 47). Recent work has shown that, in contrast to many other cytokines, IL-10 transcription can be regulated by transcription factors Sp1 and Sp3, which are expressed constitutively by many different cell types (48,49). Combined with control of IL-10 mRNA stability at the posttranscriptional level (50), this suggests that the IL-10 gene is transcribed to some degree constitutively and subject to control by alteration of posttranscriptional RNA degradation mechanisms. This situation under some circumstances may facilitate more rapid control of IL-10 expression than can be achieved just by activation of transcription. In this regard we note that a transient, massive IL-10 release attributed to liver macrophages was reported during liver transplantation (51).

Several polymorphisms have been noted in the human IL-10 gene 5'-flanking sequence. They include two areas of multiple (CA)_n repeat microsatellite polymorphisms ~1.2 kb and ~4 kb upstream of the transcription start site and three linked point mutations at -1082(G/A), -819(C/T), and -592(C/A) (52,53). Although the IL-10 promoter has not been completely defined, these polymorphisms are presumed to lie within the promoter region. Indeed, a correlation of particular microsatellite polymorphisms with LPS-induced IL-10 secretion by PBMC *in vitro* (presumably mostly from monocytes) was reported (54); the -1082(G) allele was associated with higher ConA-induced IL-10 production (likely both T cells

and monocytes) (55). While individual variation was considerable, these trends were statistically significant.

Possible linkage of IL-10 promoter haplotypes to disease susceptibility or severity has been reported. Perhaps the strongest association is for systemic lupus erythematosus (SLE), where high IL-10 expression (56, 57), and the corresponding IL-10 alleles (58), have been suggested to play a causal or exacerbatory role (59–61). To what extent high IL-10 expression actually contributes to or is just a consequence of the disease is unclear. However, healthy relatives of lupus patients also exhibit elevated IL-10 expression (57, 62), suggesting that high IL-10 levels may predispose to disease and precede onset. A recent study also indicated a 40-fold increased risk for developing SLE in individuals who have particular alleles of both the IL-10 and *bcl-2* genes (63). One of the lupus susceptibility loci in the New Zealand mouse is near IL-10 on chromosome 1 (64), and an IL-10 promoter polymorphism in this strain has been noted (65).

Genetic predisposition to high IL-10 expression is also associated with a higher rate of mortality in meningococcal disease (66). Chronically infected hepatitis C patients who are genetically predisposed to high IL-10 production were reportedly less likely to benefit from IFN α therapy (67).

Genes Related to IL-10

Recent studies identified cellular genes encoding proteins with weak (<30%) homology but unmistakable structural relationship to IL-10. A Herpesvirus saimiri-induced gene, AK155, is encoded on human chromosome 12q15 near the IFN γ locus and is also expressed at low levels by uninfected T cells (68). Mouse T cells also express an IL-9-inducible cytokine-like molecule, IL-TIF (69), the human version of which (70) has also been termed IL-22 (71). The mouse *mob-5* gene is induced by oncogenic *ras* expression (72) and encodes a secreted protein related to IL-10 and to the rat C49a (73) and human *mda-7* (74–76) proteins.

The biological activities of these IL-10-related proteins are not well characterized. AK155 has no known function. IL-TIF/IL-22 activated Stat1, Stat3, and Stat5 in mesangial and neuronal cell lines (69), a renal carcinoma, and colon, and it may inhibit to some degree IL-4 production by Th2-polarized human T cells (71). IL-TIF/IL-22 enhanced production of acute-phase reactants in the HepG2 cell line and in mouse liver in response to IL-TIF/IL-22 injection (70). The receptor for IL-TIF/IL-22 appears to consist of IL-10R2/CRF2-4 and a novel IFNR family member termed “IL-22R;” both subunits are required for signal transduction (70, 71). Although both receptor subunits detectably bind IL-TIF/IL-22, the relative ligand affinities of these IL-22R subunits and their combination are not yet known (71).

Mob-5 may be the mouse homolog of rat C49a and human *mda-7*, and as such it could share the latter’s reported ability to inhibit growth of and induce apoptosis in certain tumor cells and cell lines by an unknown mechanism (74–76). However *mob-5* is a secreted protein, whereas *mda-7* was reportedly expressed

intracellularly. The biological functions of these and potentially other relatives of IL-10 thus remain to be established.

Viral IL-10 Genes

IL-10 gene homologs have been found in the Epstein-Barr virus (EBV), equine herpes virus type 2 (EHV2), poxvirus Orf, and human cytomegalovirus genomes (2, 4, 77–79). Except for cytomegalovirus IL-10 (cmvIL-10), conservation of amino acid sequence between the viral and host cellular IL-10 (cIL-10) proteins is striking: the mature hIL-10 and EBV viral IL-10 (vIL-10) amino acid sequences are 84% identical, and most differences occur in the N-terminal 20 amino acids. Not unexpectedly, nearly all anti-hIL-10 antibodies—and ELISA assays utilizing them—cross-react with vIL-10 (10, 80, 81). Likewise, the EHV2 and Orf IL-10 homologs differ most from cellular IL-10s in the N-terminal region. vIL-10 is a 17-kDa nonglycosylated polypeptide that is expressed during the lytic phase of virus infection (82, 83) and exhibits only a subset of cIL-10 activities in vitro and in vivo (4, 5, 18, 19, 47, 81, 84–86), which as discussed later, implies the existence of distinct IL-10R complexes and/or signal transduction mechanisms on vIL-10-responsive and vIL-10-nonresponsive cells.

cmvIL-10 has several unique features among viral IL-10s. First, it is only 27% identical to hIL-10, in contrast to the much closer similarity exhibited by EBV vIL-10. Nonetheless, cmvIL-10 binds to and signals via the IL-10R complex (79). In addition, the cmvIL-10 gene has conserved the positions of introns 1 and 3 of hIL-10, while the other vIL-10s lack intervening sequences. These observations support the notion that vIL-10s represent captured cIL-10 genes, which then evolved to suit requirements of each particular virus' interaction with the host.

THE IL-10 RECEPTOR AND IL-10 SIGNALING

IL-10R Structure and Expression

The IL-10 receptor is composed of at least two subunits that are members of the interferon receptor (IFNR) family.

IL-10R1 The ligand-binding subunit (IL-10R α , IL-10R1) binds cIL-10 with high affinity ($K_d \sim 35\text{--}200$ pM) (33, 34, 81, 87). Its affinity for vIL-10 is at least 1000-fold lower (42, 81, 88). Cross-linking studies with ^{35}S -Met- or ^{125}I -hIL-10 and immunoprecipitation data indicated a molecular size of 90–120 kDa for IL-10R1 (33, 34, 81, 87), consistent with N-glycosylated hIL-10R1 and mLIL-10R1 proteins of 578 and 576 amino acids, respectively (60% homologous). Consistent with the observed species-specificity of IL-10, mLIL-10R1 binds both mLIL-10 and hIL-10, while hIL-10R1 does not bind mLIL-10. mLIL-10R1 encoded by mast cell and macrophage-derived cDNAs were identical, even though these cells respond

differently to cIL-10 and vIL-10 (87). IL-10R1 mRNA was detected in all IL-10-responsive cells tested, and neutralizing anti-IL-10R1 monoclonal antibodies (Mabs) blocked all known cIL-10 and vIL-10 activities (33, 81, 87, 89); thus IL-10R1 is required for responses to both cIL-10 and vIL-10. The hIL-10R1 gene maps to chromosome 11q23.3 (33, 90).

Although there are no reports of detection of soluble IL-10R1 (sIL-10R1) in vivo, recombinant sIL-10R1 has been expressed (81, 89, 91). High shIL-10R1 concentrations relative to ligand exhibited antagonist activity in vitro (81, 91). hIL-10/shIL-10R1 complexes can be multimeric, consisting of up to two ligand dimers bound to as many as four shIL-10R1 molecules (42, 91). Consistent with this, we have observed that at low sIL-10R1:IL-10 ratios, sIL-10R1 can potentiate, rather than inhibit IL-10 activity (Y Liu, S H-Y Wei, & KW Moore, unpublished).

Model studies (39) based on the likely related structure of the IFN γ /sIFN γ R1 complex (41) suggested that the regions of IL-10 likely involved in contact with IL-10R1 were the N-terminus, helix A, the AB loop, part of helix B, and the C-terminal helices E/F. Epitope and peptide mapping data generally supported this picture (92). The altered sequence and structure of the vIL-10 N-terminus (40) suggest impaired IL-10R1 interaction in this region and are consistent with the dramatically lower affinity of vIL-10 for IL-10R1 (81).

IL-10R1 is expressed by most hemopoietic cells, although generally at measured levels of only a few hundred per cell (33, 34, 81, 87, 93). IL-10R1 expression on T cells is downregulated by activation at both the mRNA (33) and protein levels; in contrast, activation of monocytes is associated with upregulation of IL-10R1 expression (R dW Malefyt, KW Moore, unpublished), consistent with IL-10's role as an inhibitory factor for these cells.

IL-10R1 expression has been observed on nonhemopoietic cells as well, although it is more often induced rather than constitutive. For example, IL-10R1 expression was induced in fibroblasts by LPS (94), and in epidermal cells or keratinocytes by glucocorticoids, a leflunomide metabolite, or dihydroxy-vitamin D3 (95–97). Constitutive IL-10R1 expression by placental cytotrophoblasts (98) and colonic epithelium (99, 100) has been described.

IL-10R2 Like IFN γ R (101) and IFN $\alpha\beta$ R (102), IL-10R utilizes an accessory subunit for signaling, IL-10R2 (IL-10R β). IL-10R2 was originally described as orphan IFNR family member CRFB4/CRF2-4 located in the IFNR gene complex on chromosome 21 (human) and 16 (mouse) (103–105). Several lines of evidence support IL-10R2's role in the IL-10R complex. First, hIL-10R2 complements defective hIL-10R1 signaling in transfected hamster cell lines and can be cross-linked to and coprecipitated with IL-10/IL-10R1 in IL-10-responsive cells (106). Moreover, IL-10R2 $^{-/-}$ mice, like IL-10 $^{-/-}$ animals, develop chronic severe enterocolitis, and cells from these mice are unresponsive to IL-10 (107) (however, presumably IL-TIF/IL-22 functions are also impaired in IL-10R2 $^{-/-}$ mice). Finally, anti-hIL-10R2 Mabs block IL-10 responses (Y Liu, KW Moore, R dW Malefyt, unpublished). IL-10R2 contributes little to IL-10-binding affinity; its

principal function appears to be recruitment of a Jak kinase (Tyk2) into the signaling complex (106, 107) (see below). Thus, in studies utilizing IFN γ as ligand and a hybrid receptor containing the extracellular domain of IFN γ R1 and cytoplasmic signaling domain of IL-10R1, the accessory subunit functions required to generate the expected array of "IL-10" responses could be provided by IFN γ R2 (108).

IL-10R2 is constitutively expressed in most cells and tissues examined (103, 105), and we have found no evidence for significant activation-associated regulation of IL-10R2 expression in immune cells (KW Moore, R dW Malefyt, unpublished). Thus, any stimulus activating IL-10R1 expression should suffice to render most cells responsive to IL-10.

IL-10R Signal Transduction

IL-10 and the Jak/stat System Because of widespread interest and reagent availability, the best characterized IL-10 signaling pathway is the Jak/stat system. The IL-10/IL-10R interaction engages the Jak family tyrosine kinases Jak1 and Tyk2 (109, 110), which are constitutively associated with IL-10R1 (A Mui, HY Wei, KW Moore, unpublished) and IL-10R2 (106) respectively. IL-10 induces tyrosine phosphorylation and activation of the latent transcription factors stat3, stat1, and in nonmacrophage cells, stat5 (109, 111–113).

Recent studies, both in vitro and in gene-deficient mice, have linked the biology of IL-10 to IL-10 signaling molecules and pathways. Macrophages from Jak1 $^{-/-}$ mice do not respond to IL-10 (114), which indicates that Jak1 plays an obligatory early role in IL-10 signaling. Stat3 is also implicated strongly as a key mediator of IL-10 responses. Stat3 is recruited directly to the IL-10/IL-10R complex via either of two tyrosine residues in the IL-10R1 cytoplasmic domain that become phosphorylated in response to IL-10 (113) and are required for IL-10 signalling (89, 108, 110). Overexpression of a dominant negative stat3 mutant or an inducibly active form of stat3 demonstrated that stat3 activation was both necessary and sufficient to mediate inhibition of macrophage proliferation by IL-10 (89), at least in part via enhancement of expression of the cell cycle inhibitors p19^{INK4D} and p21^{CIP1} (115). In contrast, the stat3 mutant did not detectably impair IL-10's ability to inhibit LPS-induced monokine production (the "anti-inflammatory" activity of IL-10), nor did the inducibly active form of stat3 itself effect inhibition of activation-induced monokine synthesis. These observations suggest that inhibition of macrophage proliferation and monokine production by IL-10 are governed by two distinct signaling pathways, the former requiring stat3 (89).

Recent data refined this picture. "Conditional knockout" mice, in which stat3 expression was abolished in macrophages and neutrophils, develop chronic enterocolitis, and their macrophages are completely refractory to the effects of IL-10 (108, 116). These observations seem to conflict with those of O'Farrell et al. (89), however the latter's "dominant negative" stat3 mutant likely lacks only the transcription factor activity of stat3, while other possible functions, such as that of a docking molecule that could recruit other proteins to the IL-10R complex, may

remain intact. Moreover, it appears that activation of stat3, while necessary for the anti-inflammatory action of IL-10, is not sufficient: a C-terminal ~15 amino acid segment of IL-10R1, along with stat3, plays a key functional role in inhibition of macrophage activation by IL-10, but not in other IL-10 functions (108). Thus, the current picture regards stat3 as indispensable for IL-10 signaling in all IL-10-responsive cells, but one or more additional pathway(s) must be activated to effect inhibition of macrophage activation by IL-10.

In contrast to stat3, the roles of stat1 and stat5 in IL-10 biology and signal transduction remain unclear. Stat1 and stat5 do not appear to interact directly with the IL-10/IL-10R complex (113), and overexpression of dominant negative stat1 or stat5 did not block IL-10's effects on a macrophage cell line (89). Moreover, macrophages from stat1^{-/-} mice remain responsive to IL-10 (117), although a detailed characterization of their IL-10 responses has not been reported. Furthermore, since the bulk of IL-10 signaling studies have been carried out using monocytes/macrophages, T cells, and B cells, it is possible that less understood IL-10 signaling pathways play prominent roles in other cells. For example, IL-10 has a number of effects on neutrophils but induces little Fc γ RI expression or detectable stat1 or stat3 activation in these cells (118, 119).

How does IL-10 signaling via the Jak/stat pathway result in inhibition of macrophage activation? A recent report (120) showed that IL-10's inhibition of IFN-induced gene transcription (IP-10, ISG54, ICAM-1) in human monocytes correlates with an observed inhibition by IL-10 of IFN-induced stat1 activation and tyrosine phosphorylation (120, 121). The latter inhibition diminished at higher IFN concentrations relative to IL-10, suggesting competing or interacting IL-10- and IFN-induced intracellular mechanisms, the relative strengths of which determine the degree of stat1 activation and IFN-induced gene transcription. Moreover, IL-10 rapidly induced transcription of SOCS3 (120, 122), which in some cells is a stat3-regulated gene (123). Whether IL-10-induced SOCS3 provides mainly negative feedback regulation of IL-10 signaling itself or also contributes significantly to IL-10's inhibition of the IFN response remains to be determined.

Other IL-10 Signaling Pathways Consistent with its ability to inhibit macrophage activation and monokine production, IL-10 inhibits NF κ B activation in response to stimuli in vitro (124–128). Inhibition of NF κ B activation in CD3⁺ T cells was also reported although it appears to be indirect, via the accessory cell (129). The in vitro data correlated with in vivo observations (130, 131), although in vivo effects may be direct or indirect. Mechanism studies revealed that IL-10 inhibits NF κ B activation at least two different ways: by inhibiting activation of I κ B kinase—similar to salicylate (132)—and by inhibiting NF κ B DNA binding activity (the latter mechanism is not understood) (125).

However, it was also reported that IL-10 activates AP-1 and NF κ B in CD8⁺ T cells (133). This finding, while in contrast to IL-10's effects on macrophages and CD4⁺ T cells, is nonetheless consistent with IL-10's ability to promote growth,

differentiation, and cytotoxic activity of both CD8⁺ T cells and NK cells (8, 21, 134–139), and it suggests significant differences in the responses of CD4⁺ and CD8⁺ T cells to IL-10.

IL-10 induced Bcl-2 expression in CD34⁺ progenitors and germinal center B cells (140, 141), consistent with its growth-cofactor activity on such cells. IL-10 also activated c-fos expression in human B cells (142). In monocytes, IL-10 activated p85 PI3- and p70 S6 kinases, although specific blockade of these pathways affected only the proliferation-regulating but not anti-inflammatory activities of IL-10 (143).

Activation of the raf/ras/MAP kinase cascade does not occur in response to IL-10 and may be inhibited in some cases (144–146). In this light it is unlikely that IL-10 on its own could sustain long-term cellular proliferation; rather it would act as a viability-enhancing or growth cofactor cytokine (110).

BIOLOGICAL ACTIVITIES OF IL-10

Effects of IL-10 on Monocytes, Macrophages, and Dendritic Cells

IL-10 modulates expression of cytokines, soluble mediators and cell surface molecules by cells of myeloid origin, with important consequences for their ability to activate and sustain immune and inflammatory responses. The effects of IL-10 on cytokine production and function of human macrophages are generally similar to those on monocytes, although less pronounced (147–153).

IL-10 potently inhibits production of IL-1 α , IL-1 β , IL-6, IL-10 itself, IL-12, IL-18, GM-CSF, G-CSF, M-CSF, TNF, LIF and PAF by activated monocytes/macrophages (10, 11, 154–156). The inhibitory effects of IL-10 on IL-1 and TNF production are crucial to its anti-inflammatory activities, because these cytokines often have synergistic activities on inflammatory pathways and processes, and amplify these responses by inducing secondary mediators such as chemokines, prostaglandins, and PAF.

IL-10 also inhibits production of both CC (MCP1, MCP-5, Mip-1 α , Mip-1 β , Mip-3 α , Mip-3 β , Rantes, MDC) and CXC chemokines (IL-8, IP-10, MIP-2, KC (Gro- α) by activated monocytes (152, 157–159). These chemokines are implicated in the recruitment of monocytes, dendritic cells, neutrophils, and T cells. Thus, IL-10 inhibits expression of most inducible chemokines that are involved in inflammation. Moreover, IL-10 thereby has the ability to affect both Th1 and Th2 responses: IP-10 is induced by IFN γ and attracts Th1 cells, and MDC is induced by IL-4 and attracts Th2 cells. IL-10 upregulates expression of the fMLP receptor, the PAF receptor, CCR1, CCR2, and CCR5 on monocytes, making these cells more responsive to chemotactic factors (160–162) and monocytes more susceptible to HIV infection (160, 161). In contrast, IL-12 inhibits CCR5 expression by monocytes (163).

IL-10 not only inhibits production of these effectors, but in addition, enhances expression of their natural antagonists. IL-10 enhanced production of interleukin-1 receptor antagonist (IL-1RA) and soluble p55 and p75 TNFR (164–167), and it inhibited expression of IL-1RI and IL-1RII (10, 168, 169) by activated monocytes, indicating that IL-10 not only deactivates monocytes but also induces production of anti-inflammatory molecules. In addition, the chemokine HCC4 is strongly upregulated by IL-10 in monocytes and is a chemoattractant for monocytes (170). This would suggest that HCC4 has an anti-inflammatory role, possibly by recruitment of monocytes and macrophages in the resolving phase of an inflammatory response. Moreover, pretreatment of monocytes with MCP1–4 suppressed production of IL-12p70 by inducing endogenous IL-10 production, providing further evidence for interactions between IL-10 and chemokines to regulate inflammation (171). These findings fit with a novel paradigm in which chemokines and chemokine receptors are oppositely regulated by pro- and anti-inflammatory mediators, including IL-10 and TGF β (161, 172).

Both transcriptional and posttranscriptional mechanisms have been implicated in the inhibitory effects of IL-10 on cytokine and chemokine production (9, 127, 173, 174). IL-10 regulates production of certain cytokines, such as Gro- α (KC), by destabilizing mRNA via AU-rich elements in the 3'-UTR of sensitive genes (175, 176). IL-10 also enhances IL-1RA expression via inhibition of mRNA degradation (177).

IL-10 inhibited production of prostaglandin E2 (PGE2), through downregulation of cyclooxygenase 2 (COX-2) expression (178–180). This also affected expression of matrix metalloproteinases, which are regulated by a PGE-cAMP pathway (180). Consequently, IL-10 inhibited the ability of monocytes/macrophages to modulate extracellular matrix turnover through its inhibitory effects on the production of gelatinase and collagenase (MMP2/MMP9), and also its ability to enhance production of tissue inhibitor of metalloproteinases (TIMP) and hyaluronectin, which binds and inhibits angiogenic- and migration-promoting activities of hyaluronic acid (180–184).

IL-10 inhibited expression of MHC class II antigens, CD54 (ICAM-1), CD80 (B7), and CD86 (B7.2) on monocytes, even following induction of these molecules by IL-4 or IFN γ (5, 12, 185, 186), through a posttranscriptional mechanism involving inhibition of transport of mature, peptide loaded MHC class II molecules to the plasma membrane (187). Downregulated expression of these molecules significantly affected the T cell-activating capacity of monocyte APC (5–7).

IL-10 enhanced expression of CD16 and CD64 Fc γ R on monocytes (154, 188, 189) but downregulated the expression of IL-4-induced CD23 (Fc ϵ RII) (190). Upregulation of CD64 correlated with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) (188). Upregulation of Fc γ R expression by IL-10 correlated with an enhanced capacity of monocytes/macrophages to phagocytose opsonized particles, bacteria, or fungi (191, 192), although IL-10 reduced the ability of the cells to kill the ingested organisms by decreasing the generation of superoxide anion (O $_2^-$) and nitric oxide (NO) (9, 13, 193–198). The inhibitory effects of IL-10

on production of NO by mouse macrophages occurred by an indirect mechanism involving inhibition of endogenous cytokine (TNF, IFN γ) synthesis (14, 199). Interestingly, ligation of CD23 or CD64 induced expression of IL-10 by monocytes, which was active in suppressing inflammation (200, 201). These results suggest that a regulatory loop exists whereby IL-10 (or IFN γ) upregulates CD64 expression and subsequent CD64 ligation leads to enhanced IL-10 production, which inhibits the inflammatory response. This has indeed been demonstrated by induction of peripheral tolerance to an aggregated encephalitogenic proteolipid protein-Ig fusion in a model of EAE, resulting in IL-10 production and amelioration of disease (202).

Thus, IL-10 inhibits cytokine, chemokine, and PGE₂ production (178, 179), and antigen presentation. IL-10 also downregulates expression of TLR4, the signal-transducing receptor for LPS (203), and enhances expression of CD14, CD16, CD64, and CD163, a scavenger receptor that is downregulated by LPS, IFN γ and TNF (204). Collectively these observations indicate that IL-10 induces differentiation of a macrophage-like cell that limits ongoing immune responses and inflammation, and contributes to clearance of the infection via enhanced phagocytosis.

Effects of IL-10 on Dendritic Cells

Mouse and human dendritic cells (DC) are defined by their ability to activate and prime naïve resting T cells and initiate an immune response. However, different DC subsets have been described, and *in vitro* culture methods to obtain cells with characteristics closely resembling their *in vivo* counterparts were developed using either human CD34⁺ stem cells or monocytes or rodent bone marrow (205).

When considering the effects of IL-10 on DC, it is important to note that mouse and human DC populations are not necessarily equivalent between species. Earlier work showed that IL-10 inhibited production of IL-12 and expression of costimulatory molecules by various types of DC (206–210), which correlated with its ability to inhibit primary alloantigen-specific T cell responses (211, 212). Recently, these observations have been extended and, in general, have shown that IL-10 treatment of DC can induce or contribute to a state of anergy in allo-antigen- or peptide-antigen- activated T cells (213–218). In addition, treatment of DC/T cell cocultures with glucocorticosteroids, vitamin D₃, prostaglandins, or IFN α resulted in IL-10-producing T cell populations with either Th2 or Tr1 characteristics (219–224). Whether in these experiments such agents act on DC, on the T cell, or both remains unclear.

Culture of human monocytes with GM-CSF and IL-4 for 6 days induces a population of immature DC that can be activated by LPS, CD40 ligand, or TNF to mature into highly efficient APC that secrete IL-12 and induce differentiation of naïve T cells to Th1 cells. Addition of IL-10 during culture with GM-CSF and IL-4 or at the activation step inhibits generation and maturation of monocyte-derived DC. Instead, as observed with monocytes cultured in the absence of GM-CSF and IL-4, IL-10 induced differentiation of these immature DC into macrophage-like

cells that expressed reduced levels of costimulatory molecules and MHC class II, did not produce IL-12, and exhibited enhanced phagocytosis (225–227). Increased expression of MCSF and MCSFR, as well as defined effects on expression of signal-transducing molecules, accompany these changes (145, 228). In contrast, IL-10 did not affect mature monocyte-derived DC; these cells may have lost IL-10R1 expression (KW Moore, R deW Malefyt, unpublished) in a way similar to fully differentiated DC from rheumatoid synovium (229).

IL-10 also affects lymphoid or plasmacytoid DC, defined in the human system by expression of IL-3R, CD4, and lack of CD11c. These cells produce large amounts of IFN α following activation by virus, and they differentiate in vitro with IL-3 and CD40L into “DC2” cells that can support differentiation of Th2 cells producing IL-10. IL-10 induced apoptosis of freshly isolated or cultured plasmacytoid DC (230), which could account for reduced production of IFN α observed following treatment of virus-activated PBMC with IL-10 (231). Interestingly, this DC population is enhanced in GCSF- or Flt-3 ligand-mobilized blood and, through its priming capacity for IL-10-producing Th2 cells, could contribute to prevention of GvHD and graft acceptance in peripheral blood stem cell transplantation (232, 233). The mouse DC population that has been designated lymphoid DC is defined by expression of CD8 α . Interestingly, these cells produce IL-10 and can efficiently inhibit tumor antigen-specific responses induced by CD8- DC (234).

Different DC populations producing IL-10 have been identified from Peyer's patches and liver; these populations are associated with development of either Th2 responses or hyporesponsiveness (235, 236). In contrast, human DC derived from CD34⁺ stem cells as well as mature Langerhans cells do not produce IL-10, although CD14⁺ DC that are equivalent to CD11c positive cells do produce IL-10 (237–240). In general, the effects of IL-10 on DC are consistent with inhibition of Th1 inflammatory responses and can be achieved by inhibitory effects on “inflammation-inducing DC” or by induction of anti-inflammatory T cell populations by IL-10-producing DC.

Effects of IL-10 on Neutrophils

LPS, LPS plus IFN γ or TNF, opsonized yeast, or the MP-F2 manno-protein fraction of *Candida albicans* variously induce production of TNF, IL-1 α/β , IL-8, IL-12p40, GRO α , MIP1 α/β , MIG, ITAC and IP10 by neutrophils; this cytokine and chemokine production is inhibited by IL-10 (177, 241–245). The inhibitory effects of IL-10 on cytokine and chemokine production were delayed, observed only from 2 h post-stimulation onward, and at least for LPS-induced production of chemokines were dependent on the inhibitory effects of IL-10 on endogenous TNF and IL-1 β production (119, 241, 242). IL-10 also attenuated production of other inflammatory mediators such as platelet activating factor (PAF) (246).

Contradictory findings have been reported concerning the effects of IL-10 on prostaglandin (PG) production by PMN. LPS, TNF, and IL-1 β induce expression of cyclooxygenase 2 (COX-2). Niiro et al. reported a reduction of COX-2 expression by IL-10, but others failed to confirm this (247, 248). In the same studies, Niiro

et al. described effects of endogenously produced IL-10 by PMN, whereas others failed to demonstrate IL-10 production by human neutrophils (249, 250). It is possible that PMN populations used by Niirö were contaminated by monocytes. It is also controversial whether IL-10 can directly inhibit generation of superoxide anion production and the respiratory burst or whether it regulates the enhancing effects of IFN γ on these processes (119, 251, 252).

However, in vivo, IL-10 suppressed killing of phagocytosed bacteria, and neutralization of endogenous IL-10 led to enhanced survival in murine models of *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and *Mycobacterium avium* infections (253–255). Furthermore, IL-10 inhibited phagocytosis of *E. coli* and attenuated neutrophil microbicidal activity toward internalized bacteria (256), which correlated with a reduction in CR3 expression. Interestingly, in contrast to human monocytes, IL-10 did not induce expression of CD64 (Fc γ RI) on neutrophils and did not modify ingestion of IgG-coated SRBC, C3-coated zymosan particles, or *Candida*, although inhibition of ADCC by IL-10 has been described (118, 252). As noted above, the absence of CD64 modulation correlated with the lack of stat1 and stat3 phosphorylation in freshly isolated neutrophils by IL-10 (118, 122).

As for monocytes, IL-10 enhanced production of IL-1RA by neutrophils (177, 257). Together with the inhibitory effects on IL-1 α/β production, this resulted in a significant shift in the IL-1 α/β :IL-1RA ratio and diminished the proinflammatory effects of IL-1. These inhibitory effects of IL-10 on cytokine and chemokine production are responsible for the observed reduction of neutrophil migration in IgG complex-induced lung injury and LPS- or antigen-induced pulmonary inflammation (258–262).

IL-10 does not directly affect the spontaneous rate of human neutrophil apoptosis (263). However, whether LPS- or cytokine-induced survival of neutrophils and eosinophils is inhibited by IL-10 is controversial (245, 249, 260, 264).

Inhibition by IL-10 of production of chemokines, proinflammatory cytokines, and mediators of granulocyte survival no doubt helps to limit the duration and harmful pathology of inflammatory responses.

Effects of IL-10 on B Cells and Immunoglobulin Production

IL-10 enhanced expression of MHC class II antigens and survival of resting mouse B cells (18), and it inhibited motility and IL-5-induced antibody production against thymus-independent type I and II antigens (produced by B-1 cells) (265–267); serum immunoglobulin levels and development of B-1 cells were nonetheless normal in IL-10 $-/-$ mice (26). Furthermore, inflammatory bowel disease (IBD) that develops in IL-10 $-/-$ mice is not dependent on B cells (268), as the incidence and severity of the disease is not altered in IL-10 $-/-$ \times Ig μ $-/-$ mice. Studies involving administration of IL-10 protein, IL-10 gene delivery, IL-10 transgenic mice, or inhibition of IL-10 production by neutralizing mAbs or gene targeted animals all suggest that the in vivo role of IL-10 in murine B cell function is limited (269–271). A notable exception is the delayed onset of autoimmunity in lupus-prone NZB mice treated with anti-IL-10 Mab (25); however, it is not clear

whether IL-10 directly affects B cells or instead acts on underlying autoimmune mechanisms that induce disease onset.

IL-10's effects on survival, proliferation, and differentiation of human B cells have been more extensively studied. IL-10 enhanced survival of normal human B cells (depending on their activation state), which correlated with increased expression of the anti-apoptotic protein bcl-2 (140, 272). IL-10 also induced hTERT expression and upregulated telomerase activity in B cells activated by anti-IgM (273). IL-10 is a potent cofactor for proliferation of human B cell precursors and mature B cells activated by anti-IgM, SAC, or CD40 cross-linking (20, 274). This IL-10-induced proliferation of activated B cells was further enhanced by both IL-2 and IL-4, which in the case of IL-2 correlated with IL-10-enhanced expression of the high-affinity IL-2 receptor on B cells (275).

B cell-derived and exogenous IL-10 affected B cell differentiation and isotype switching (276). Isotype-committed B cells, activated by SAC or anti-CD40 Mabs, produced large amounts of IgM, IgG1-3, and IgA in the presence of IL-10, and of IgG4 and IgE in the presence of both IL-10 and IL-4 (20, 277–280). Anti-CD40 and IL-10 stimulation of sIgD⁺ naive B cells also resulted in production of IgD, IgM, IgG1-3, and IgA (281–283), and it was shown that IL-10 is a switch factor for IgG1, IgG3 (284), and in combination with TGF β , for IgA1 and IgA2 (281, 285). Interestingly, in PBMC cultures, IL-10 enhanced IgG4 production, possibly by potentiating IL-4-induced IgG4 switching, and inhibited IgE production when added at the onset of culture, providing evidence that under certain conditions, it can differentially modulate IgG4 and IgE responses (277, 286). Long-term culture of B cells stimulated by either anti-CD40, activated T cells or follicular dendritic cells, and IL-10 resulted in differentiation of B cells into plasma cells (287–289) and IL-10 acted synergistically with CD27/CD70 signals to induce plasma cell differentiation from CD27⁺ memory B cells (290).

The effects of IL-10 on B cell function suggest its therapeutic use in at least two indications. IL-10 may enhance Ig production or isotype switching in patients suffering from common variable immunodeficiencies (CVI). IL-10 induced production of IgA by anti-CD40 activated B cells of patients suffering from IgA-deficiency, although no defects in IL-10 production were observed in these patients (291). In addition, IL-10 and CD40 activation induced IgG production by X-linked hyper-IgM-syndrome patients (292). Secondly, antagonists of IL-10 could be useful in treatment of antibody-mediated autoimmune diseases such as systemic lupus erythematosus (SLE). Indeed, positive correlations were demonstrated between serum IL-10 levels and severity of disease, and between the production of IL-10 and auto-antibodies by SLE patients' B cells (56, 293–296); anti-IL-10 treatment of SLE patients ameliorated disease in a pilot trial (297).

Direct Effects of IL-10 on T Cells

IL-10 strongly inhibited cytokine production and proliferation of CD4⁺ T cells and T cell clones via its downregulatory effects on APC function (5, 6). IL-10 also

directly affects the function of T cells and inhibits IL-2, TNF, and IL-5 production depending on activation conditions (17, 298, 299) as well as expression of CXCR4 and chemotaxis in response to the CXCR4 ligand SDF1 (300). In contrast, IL-10 has stimulatory effects on CD8⁺ T cells and induces their recruitment, cytotoxic activity, and proliferation (135, 136, 138, 301). Stimulatory activities of IL-10 on mouse T cells were also described where it acts as a thymocyte growth factor and augments outgrowth of cytotoxic T cell precursors (19, 21).

Interestingly, activation of T cells in the presence of IL-10 can induce nonresponsiveness/anergy, which cannot be reversed by IL-2 or stimulation by anti-CD3 and anti-CD28 (213). A role for IL-10 in induction and maintenance of nonresponsiveness or anergy was suggested by studies of anti-tumor cell responses, uv-induced tolerance, hapten-specific tolerance, parasitic and HIV infections, and superantigen-induced hyporesponsiveness (86, 302–309); such anergy can be induced by specific immunotherapy (310) or by continuous antigenic challenge in vivo (311). IL-10-mediated anergy can be associated with induction of a population of regulatory T cells that produce high levels of IL-10 and can suppress antigen-specific responses in vivo and in vitro (312–320) as is discussed later.

Biological Functions of EBV vIL-10

EBV vIL-10 mimics several activities of IL-10, including CSIF/macrophage deactivating factor activity on mouse and human cells (3–5, 8, 10, 178, 194) and mouse and human B cell stimulatory activities (18, 20, 281). However, the ability of vIL-10 to manifest several other IL-10 activities on mouse and human cells is markedly reduced. vIL-10 did not enhance class II MHC expression on mouse B cells (18) or effectively costimulate mouse thymocyte or mast cell proliferation (4, 19). Similarly, vIL-10 had greatly reduced (~1000-fold) ability to inhibit IL-2 production by an activated human CD4⁺ T cell clone, consistent with 3-log lower binding affinity for IL-10R1 (81). Nonetheless, sufficiently high vIL-10 concentrations did exhibit this latter activity.

These in vitro observations are consistent with animal model studies involving mL-10 or vIL-10 gene transfer into immunogenic and allogeneic mouse tumor cells (84, 86). mL-10-expressing tumors were more rapidly rejected compared to controls, but vIL-10-transduced tumor cells were either not rejected at all, or their mean survival time was significantly enhanced. Rejection of mouse heart allografts expressing vIL-10 was also inhibited (85). The results of such studies indicate that (a) vIL-10 has retained some—but not all—cIL-10 activities, and (b) by engaging only a subset of IL-10-responsive cells, vIL-10 can have a profoundly different effect on the outcome of an in vivo immune response than that of cIL-10.

What is the molecular basis for the different activity profiles of cIL-10 and vIL-10? That vIL-10 and cIL-10 differ most in sequence and structure in the N-terminal ~20 amino acids (4, 40) suggests that this region should be important. However, an isoleucine/alanine interchange at position 87 of hIL-10/vIL-10

had significant effects on the proteins' activities (88). hIL-10 and mIL-10 when substituted at position 87 with alanine (cIL-10 I87A) lost most or all ability to stimulate proliferation of mouse thymocytes and a murine mast cell line, while retaining the CSIF activities of cIL-10. Likewise vIL-10 substituted at position 87 with isoleucine (vIL-10 A87I) acquired significant mast cell stimulating activity. Moreover, hIL-10 (I87A), like vIL-10, exhibited substantially (~100-fold) lower binding affinity for IL-10R1, whereas vIL-10 (A87I) was only ~30-fold reduced in its receptor-binding ability compared to hIL-10. These *in vitro* biological activities of mutant c,vIL-10 were paralleled by survival kinetics of mouse heart allografts transfected to express wild-type and mutant c,vIL-10s: hIL-10 (I87A), similar to vIL-10, enhanced survival compared to wild-type hIL-10, while vIL-10 (A87I) was significantly less able to prolong graft survival than vIL-10. While other sequence differences between cIL-10 and vIL-10 are doubtless important, the significance of position 87 is striking and awaits clarification via structural studies.

It is not yet certain if the restricted activities of vIL-10 developed via evolutionary drift or are of actual benefit to EBV. However, since vIL-10 is expressed during the lytic phase (82, 83), presumably the target cells for which it retains specificity—dendritic cells, macrophages/monocytes, B cells—are those specifically relevant to that portion of the EBV life cycle. vIL-10's ability to inhibit dendritic cell/macrophage/monocyte activation probably suppresses an anti-viral immune response, thus allowing the virus to establish latency. This idea was supported by studies showing that cells infected with a vIL-10-deleted EBV were, unlike wild-type virus-infected cells, unable to block IFN γ production by autologous human peripheral blood cells (321). In addition, the B cell growth and differentiation promoting activity could enhance the numbers and susceptibility to infection of EBV's principal host cell. However, in the absence of good animal models of EBV infection, it has proven difficult to confirm such notions. Whether vIL-10 plays any part in EBV-induced B cell transformation is controversial (321–323). Low IL-10 receptor (IL-10R1) binding affinity may restrict vIL-10 to local effects in the vicinity of the infected cell, as suggested by *in vivo* studies (85, 86). In any case, because it has been so highly conserved, vIL-10 likely confers a number of adaptive advantages upon EBV in its interaction with the immune system. Moreover, capture of an IL-10 gene by the ancestor of EBV was likely an important event in the development of the virus as a sophisticated, mostly benign parasite.

SYSTEMIC AND LOCALIZED ACUTE INFLAMMATION

A systemic inflammatory response can occur following septicemia or endotoxemia, as well as after non-infectious events such as severe trauma, burn, or ischemia-reperfusion injuries. A cascade of events including pro-inflammatory cytokine production, cell trafficking, extravasation, mediator production, coagulation, fibrinolysis, and changes in hemodynamic parameters and microvascular permeability can ultimately lead to disseminated intravascular coagulation (DIC), multiple

organ failure, and death. It is important to note that the initial systemic inflammatory response syndrome (SIRS), which includes production of TNF and IL-1, can be followed by a state of immunosuppression or immunoparalysis (324).

TNF and IL-1 play a central role in the initiation and propagation of these events, since their administration can mimic—and inhibition of their production can prevent and ameliorate—this inflammatory response. The inhibitory effects of IL-10 on proinflammatory cytokine production and physiology of individual cell types suggest that it could have potent anti-inflammatory activities *in vivo*. Indeed, a protective role of IL-10 in experimental endotoxemia has been demonstrated. IL-10 rescued Balb/c mice from LPS-induced toxic shock, which correlated with reduced serum levels of TNF (325, 326). Inhibition of TNF production in experimental endotoxemia was also observed following IL-10 administration in baboons and humans (327, 328). Both IL-10 protein and intratracheal IL-10 gene transfer protected mice from a lethal intra-peritoneal endotoxin challenge and furthermore reduced pulmonary TNF levels and neutrophil infiltration following LPS challenge (329).

Administration of endotoxin induced IL-10 production in mice, chimpanzees, baboons, and humans (328, 330–332). This endogenous IL-10 confers significant protection from the harmful effects of endotoxin challenge and reduces TNF, IFN γ , and MIP-2 levels (333, 334) as well as regulates hemodynamic parameters, leukocyte-endothelial cell interactions, and microvascular permeability (335). Its protective role in endotoxemia is also clearly observed in mice treated from birth with anti-IL-10 Mabs and in IL-10 $-/-$ mice, which are killed by 20-fold lower doses of LPS than kill wild-type mice (24, 28). IL-10 $-/-$ mice were also extremely vulnerable to a generalized Schwartzmann reaction in which prior exposure to a small amount of LPS primes the host for a lethal response to a subsequent, otherwise sublethal dose (28). IL-10 is implicated in *in vitro* induction of endotoxin tolerance (336) and is involved in impaired antigen presentation observed under these conditions (337, 338). Interestingly, reduced expression of HLA-DR antigens on monocytes can be used as a prognostic marker for identification of patients with high risk of infection (339). As in endotoxin challenge models, IL-10 has shown efficacy in ischemia reperfusion and burn models (340–342).

The effects of IL-10 have also been assessed in infectious sepsis models using live microorganisms. In a model of septic peritonitis in which mice undergo cecal ligation and puncture, endogenous IL-10 was protective (334, 343, 344), and IL-10 protected neonatal mice from lethal streptococcal B infections (345). Furthermore, IL-10 prevented lethality due to SEB-induced shock, which is dependent on IL-2 and IFN γ production by T cells (346, 347).

Human IL-10 production during septicemia and septic shock correlated with intensity of the inflammatory response, severity of injury (348–353), and with clinical outcome. This was especially evident in patients suffering from septic shock associated with meningococcal infections (354–356). In addition, many strategies that are used to intervene in sepsis affect IL-10 production (357–359), indicating an important role for this cytokine in controlling systemic inflammatory responses.

Similarly, IL-10 exhibited protective effects in several experimental models of local inflammation, such as pancreatitis (360), uveitis (361–364), keratitis (365), hepatitis (366), peritonitis (334, 343, 344), lung injury (259, 261, 367, 368), and brain or spinal cord injury (369, 370).

IL-10 IN INFECTIOUS DISEASE

The challenge faced by the immune system of an infected host is to respond with sufficient intensity and duration to control and eliminate the infection while minimizing nonspecific injury to host tissue. IL-10 plays a central role in striking a balance between pathology and protection; indeed, the phenotype of IL-10^{−/−} mice suggests that this is the most essential of its many functions.

Certain aspects of IL-10 biology can be studied *in vitro* by measuring the effect of IL-10 on the responses of individual cell types to microorganisms or microbial products. However, host-pathogen interactions typically are complex, varying in time and location according to the life cycle of the pathogen and the evolution of the host response. Most of what has been learned about IL-10 in infectious disease derives from animal model (principally mouse) experiments in which pathology, protection, or both are altered by manipulating levels of IL-10 *in vivo*.

Innate and Specific Immune Responses to Intracellular Bacterial, Fungal and Protozoan Infections

Many of the inflammatory responses triggered by infectious microorganisms and regulated by IL-10 have been described in the previous section. The central features of the innate and adaptive immune responses against most intracellular pathogens are shown in Figure 1. A key concept in this scheme is the integral link between innate and adaptive immunity (371). Experimental support derives primarily from a few well-studied infections in mice, including *L. monocytogenes* (372, 373), *C. albicans* (374, 375), *L. major* (376), and *T. gondii* (377). However, a large body of data now confirms the generality of these mechanisms in humans and experimental animals, with, of course, many individual variations.

This “typical” response (Figure 1) to infection with a wide range of bacterial, fungal, and protozoan pathogens can be expressed as a sequence of distinct intercellular interactions leading to induction of an array of microbiocidal effector functions:

1. Recognition of the microbe or specific microbial products by macrophages, neutrophilic granulocytes, and/or dendritic cells. Many types of receptors can be involved in this recognition, and our understanding of this “primitive” form of immunity is far from complete. Many recognize molecules and chemical structures common to groups of microorganisms, such as bacterial endotoxin (recognized by Toll-like receptor 4) or cell-wall polysaccharides (recognized by a variety of lectins).

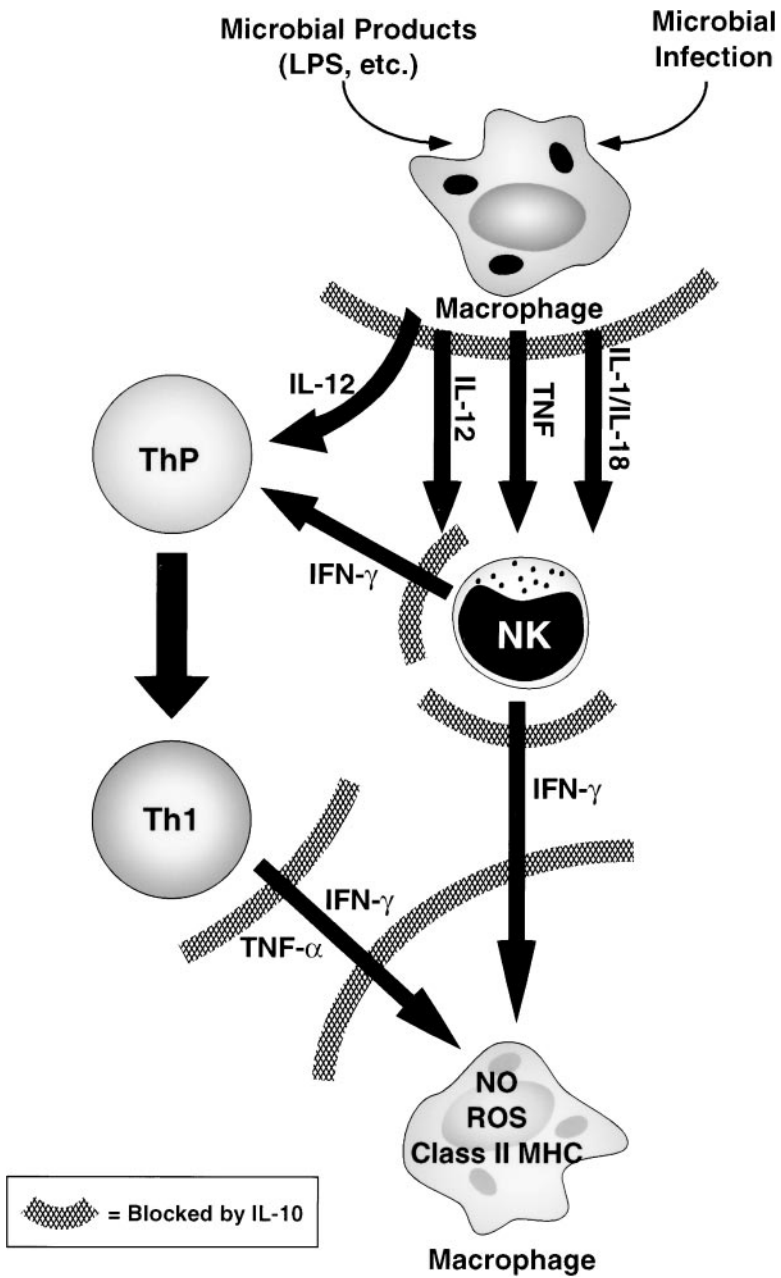


Figure 1 A schematic depiction of IL-10's roles in regulating the innate and adaptive immune responses to infection.

2. Recognition of microbial structures leads to production of multiple cytokines, especially IL-12, IL-18, TNF, and IL-1 by macrophages and monocytes. The combination of IL-12, IL-1, and TNF is particularly efficient in stimulating rapid production of IFN γ by NK cells. For fungal pathogens, such as *Candida*, neutrophils can be the major cell type producing IL-12 at this stage (119, 378).
3. NK-produced IFN γ induces multiple microbiocidal functions in macrophages, such as phagocytosis and production of nitric oxide and reactive oxygen intermediates, and stimulates cell infiltration by both macrophages and neutrophils. These mechanisms, in aggregate, can be very effective in controlling infections, even in the absence of subsequent specific T cell responses.
4. T cells responding to microbial antigens in a microenvironment dominated by this set of cytokines, especially IL-12 and IFN γ , preferentially differentiate into Th1 cells.
5. Th1 cells, largely through the production of IFN γ and TNF, continue to mediate essentially the same effector functions as the innate response, but with increased specificity and memory.

IL-10 inhibits many of the individual steps in this pathway of antimicrobial immunity (Figure 1). The inhibitory effect on some individual processes, even under optimized conditions, is often no more than 3- to 10-fold. However, this modest inhibition can be multiplied at sequential steps in the pathway, resulting in profound inhibition of the ultimate effector functions. Thus, the differences in response to infection between IL-10-overexpressing and IL-10-nonexpressing mice (Table 1) can sometimes be quite dramatic, greater than would be expected from a single in vitro analysis.

IL-10 in Animal Models of Infectious Disease

The overall role of IL-10 in animal models (principally mouse) of infectious disease has been determined by experimentally elevating or reducing IL-10 during the course of infection. In virtually all cases, elevated IL-10 levels have been produced by frequent injections of recombinant IL-10 or by the use of IL-10 transgenic mice. Likewise, reduction or elimination of IL-10 is effected either by treatment with neutralizing anti-IL-10 Mab or via the use of IL-10 $-/-$ mice. In general, these experiments are structured to produce mice with either little or no IL-10, or with high IL-10 levels effecting full IL-10R occupancy, thus defining the maximum range of IL-10 effects in these infections.

The effects of manipulating IL-10 in bacterial, fungal, and protozoan infections are summarized in Table 1, in terms of the effect on control or clearance of the infectious agents itself. Despite model-specific variations in treatment regimens and readouts, it is clear that resistance to infection can nearly always be improved by reducing IL-10 levels. Thus, even normal IL-10 levels tend to limit the

effectiveness of the immune response to most pathogens. The inhibition imposed by endogenous IL-10 is far from complete, however, as administration of exogenous IL-10 nearly always further impairs an anti-pathogen response.

Based on the known effects of IL-10 on inflammatory responses (Figure 1), both innate and adaptive immune responses should be enhanced or impaired by experimental depletion or elevation, respectively, of IL-10 in vivo. This has been confirmed in mouse models in which the two forms of immune response can be clearly distinguished. For example, elevated IL-10 severely compromises resistance to *Listeria* in *scid* mice, which are deficient in the T and B cells required for adaptive immunity, but retain normal innate immunity (379,380). Similarly, the enhanced innate response to *Listeria* in IL-10^{-/-} (381) and anti-IL-10-treated (382) mice leads to rapid control of *Listeria* within the first few days of infection. Similar enhancement of early innate responses has been reported in *C. albicans* (383), *T. gondii* (384, 385), and *T. cruzi* (386) infections.

The effects of altering IL-10 levels in viral infection models have not been included in Table 1, as there are very few reports in which viral titers have been measured. IL-10^{-/-} mice have more severe pathology and morbidity than do wild-type mice in a neurotropic mouse hepatitis virus model, but do not clear the virus more effectively (387). Similarly, rIL-10 reduced lesion formation and mortality in a viral myocarditis model, but did not lead to increased virus titers (388). The relative lack of influence of IL-10 on these antiviral responses may reflect the greater involvement of CD8⁺ T cells in most antiviral responses. In contrast, Vaccinia virus replication is significantly impaired in IL-10^{-/-} mice (389), perhaps reflecting a greater contribution of CD4⁺ T cells to this response.

Modulation of Immunopathology by IL-10

The effects of IL-10 on pathogen control are only part of a complete view of IL-10 in infectious disease. The potent antimicrobial effector mechanisms induced via the pathway illustrated in Figure 1 can also cause significant collateral damage to the host that is often more harmful than the infection itself. This damage can range from localized destruction of infected cells to widespread tissue necrosis, from transient cellular infiltration to chronic granuloma formation with fibrosis and replacement of normal tissue. Moreover, destruction of small areas of critical tissues, such as cardiac muscle or myelin sheath, can have serious consequences. A sufficiently strong systemic response to microbes or their products can also lead to septic/toxic shock resulting in death from multiple organ failure. These consequences can occur in a host that is, paradoxically, controlling or clearing the primary infection quite effectively.

Thus, the critical role of IL-10 in infectious disease appears to be modulation of the pathological consequences of inflammatory responses to microbial pathogens. As described above for viral infections, this protection from immunopathology can occasionally involve minimal inhibition of the antimicrobial response by IL-10. More frequently, decreased immunopathology is at the expense of less efficient

TABLE 1 Low IL-10 increases resistance and high IL-10 increases susceptibility to intracellular pathogens in mouse models

Organism	Enhanced disease susceptibility when IL-10 increased by:			Enhanced disease resistance when IL-10 decreased by:		
	Method	Result	References	Method	Result	References
Bacteria						
<i>Listeria monocytogenes</i>	rIL-10	Yes	(379)	Anti-IL-10	Yes	(382)
	IL-10 TG	Yes	(269)	IL-10 KO	Yes	(381)
	induced IL-10	Yes	(380)	—	—	—
<i>Salmonella choleraesuis</i>	—	—	—	Anti-IL-10	Yes	(644)
<i>Klebsiella pneumoniae</i>	—	—	—	Anti-IL-10	Yes	(254, 645)
<i>Streptococcus pneumoniae</i>	rIL-10	Yes	(255)	Anti-IL-10	Yes	(255)
<i>Staphylococcus aureus</i>	—	—	—	Anti-IL-10	Yes	(646)
<i>Borellia burgdorferi</i>	—	—	—	IL-10 KO	Yes	(394)
<i>Chlamydia trachomatis</i>	—	—	—	Anti-IL-10	Yes	(647)
	—	—	—	IL-10 KO	Yes	(648)

<u>Mycobacteria</u>					
<i>Mycobacterium avium</i>	—	—	Anti-IL-10	Yes	(253, 649)
<i>M. tuberculosis</i>	—	—	IL-10 KO	No	(650)
<i>M. bovis BCG</i>	IL-10 TG	Yes	IL-10 KO	Yes	(652)
<u>Fungi</u>					
<i>Candida albicans</i>	rIL-10	Yes	Anti-IL-10	Yes	(654)
	—	—	IL-10 KO	Yes	(383, 655)
<i>Cryptococcus neoformans</i>	—	—	IL-10 KO	Yes	(656)
<i>Coccidioides immitis</i>	—	—	IL-10 KO	Yes	(657)
<i>Aspergillus fumigatus</i>	—	—	Anti-IL-10	Yes	(658)
	—	—	IL-10 KO	Yes	(655)
<u>Protozoa</u>					
<i>Leishmania major</i>	rIL-10	No	Anti-IL-10	No	(659)
	IL-10 TG	Yes/No	IL-10 KO	Yes	Coffman, unpublished
<i>Trypanosoma cruzi</i>	rIL-10	Yes	Anti-IL-10	Yes	(660)
	—	—	IL-10 KO	Yes	(386, 391, 392)
<i>Trypanosoma congolese</i>	—	—	Anti-IL-10	Yes	(661)
<i>Toxoplasma gondii</i>	—	—	IL-10 KO	Yes	(384)
					(scid mice)

control or clearance of the infection. Experiments (Table 1) exploring extremes of high or low IL-10 demonstrate the consequences of inappropriate balance between inflammation and IL-10. IL-10^{-/-} mice infected with *T. gondii* (384, 385), *P. chabaudi* (390), or certain strains of *T. cruzi* (391, 392) have greatly elevated IFN γ , IL-12 and TNF levels and reduced parasitemia, but a substantially increased risk of death from a toxic shock-like syndrome, compared to wild-type controls.

Similarly, infection of IL-10^{-/-} mice with *H. hepaticus* leads to enterocolitis (393), and infection with *B. burgdorferi* leads to more severe Lyme arthritis in IL-10^{-/-}, compared to wild-type mice (394). To the viral infection models mentioned previously can be added the model of herpes simplex virus-induced keratitis, which can be substantially inhibited by topical administration of IL-10 (365, 395, 396). In these examples, immunopathology is dependent upon Th1 (CD4⁺) or Tc1 (CD8⁺) T cells, but IL-10 also inhibits Th2-mediated granulomas and fibrosis in mouse models of schistosomiasis (397–400).

The clinical promise of IL-10 in treating viral immunopathology was shown by a recent study in which hIL-10 reversed liver fibrosis without increasing viral titers in patients with chronic hepatitis C infection (401).

Evidence for a Role of IL-10 in Human Infectious Disease

As experimental tests of IL-10 in vivo of the sort that have been so informative in mouse models are not feasible in humans, it is necessary to rely upon correlative evidence in vivo and experimental evidence in vitro to show similarities or differences in IL-10 function between human and mouse.

Strong correlation exists between IL-10 protein or mRNA levels and a number of chronic or progressive human infectious diseases, including visceral leishmaniasis, (402–405), malaria (406, 407), filariasis (408–410), leprosy (411), tuberculosis (412, 413), candidiasis (414), and *M. avium* infection (415). In some diseases, IL-10 levels decreased upon successful resolution of the infection by drug therapy. Thus, much of the human data corresponds to data obtained, often with the same pathogens, in mouse models. However, correlative data do not allow one to distinguish whether high pathogen burdens are the cause of elevated IL-10 or vice versa. In actuality, it is likely that both scenarios occur.

The second type of evidence that IL-10 inhibits protective immunity in human, as in mouse, comes from experiments in which anti-IL-10 Mabs restore responses of pathogen-specific T cells from infected patients in vitro. This has been demonstrated in a number of chronic diseases, including visceral leishmaniasis, (403, 416), filariasis (409, 410), schistosomiasis (307), leprosy (417), and tuberculosis (418). Typically, PBL from such patients make little or no recall response in vitro to the pathogen or to antigenic fractions thereof. In most of these diseases, patients have been deemed “anergic” or “unresponsive” to the pathogen, despite quite high microbial burdens. However, neutralization of IL-10 during a 2–3-day culture period usually reveals a significant response of the Th1 or Th2 type, demonstrating active suppression by IL-10. The combination of elevated

IL-10 *in vivo* and IL-10-mediated unresponsiveness to antigen *in vitro* in many of these chronic diseases suggests strongly that IL-10 is a major cause of ineffective antipathogen immune responses. Such correspondence between mouse and human infections with the same or closely related organisms suggests that extrapolation from animal models is valid.

IL-10 has been studied extensively in HIV infection as well. Asymptomatic HIV⁺ individuals frequently have defective responses not only to HIV proteins, but also to common antigens such as influenza and tetanus toxoid (419). As in the above examples, responses of blood lymphocytes from these patients can be enhanced *in vitro* by neutralization of IL-10 (420–422). It is not clear whether IL-10 plays a similar role in AIDS patients with low CD4⁺ T cell counts, however. Understanding the role of IL-10 in AIDS is complicated by evidence that IL-10 has direct effects on virus production by infected cells. The significance of these *in vitro* observations is not yet clear, especially as IL-10 has been reported to either stimulate (423–425) or inhibit (426–428) HIV production by monocytic cells *in vitro*.

In summary, there is now extensive evidence in the mouse, and significant confirmation in human, that IL-10 production usually imposes some limits on the effectiveness of antipathogen immune responses, especially innate immunity and adaptive Th1 responses. This cost is often outweighed by the ability of IL-10 to protect the host from collateral damage by antimicrobial cytokines and effector molecules. A successful response must strike a balance between protection and pathology, and IL-10 appears central to the establishment of this balance. Thus, both IL-10 and IL-10 inhibitors may offer therapeutic promise in the treatment of either infectious diseases or infection-related immunopathologies.

THE ROLE OF IL-10 IN PROTECTION FROM ORGAN-SPECIFIC AUTOIMMUNITY

IL-10 plays a very important role in limiting the immune response to pathogens to eradicate the pathogen with minimum immunopathology to the host. Likewise, IL-10 has been suggested to play a role in peripheral tolerance and in protection against autoimmunity. In chronic autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), diabetes, insulin-dependent diabetes mellitus (IDDM), and rheumatoid arthritis (RA), pathogenic roles have been ascribed to Th1 cells, due to their production of cytokines such as IFN γ , lymphotoxin, and TNF (429–433). In contrast, a protective role was attributed initially to Th2 cells because of their ability to produce the cytokines IL-4 and IL-10. However, this latter notion may not be accurate, since IL-10 is produced by a wide variety of cells. In this context CD4⁺ T cell regulatory populations producing high levels of IL-10 have been described that can inhibit the proliferation of naive CD4⁺ T cells and/or the induction of pathology by mucosal antigens, such as in inflammatory bowel disease (213, 312, 317, 434, 435). IL-10, as well as IL-4 and TGF β ,

may play an essential role in tolerance to self antigens (436–440) and to mucosal antigens (312, 317, 434, 440, 441). However, $TGF\beta^{-/-}$ mice develop a *multi-organ* autoimmune syndrome (442), whereas IL-4 and IL-10-deficient mice do not. IL-10-deficient mice do spontaneously develop inflammatory bowel disease (26, 443), which appears due to a defect in IL-10-producing regulatory T cells that moderate responsiveness to intestinal flora (317).

In this section the possible role of IL-10 in regulation of responses to auto- as well as mucosal antigens is discussed, as well as the potential use of IL-10 as a therapeutic in autoimmune and other inflammatory diseases. Regulatory T cells as a source of IL-10 and their potential in regulating both Th1 and Th2-mediated pathologies are discussed, as well as factors that induce IL-10 production.

IL-10 and Regulation of Experimental Autoimmune Encephalomyelitis (EAE)

Initial studies showed that spontaneous recovery of rats and mice from EAE correlated with expansion of Th2-like cells producing IL-4 and/or IL-10 (444–446). Furthermore, low IL-10 production was observed in chronic relapsing EAE (447), suggesting that endogenous IL-10 may regulate such pathologies of the central nervous system (CNS). IFN β , which has been used with some success to treat MS patients, can induce expression of IL-10 in peripheral blood mononuclear cells (448), suggesting that one mechanism for protection involves IL-10 production.

Direct support for a role of IL-10 in regulating CNS autoimmune pathologies was provided by studies showing that neutralization of endogenous IL-10 increased the severity and incidence of SEB- or TNF-induced EAE relapse (449) and that disease is more severe in IL-10 $^{-/-}$ than in wild-type mice (450–452).

Attempts to treat EAE with recombinant IL-10 yielded contradictory results. Systemic treatment of rats or mice with IL-10 partially inhibited disease progression in EAE induced by active immunization with CNS antigens, but only if treatment was begun at the time of initial immunization (453, 454). In this study, the initial use of site-directed delivery of IL-10 to the CNS at first yielded conflicting results. Intracranial injection of IL-10 or of plasmids expressing IL-10 cDNA under the control of a retroviral promoter 12 days after active immunization did not suppress EAE (455), nor did adoptive transfer of a myelin basic protein (MBP)-specific hybridoma transduced with IL-10 (456). This lack of effect could also reflect the timing of IL-10 expression. In contrast, IL-10 administration exacerbated disease in an adoptive transfer model of EAE (457). This latter result might have been obtained because (a) appropriate levels of IL-10 in the CNS were not attained, and/or (b) IL-10 may be necessary to inhibit development and/or migration of pathogenic encephalitogenic Th1 cells.

However, several other reports showed that IL-10 can effect virtually complete inhibition of EAE. Antigen-inducible IL-10 expressed under control of the IL-2 promoter in proteolipid protein (PLP)-specific T memory cells suppressed EAE when T cells were adoptively transferred to PLP-immunized mice one day prior to

expected disease onset (458). Transgenic FVB X SJLF1 mice expressing murine IL-10 under control of the CD2 promoter were resistant to EAE induced by PLP immunization (450). Similarly, mice transgenic for human IL-10 (hIL-10-Tg) expressed under the control of the MHC class-II promoter were completely protected from induced EAE (459).

In hIL-10Tg mice several mechanisms are possible for the regulatory effect of hIL-10 in EAE: inhibition of the initial development of autoreactive Th1 cells; inhibition of Th1 effector function by IL-10; immune deviation toward a Th2-type response; or development of T regulatory populations which themselves produce IL-10. Generation of Th1 autoantigen was not impaired in hIL-10Tg mice, nor was there evidence of immune deviation to a Th2 response. IL-10-producing regulatory T cells were not implicated, as protection did not require T-cell-derived endogenous mIL-10. Furthermore, pathogenic Th1 populations passively transferred to hIL-10Tg mice caused no disease, whereas they did in nontransgenic controls. These observations suggested that the principal action of transgenic hIL-10 was inhibition of the effector stage of the autoimmune response (459). Such an effect of IL-10 on effector functions induced by Th1 cytokines, rather than on the Th1 cells themselves, was also evidenced by the ability of a replication-defective adenovirus vector expressing hIL-10 (hIL-10-rAdV), delivered intracranially, to completely inhibit EAE when given only 2–4 days prior to the onset of symptoms (460). Additionally, this treatment halted progression and accelerated remission when given to mice with active disease and prevented relapses when given during the first remission in a relapsing-remitting disease model.

The importance of the site and timing of IL-10 administration to therapeutic success was also demonstrated in experiments with hIL-10-rAdV (460). Intravenous injection of hIL-10-rAdV produced approximately the same systemic hIL-10 levels as intracranial injection, but was undetectable hIL-10 in the CNS and poor protection from EAE. Similarly, daily intracranial injection of hIL-10 protein could protect from EAE, but protection was rapidly lost when injections ceased. This need for sustained high hIL-10 levels at the site of potential inflammation indicates that IL-10 acts primarily by blocking entry and/or activity of pathogenic T cells in the CNS.

How Does IL-10 Affect Insulin-Dependent Diabetes Mellitus in the Nonobese Diabetic Mouse?

The nonobese diabetic (NOD) mouse is an animal model of human insulin-dependent diabetes mellitus (IDDM) which develops spontaneous clinical disease at 4–7 months with destruction of the β cells of the islets and elevations in blood glucose (432, 461, 462). The disease is both CD4⁺ and CD8⁺ T cell dependent (463) and a role for macrophages (464) has been described. Th1 cells are clearly implicated in the pathology of diabetes (429–431), thus suggesting that IL-10 might inhibit the onset or severity of IDDM in NOD mice.

However, the effects of IL-10 on diabetes in this model are surprisingly complex. Some experiments support the predicted role of IL-10 as an immunosuppressive factor in IDDM. Daily subcutaneous treatment of 9–10-week-old NOD mice delayed onset of diabetes and significantly reduced disease incidence (465). Treatment with IL-10 also reduced the severity of insulinitis and prevented cellular infiltration of islet cells. Furthermore, systemic administration with a noncytolytic IL-10/Fc fusion protein in mice from 5 to 25 weeks of age completely prevented the occurrence of diabetes in NOD female mice and appeared to confer lasting protection following cessation of therapy (466). Passive transfer of splenic leukocytes from IL-10/Fc-treated NOD mice inhibited disease caused by simultaneous transfer of splenic leukocytes from acutely diabetic mice into irradiated, prediabetic NOD recipients (466). Moreover, adoptive transfer of islet-specific T cell clones transduced with IL-10 cDNA also prevented diabetes (467).

In contrast to these immunosuppressive effects of IL-10, expression of an IL-10 transgene by insulin-producing pancreatic β cells led to an accelerated onset of diabetes in NOD mice (468, 469), with no inhibition of immune-mediated destruction of islets (470). NOD mice expressing an IL-10 transgene in glucagon-producing pancreatic α cells also developed accelerated diabetes (471). This apparently contradictory effect of IL-10 on IDDM depended upon transgene expression in early life and was accompanied by enhanced leukocyte extravasation into the pancreatic tissue (468). Consistent with the notion that it is the timing of IL-10 expression that is important for its immunostimulatory effects in IDDM, neutralization of endogenous IL-10 in female NOD mice at three weeks of age inhibited development of insulinitis in NOD mice (472), whereas treatment at a later age with anti-IL-10 had no effect on the onset of diabetes (465).

Protective Effects of IL-10 in Models of Rheumatoid Arthritis

IL-10 is also expressed at inflammatory foci in other autoimmune diseases where Th1 cytokines are believed to play a pathogenic role, such as in the joints of rheumatoid arthritis (RA) patients (293, 473–475). Endogenous IL-10 produced in the joint by synovial macrophages and T cells (473, 474), inhibited production of inflammatory cytokines by synovial cells, suggesting that IL-10 may have a protective role *in vivo* (474). Although IL-10 expression in RA has been linked to increased autoantibody production and B cell activation (476), IL-10 was protective in animal models of RA. When administered to animals before and/or after induction of disease, IL-10 reduced joint swelling, infiltration, cytokine production, and cartilage degradation in collagen- and streptococcal cell wall-induced arthritis (477–483).

IL-10 in the Pathogenesis of Systemic Lupus Erythematosus (SLE)

SLE is a complex autoimmune disorder characterized in part by polyclonal B cell activation, high levels of serum autoantibodies and glomerular immune complex

deposition. Both B cells and macrophages from SLE patients spontaneously produce high levels of IL-10 in vitro (484), and several studies have shown a correlation between serum levels of IL-10 and disease activity (57, 294, 485, 486). Studies in both a mouse model of SLE (25) and in *scid* mice reconstituted with PBL from SLE patients (56) showed that autoantibody production and immune complex pathology could be substantially inhibited by treatment with anti-IL-10 antibodies. These studies suggested that IL-10 stimulation of immunoglobulin production by B cells plays a major role in the pathogenesis of SLE. More recently, treatment of 6 SLE patients with a mouse anti-hIL-10 Mab achieved a long-lasting reduction of most disease parameters in 5/6 patients (297). As noted, overproduction of IL-10 in SLE patients may have a genetic basis.

IL-10 Modulates Allergic Responses

Airway infiltration by inflammatory cells, particularly eosinophils, basophils, and mast cells, along with production of IgE, plays an important role in the pathology of asthma and other allergic diseases (487–489). Th2 cells secreting IL-4, IL-5, and IL-13 induce, prolong, and amplify the allergic response by enhancing production of IgE and the recruitment, growth, and differentiation of eosinophils and mast cells; and themselves directly cause airway hyperreactivity (487–491). Therapies for asthma have thus focused on eliminating eosinophils, lymphocytes, or IgE, or on directly antagonizing pathology-inducing mediators such as histamine or leukotrienes (487, 488).

It has been suggested that Th2-mediated allergic diseases such as asthma result from inadequate Th1 cytokine production (487, 492). However, allergen-specific Th1 cells are not prominent in the lungs of normal, nonasthmatic individuals, suggesting other mechanisms for regulation of responses to allergens. Furthermore, the presence of activated Th1 cells in the lung can also lead to inflammatory pathologies (487).

A role for IL-10 in regulation of immune responses to allergens was first suggested by studies showing that IL-10 could inhibit survival of and cytokine production by eosinophils stimulated with LPS (264). Later it was shown that IL-10 could also inhibit production of cytokines such as TNF and IL-6 by stimulated mast cells (493, 494). These in vitro findings were corroborated by in vivo studies in which a single intranasal dose of IL-10 concurrent with antigen challenge in previously sensitized mice specifically inhibited airway neutrophilia and eosinophilia and TNF production induced by antigenic challenge (258).

Expression of IL-10 via gene transfer in mouse lung also inhibited mucosal sensitization to aerosolized ovalbumin (OVA) in the context of nasal administration of a replication-deficient adenovirus carrying the GM-CSF gene (Ad/GM-CSF) (270). Cotransfer of the IL-10 gene (Ad/IL-10) inhibited the marked Th2 cytokine profile and eosinophilia otherwise observed, decreased the number of mononuclear cells, neutrophils, and eosinophils in the BALF, and reduced antigen-specific IgE levels. These effects were not mediated by IFN γ , indicating that a Th2 to Th1

switch was not involved. Mice exposed to OVA in the context of Ad/GM-CSF or the vector control were hyperresponsive to methacholine (McH) when re-exposed to aerosolized OVA 6 months later. However, responsiveness of IL-10-treated mice to McH was similar to that of naive mice. An IL-10-induced decrease in grain dust-induced airway inflammation and hyperreactivity was also observed (495). In contrast, other studies showed that, although IL-10 can indeed inhibit a pulmonary inflammatory response, it can also in some cases enhance airway hyperreactivity in allergen-sensitized mice and actually appears to be required for airway hyperresponsiveness (496, 497). This difference may reflect the timing of IL-10 administration relative to allergen sensitization and/or the time after administration that the mice were examined.

Consistent with a role for IL-10 in allergic inflammation is the observation that significantly less IL-10 is found in the lungs of asthmatic patients (498, 499). Thus, IL-10 production in lungs of nonasthmatic patients may play a role in limiting pathology-inducing inflammatory Th2 responses. The anergic state arising in peripheral T cells after allergen (bee-venom)-specific immunotherapy (BV-SIT) results from increased production of IL-10 (310), initially by activated CD4⁺ CD25⁺ allergen-specific T cells, later by B cells and monocytes. Neutralization of IL-10 in PBMC from patients undergoing BV-SIT fully reconstituted allergen-specific proliferative and cytokine responses. A role for endogenous IL-10 in the regulation of Th2 responses was also demonstrated in a murine model of allergic bronchopulmonary aspergillosis (500). Lung cells and BALF obtained from IL-10^{-/-} mice after repeated *Aspergillus fumigatus* inhalation produced highly elevated levels of IL-4, IL-5, and IFN γ . IL-10^{-/-} animals exhibited exaggerated airway inflammation compared to wild-type control mice (500).

IL-10 in Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis are complex chronic diseases of the gut, the etiology and pathogenesis of which are poorly understood. CD4⁺ T cells are responsible for much of the disease pathogenesis, but subsets of CD4⁺ T cells also play a role in normal regulation of responses to mucosal antigens (501, 502). That IL-10 plays an important role in mucosal immune regulation was demonstrated by the observation that IL-10^{-/-} mice develop enterocolitis (26). Development and persistence of colitis in IL-10^{-/-} mice is dependent on IL-12 (503) and requires the presence of resident enteric bacteria (504). Transfer of CD45RB^{high} CD4⁺ T cells from normal donors into C.B-17 SCID mice also led to development of a severe inflammatory response in the colon (505, 506) that is IFN γ - and TNF-dependent (505). Administration of mIL-10 prevented colitis in SCID mice reconstituted with CD45RB^{high} CD4⁺ T cells (505). Furthermore, CD45RB^{high} CD4⁺ T cells isolated from transgenic mice expressing IL-10 under control of the IL-2 promoter failed to transfer colitis but, rather, were able to inhibit colitis induced by wild-type CD45RB^{high} CD4⁺ T cells (507). Oral administration to mice

of *Lactococcus lactis* secreting mIL-10 reduced dextran sulfate sodium-induced colitis and prevented colitis onset in IL-10^{-/-} mice (508). Taken together, these studies provide evidence that IL-10 is an important regulator of intestinal immune responses.

IL-10-Producing Regulatory T Cell Subsets Distinct from Th1 and Th2 cells

Multiple studies now suggest that regulatory T cell populations exist that are distinct from Th2 cells. Regulatory CD4⁺ T cell subsets have been described that inhibit cell-mediated immune responses and/or inflammatory pathologies (312, 434, 436–441, 509–511). These T regulatory cell subsets have been isolated under different conditions and exhibit different cytokine expression profiles. It is yet uncertain whether they represent one or multiple distinct CD4⁺ T cell subsets capable of regulating both Th1- and Th2-mediated responses. Many of the characterized populations are heterogeneous, and the molecular mechanisms for their derivation and full effector function have not been clearly defined.

CD45Rb^{low} CD4⁺ T cells contain a regulatory population that can inhibit CD45Rb^{high} CD4⁺ T cell-mediated colitis; this suppression of colitis is inhibited by anti-TGF β and/or anti-IL-10R1 mAbs (317, 441), suggesting a role for both cytokines in regulation of mucosal inflammation. A role for TGF β has also been demonstrated for a number of T regulatory populations, including Th3 and T regulatory 1 (Tr1) cells, in inhibition of autoimmune pathologies, gut inflammation, and/or proliferation of antigen-specific T cells (312, 434, 437, 438, 440, 512). Asseman et al. (317) implicated both TGF β and IL-10 as key factors in the ability of CD45Rb^{low} CD4⁺ T cells to inhibit CD45Rb^{high} CD4⁺ T cell-mediated colitis.

The relationship between these two cytokines in regulating inflammatory pathologies is unclear. It is unlikely that IL-10 is required for production of TGF β because IL-10^{-/-} mice show inflammatory pathology only of the intestine (26), whereas TGF β ^{-/-} mice develop inflammatory diseases of multiple organs (442). However, TGF β induces production of IL-10 by APC (513), suggesting that these molecules may act in concert to influence development and function of regulatory T cells, which is favored by chronic stimulation in the presence of IL-10 (213, 312, 434). These cells are reminiscent of CD4⁺ T cells previously isolated from peripheral blood of SCID-reconstituted patients, in whom high levels of IL-10 were associated with successful allogeneic stem cell transplantation (514). Whether IL-10 induces development of these IL-10-producing T cells by acting on APC and/or directly on the T cell is as yet unclear. However, in view of (a) IL-10's inhibitory effects on DC and macrophage function, and (b) the observation that IL-10-treated DC induce tolerance (214, 217), an effect of IL-10 on APC is likely required. Additional studies are necessary to clarify mechanisms involved in development and function of T regulatory cells, and the respective roles of IL-10, TGF β and other mediators.

Factors Inducing IL-10 Production and Conditions Under Which IL-10 Acts as a Regulatory Molecule In Vivo

Regimens of antigen administration that have been suggested to generate anergy/tolerance in vivo induce production of IL-10. For example, influenza hemagglutinin (HA)-specific CD4⁺ T cells rendered anergic in vivo in mice expressing HA under the control of the Ig κ promoter produced 100-fold higher levels of IL-10 than did naive or recently activated T cells (311). These anergic HA-specific T cells exhibited an impaired ability to cause diabetes in vivo compared to naive counterparts when transferred into immunodeficient recipients expressing HA under the control of the insulin promoter (311). Similar findings were obtained with CD8⁺ T cells specific for the male antigen H-Y, which were rendered anergic in vivo (313). These T cells did not proliferate or mobilize calcium upon activation, and they failed to express IL-2 or IL-2R but secreted IL-10 and survived for extended periods in vivo. A potential role of IL-10 in tolerance was also demonstrated in a model involving multiple injections of superantigen A (SEA) into TCR-V β transgenic mice. IL-10 production was detected after the second injection of SEA, and it dominated the response after the third (309). Coadministration of anti-IL-10 Mab with SEA prevented suppression of in vivo IFN γ , TNF, and IL-4 responses but had no effect on IL-2 production. That repeated administration of superantigen generates a regulatory population of CD4⁺ T cells has been suggested by experiments using a viral superantigen (515,516) that generated a population of CD25⁺CD4⁺ T cells resistant to clonal deletion and producing high amounts of IL-10. These cells were IL-2 dependent and could not be induced in IL-2^{-/-} mice (515,516).

Immune responses to antigens in the eye are regulated by the ocular environment and can induce systemic alterations in the immune response referred to as immune deviation (517). The eye itself contributes to immune deviation, in part via immunoregulatory molecules present in aqueous humor and/or expressed by ocular cells. When T cells encounter antigen in the eye, they become anergic, undergo apoptosis, and/or secrete cytokines such as TGF β that suppress subsequent inflammatory responses, thus avoiding inflammatory injury. Apoptosis of inflammatory cells is required for induction of immune deviation via antigen presentation in the eye (518). Thus, Fas-mediated apoptosis of lymphoid cells was accompanied by rapid production of IL-10 and subsequent inhibition of APC function and Th1 responses (518). Whereas apoptotic cells from wild-type mice "fed" to APC in vitro promoted Th2 development with production of IL-4 and IL-10, those obtained from IL-10^{-/-} mice favored development of Th1 cells. However, immune deviation could be induced in IL-10^{-/-} mice when IL-10-containing apoptotic cells were presented in the eye.

A connection between the DNA damage that occurs in apoptotic cells and IL-10 production has been demonstrated (519). Induction of IL-10 expression was linked to pyrimidine dimer formation in keratinocytes in UV-exposed skin. Furthermore, IL-10 mediates at least some of the suppressive effects of UV-irradiation

on cell-mediated immunity (520). UV-induced apoptosis is mediated by Fas (521), consistent with a link between Fas-mediated death and IL-10 production. This association is strengthened by detection of monocyte IL-10 expression induced by exposure to UVB-irradiated apoptotic PBL (522).

Collectively, these observations demonstrate an antiinflammatory component of apoptosis, mediated by IL-10, that helps control potentially harmful immune responses. However, a comprehensive pathway linking induction of DNA damage, apoptosis, production of IL-10, and induction of tolerance by repeated exposure to self/neo-antigen or superantigen as described earlier remains to be elucidated.

CANCER AND TRANSPLANTATION

The profound immunosuppressive effects of IL-10 have prompted numerous studies of its expression and function in association with cancers and both bone marrow and solid organ transplantation. A thorough perspective on this large and seemingly contradictory literature is beyond the scope of this review. Because of its multiple activities, the ultimate consequences of IL-10 expression or therapy are a net outcome of many variables, including IL-10 levels, systemic vs. local expression/therapy, effects during induction vs. effector stages of an immune response, and growth-inhibitory or -cofactor activity for tumor or graft cells.

Cancer

IL-10 Expression in Cancer Several reports have described association of elevated IL-10 expression levels with certain cancers, for example ovarian (523–525), various carcinomas (526–532), melanoma (529, 533–538), and lymphoma/ myeloma (reviewed by 539; 540–545). We note that elevated IL-10 expression can occur for multiple reasons with very different implications. IL-10 can be expressed by tumor cells themselves, possibly suppressing antitumor responses. In other cases, IL-10 could be produced by activated cells involved in a host antitumor reaction, and thus it could be an indicator of a potent inflammatory response rather than immunosuppression. Thus, in the absence of expression data for a broader panel of cytokines and other immune response parameters, it is difficult to interpret the significance of elevated IL-10 expression in many such studies.

IL-10 Expression as a Prognostic Indicator in Cancer A more specific issue is whether elevated IL-10 expression correlates with favorable or adverse patient outcomes. Elevated IL-10 serum levels have been reported as a negative prognostic factor for survival or response to treatment in Hodgkin's and non-Hodgkin's lymphoma (546–551), although evidence suggested (550) that such "correlation" may be due to EBV vIL-10 (which is also detected by most hIL-10 ELISA assays) rather than to hIL-10. Detectable IL-10 in serum was also described as a negative indicator for clinical outcome in hepatocellular carcinoma (526), lung cancer

(528, 552), renal carcinoma (532), gastric or colorectal carcinoma (553), and other solid tumors (527). The presence of strongly staining IL-10-producing cells of undetermined origin correlated with a poor outcome in one group's studies of patients with oral, oropharyngeal, and nasopharyngeal (NPC) carcinomas (530, 554), although EBV vIL-10 and hIL-10 again were not distinguished, an issue of particular relevance to NPC. In contrast, serum IL-10 levels did not correlate with prognosis in a study of diffuse large cell lymphoma (555), and an assessment of IL-10 mRNA in B-CLL indicated association of *favorable* prognosis with higher IL-10 mRNA expression (556).

How might the presence of IL-10 contribute to a poor prognosis for some cancers? One possibility is growth-factor or -cofactor activity for tumor cells. IL-10 stimulates growth and differentiation of B cells (20), and exogenously provided IL-10 enhances growth of some B cell tumor cells in vitro (275, 557–559). Experiments involving neutralization of IL-10 activity or expression have suggested a possible role as an autocrine growth (co)factor for certain types of B-lymphoma (545, 558, 560). Similar data were also reported for melanoma (537). IL-10 stimulated proliferation of myeloma cells (557), although the effect appeared to be indirect, via induction of autocrine oncostatin M growth factor expression (542, 561). However, in contrast, IL-10 inhibited production of the autocrine growth factor GM-CSF by myelogenous leukemic blast cells (562–564). Thus, while IL-10 may contribute to growth of B cell tumors, there is little evidence supporting a general role for IL-10 as a tumor growth factor.

A second possibility is that IL-10 produced by or in the vicinity of a tumor could hinder induction or effector function of an antitumor immune response. As already discussed, IL-10 inhibits dendritic cell (DC) function, which could blunt induction of a response against tumor cells (207, 212, 214–218, 565–567). At least one in vivo model suggests that this notion is plausible: A Lewis lung carcinoma cell line grows more rapidly in a transgenic mouse expressing IL-10 under control of an IL-2 promoter than in nontransgenic control mice (507, 568).

However, the impact of this activity of IL-10 cannot be assessed or predicted outside the context of its other relevant functions, such as leukocyte recruitment via both chemotaxis (138, 161, 170, 569) and induction of endothelial cell adhesion molecule expression (468, 570, 571), stimulation of the growth and function of cytotoxic cells (8, 21, 137, 572), ability to increase the sensitivity of target cells to NK-mediated lysis (573, 574), and enhancement of antibody-mediated immunity (20, 134, 575). In contrast to an inhibitory effect on DC function, these latter activities would likely contribute to inhibition of tumor establishment, growth, or even metastasis.

Effects of cIL-10 and vIL-10 Protein or Gene Therapy in Animal Models of Cancer The ultimate effect of IL-10 in vivo has been addressed by a number of studies of IL-10 protein administration or IL-10 gene therapy in animal models of tumor establishment and growth. In mastocytoma (576), breast cancer (134, 573, 577–580), melanoma (84, 139, 534, 581, 582), prostate cancer

(583–585), and colon carcinoma (84, 586) models, IL-10 expressed by gene transfer into tumor cells, or administered as protein, effected a profound inhibition of tumor establishment, growth, and metastasis. Much of this process occurred in SCID or nude mouse tumor recipients (139, 183, 534, 582–585), suggesting that an important component of the response is T cell-independent. Consistent with this notion, intratumor cellular infiltrates in the presence of IL-10 include not only T cells, but macrophages, NK cells, and neutrophils (139, 581, 586, 587). In addition, several studies utilizing non-immunodeficient mice as hosts demonstrated that effective and prolonged anti-tumor immune responses were established in the presence of IL-10 (84, 134, 581, 586, 588). Inhibition of tumor angiogenesis was also implicated (183, 534, 582, 585).

The above observations indicate that in these *in vivo* tumor model systems the pleiotropic (i.e., non-CSIF) activities of IL-10 exert a dominant influence on the outcome of IL-10 expression or protein therapy. Consistent with this idea are the strikingly different results obtained when EBV vIL-10, the pleiotropic activities of which are substantially impaired (4, 18, 19, 81, 88), was used instead of cIL-10. In contrast to the accelerated tumor rejection and induced antitumor immunity obtained with cIL-10, when vIL-10 expression was employed in melanoma, colorectal carcinoma, or sarcoma models, prolonged or indefinite tumor growth was observed, accompanied by a locally impaired immune response (84, 86). Similar results were observed in a mastocytoma model (589, 590), although some rejection phenomena were observed, perhaps due to apparently 10- to 20-fold higher levels of vIL-10 expression achieved in these latter studies.

Collectively, studies of IL-10 expression and function in cancer present a complex picture of varied outcomes that can be obtained depending on level, source, timing, and duration of IL-10 expression during tumor development. The well-characterized immunosuppressive CSIF activity of IL-10 clearly functions *in vivo*, most likely during induction of an immune response, but under some conditions it can be overshadowed by alternate mechanisms engaged by IL-10 that induce an anti-tumor response.

Transplantation

The ability of IL-10 to inhibit induction and effector function of T cell-mediated and inflammatory immune responses led to numerous studies of its expression, function, and potential utility in bone marrow and organ transplantation. The current picture is complex but is, in our opinion, amenable to a few general conclusions.

IL-10 Pretreatment of, or Pre-existing Elevated Spontaneous IL-10 Expression by Graft Recipients Is Associated with Improved Graft Acceptance In studies of vascularized heart allografts in mice, IL-10 treatment of recipient animals prior to grafting enhanced graft survival (390, 591), whereas providing IL-10 at or after the time of grafting had little beneficial effect or even enhanced rejection

(592–594). Similar results were also obtained for rat liver allografts (595). Studies of bone marrow transplantation (BMT) and graft-vs-host disease (GVHD) also support this idea: Patients exhibiting elevated levels of IL-10 production prior to BMT have lower incidence of GVHD and improved survival (514, 596, 597). Taken together, such observations suggest a key inhibitory/tolerogenic role for IL-10 prior to and during the initial priming events in organ transplantation and BMT. As noted earlier, this presumably reflects IL-10's ability to inhibit the function of DC and other accessory cells and to influence subsequent development of the T cells that they stimulate (213, 218, 434).

IL-10 Treatment or Expression at the Time of or Posttransplantation Can Enhance Graft Rejection or GVHD In contrast to pre-BMT patients discussed above, high IL-10 levels in post-BMT GVHD patients indicate a poor prognosis for survival (598). Furthermore, posttransplant administration of IL-10 protein to mice in models of BMT/GVHD was generally deleterious, resulting in unimproved or increased mortality (599–601).

However, when given to mice in small amounts, 10^{-3} – 10^{-4} of the amount that increased mortality, IL-10 protected against GVHD-associated lethality (602), suggesting that low in vivo IL-10 concentrations preferentially induce the immunosuppressive effects of IL-10. Consistent with this notion, we have observed that IL-10 is about 10-fold more potent in vitro in assays measuring its immunosuppressive activity than in assays measuring other activities such as costimulation of mast cell and thymocyte proliferation (KW Moore, R deW Malefyt, unpublished).

Organ transplantation studies have been carried out utilizing IL-10 protein, IL-10 gene transfer, and IL-10 transgenic mice. Some of these reports described prolongation of graft survival time due to IL-10 protein treatment (595) or IL-10 expression via gene transfer (603–605) in liver transplant models. In this connection, it was noted that liver allografts tend to be less immunogenic than other organs (604), an observation that could be related to transient but massive IL-10 release attributed to liver-resident macrophages during transplantation (51). As noted above, lower doses of exogenous IL-10 protein tended to be protective, while a higher dose exacerbated rejection (595). This aspect is more difficult to evaluate in gene transfer studies because the amounts of bioavailable IL-10 are a complex function of vector delivery efficiency, expression levels in infected cells and their physical location in vivo, how quickly their expression or viability is compromised by host reactions, and the half-life of IL-10 in vivo. A recent study of rat cardiac allografts utilizing rat IL-10 adenovirus also described a modest prolongation of graft survival in association with IL-10 expression (606).

In contrast, a number of studies have reported neutral or unfavorable effects of IL-10 expression in allograft models. Expression of transgenic IL-10 in pancreatic β -cells enhanced accumulation of leukocytes, did not impair induction of autoimmune diabetes, and did not inhibit rejection of transgenic islets transplanted to MHC-disparate mice (468, 470). Likewise an IL-10-Fc fusion protein accelerated islet allograft rejection in mice (607). Posttransplant injection of IL-10

protein in mouse cardiac allograft recipients enhanced rejection and arterial disease (593, 594, 608) and inhibited the therapeutic effects of cyclosporine treatment (594). Antagonism of IL-10 via administration of anti-IL-10 Mab also prolonged cardiac and liver allograft acceptance in mice (609). IL-10 treatment did not enhance acceptance of corneal allografts (610).

Clearly the effects of IL-10 on BMT and organ allografts are a complex outcome of multiple factors including timing, kinetics, and amounts of cytokine, as well as the relative impact of the different activities of IL-10 in each particular experimental scheme and model system. We also emphasize that in most such studies the experimental endpoint ("rejection") is defined by necrosis or loss of function; little attention has been devoted to defining potentially significant cellular and mechanistic differences leading to rejection in the presence or absence of IL-10, as pointed out by others (611, 612). Thus, in models where IL-10 protein or expression enhances rejection, it may be that completely different rejection mechanisms elicited by IL-10 are at work compared to those active in its absence. As discussed below, a somewhat clearer picture has developed via use of natural (vIL-10) and more recently artificial (88) IL-10 variants with a more restricted biological activity profile.

Viral IL-10 Expression, in Contrast to cIL-10, Is Consistently Beneficial for Graft Acceptance and Survival As observed in in vivo tumor models, gene transfer-mediated vIL-10 expression by vIL-10-transduced graft cells or by cells in the vicinity of the graft enhanced graft acceptance, although to varying extents in different allograft models (85, 88, 589, 613–618). These results are paralleled by experiments involving human (619) and rat (620) cells showing that vIL-10 expression by graft cells or by DC (215) inhibited alloreactivity in vitro. Moreover Nast et al. (621) described a kidney transplant patient with transplant-associated lymphoproliferation who exhibited prolonged graft acceptance, with minimal immunosuppressive therapy, which was associated with intra-graft vIL-10 expression. These data collectively indicate that vIL-10, with its restricted bioactivity profile favoring the CSIF or immunosuppressive activities of IL-10 and ability to effectively engage only a limited subset of IL-10-responsive cells in vivo, is in contrast to cIL-10 a potent and consistent immunosuppressive cytokine in in vivo models of organ transplantation.

CLINICAL STUDIES

IL-10 has been considered an attractive candidate for therapeutic use based on its potent in vitro immunomodulating activities and proven effects in animal models of acute and chronic inflammation, autoimmunity, cancer and infectious disease. Phase I and II clinical trials investigating safety, tolerance, pharmacokinetics, pharmacodynamics, immunological and hematological effects of single or multiple doses of IL-10 administered by intravenous (iv) or subcutaneous (sc) route

have been performed in various settings on healthy volunteers and specific patient populations (622–624). These studies showed that IL-10 is well tolerated without serious side effects at doses up to 25 $\mu\text{g/kg}$; mild to moderate flu-like symptoms were observed in a fraction of recipients at doses up to 100 $\mu\text{g/kg}$.

In vivo administration of IL-10 inhibited the ex vivo LPS-induced production of IL-6, IL-1, and TNF in whole blood cell assays and decreased proliferative responses and IFN γ production following PHA stimulation of PBMC, indicating that IL-10 retains immunomodulatory activities when administered in vivo. The doses required to effect 50% of maximal inhibition (IC_{50}) of TNF and IL-1 β production and a maximal fraction of inhibition (I_{max}) indicated that IL-10 inhibited production of proinflammatory mediators in vivo at concentrations similar to those used in in vitro experiments (625).

Single intravenous (iv) or subcutaneous (sc) doses of IL-10 resulted in transient dose-dependent changes in white blood cell populations, including increases in total white blood cells and neutrophils. A reduction was observed in the number of CD3 $^{+}$ CD4 $^{+}$ and CD3 $^{+}$ CD8 $^{+}$ lymphocytes accompanied by an increase in the percentage of CD14 $^{+}$ HLA-DR $^{+}$ monocytes. Furthermore, transient decreases in expression levels of CD11a (LFA1) on CD3 $^{+}$ T cells, which may account for some of the observed changes in lymphocyte circulation, and a decrease in the expression levels of HLA-DR on CD14 $^{+}$ monocytes, but not on CD20 $^{+}$ B cells, were measured following a single iv dose of IL-10 in healthy volunteers (626, 627). Downregulation of HLA-DR expression on monocytes but not B cells correlates well with in vitro effects of IL-10 and is associated with inhibition of antigen presentation.

In addition to transient neutrophilia, lymphocytopenia, and monocytosis, a delayed decrease in platelet counts was observed following a single sc dose of IL-10 (624). Decreases in platelet counts were also reported following multiple dose regimens in a proportion of patients receiving 10–20 $\mu\text{g/kg}$ doses (628, 629). Platelet counts reached nadirs of 20–50% of baseline generally at day 7 of treatment, but they did not attain clinically compromising levels and either stabilized or returned to normal during or following cessation of IL-10 therapy.

Because several of IL-10's potential indications are chronic inflammatory diseases for which steroid treatment is an accepted therapy, its interaction with such drugs was studied. Single doses of IL-10 resulted in statistically significant but clinically insignificant 20% increases in 24 h plasma cortisol area under serum concentration–time curve (AUC). However, coadministration of IL-10 and prednisolone did not result in pharmacokinetic alterations of either drug and showed net responses that were similar to or greater than effects produced by the more strongly acting agent (630, 631). In addition, IL-10 administration did not significantly alter cytochrome P450 (CYP)-mediated drug metabolism as characterized by CYP1A2, CYP2C9, and CYP2D6 activities and by a 12% reduction of CYP3A-mediated biotransformation (632).

Pharmacokinetic parameters of IL-10 clearance were determined following iv or sc administration of doses ranging from 0.1 to 100 $\mu\text{g/kg}$. Following iv

administration, IL-10 serum levels initially declined fairly rapidly but yielded a less steep terminal phase with a $t_{1/2}$ of 2–3 h. Mean exposure parameters (maximum serum concentration, C_{\max} , and AUC) were linearly related to dosage, and IL-10 tended to remain in the vascular compartment. Because hIL-10 is nonglycosylated, it is cleared mainly through the kidney, as indicated by the increased $t_{1/2}$ and AUC of IL-10 in patients with moderate to severe renal insufficiencies. Administration of IL-10 did not produce adverse effects in this patient population (633). Subcutaneous administration of IL-10 resulted in slow absorption from the IL-10 depot formed at the injection site, which reached C_{\max} at 2–6.5 h post injection. The slower absorption of IL-10 following sc versus iv administration led to prolonged but lower AUC with a mean terminal $t_{1/2}$ of 2.7–4.5 h and so resulted in a prolonged immunosuppressive effect. Mean exposure parameters were also linearly related to dosage (625). Production of neutralizing antibodies was not observed in any of the studies.

IL-10 administered iv at 25 $\mu\text{g/kg}$ inhibited LPS-induced rises in temperature and release of TNF, IL-6, IL-8, and IL-1RA in healthy human volunteers, when given 2 min before but not 1 h after endotoxin (328). Such “pretreatment” with IL-10 also reduced endotoxin-induced granulocyte accumulation in the lungs, granulocyte degranulation, cortisol levels, activation of the fibrinolytic system, inhibition of fibrinolysis, activation of the coagulation system, and inhibition of expression of the CC chemokines Mip1 α , Mip1 β and MCP1 (634, 635). Delay in administration of IL-10 for 1 h only reduced IL-6 and Mip1 β production, cortisol levels, inhibition of fibrinolysis, and activation of the coagulation system, indicating that timing of IL-10 administration is important for its full anti-inflammatory activity during experimental endotoxemia. However, IL-10 failed to alter proinflammatory cytokine production or physiological changes associated with the Jarisch-Herxheimer reaction, an acute systemic inflammatory response that follows antibiotic treatment of *Borrelia recurrentis* infection (636). In addition, the effects of IL-10 on systemic production of proinflammatory cytokines in renal transplant patients who received OKT3 as induction therapy (575) were investigated. Pretreatment with IL-10 reduced release of TNF induced by OKT3, but high IL-10 doses may have promoted early sensitization to OKT3 and exerted reversible adverse effects on graft acceptance.

IL-10 has been tested in specific patient populations including those with Crohn’s disease, RA, psoriasis, and patients suffering from chronic hepatitis C infections. Administration of IL-10 (7 days iv) reduced the Crohn’s disease activity index (CDAI) score in patients with steroid-refractory Crohn’s disease and showed some clinical benefit in a larger 28-day sc safety and efficacy study in patients with chronic active Crohn’s disease (CACD) (628, 637). Similarly, a trend towards efficacy and a good safety profile was observed when IL-10 was administered for 28 days to RA patients (629). Both Crohn’s disease and RA are heterogeneous diseases, and IL-10 alone or in combination with other therapies, such as low dose steroid or therapeutic anti-TNF Mab (638, 639), may yet benefit a significant patient population.

An open label phase II trial on ten psoriasis patients indicated that sc IL-10 treatment for seven weeks was well tolerated and efficacious: significant decreases of psoriatic area and severity index were observed in 9/10 patients (640, 641). IL-10 likely affects monocytes and T cells rather than keratinocytes in this disease that is characterized by Th1-mediated IFN γ production (642).

Two recent trials investigated use of IL-10 to suppress pathology associated with chronic hepatitis C (HCV) infection (401, 643). IL-10 was administered sc at 4 or 8 $\mu\text{g/kg}$ for 28 or 90 days in patients who had not received any therapy or who did not respond to interferon-based therapy, the current standard of care. IL-10 normalized serum levels of alanine aminotransferase, a marker for hepatic inflammation, improved liver histology and reduced liver fibrosis in over 50% of treated patients. However, IL-10 did not reduce serum HCV RNA levels, indicating that it did not affect viral load, but instead limited pathogen-induced pathology as discussed earlier. The safety profile and biological activities of IL-10 suggest its potential utility as a therapeutic, and results from several early clinical trials are encouraging. It is not easy to predict which condition will benefit most from IL-10 therapy, but IL-10–cIL-10 or vIL-10—either alone or in combination with other agents may hold significant promise.

CONCLUSIONS

IL-10 is a pleiotropic cytokine that regulates a variety of functions of hemopoietic cells. Its principal everyday function seems to be containment and eventual termination of inflammatory responses; by doing so, IL-10 facilitates elimination of infectious organisms with minimal damage to host tissues. In addition, IL-10 plays important roles in immune tolerance, T cell and DC development, and growth and differentiation of B cells. Early clinical trials suggest that IL-10 has a good safety profile and possible utility in treatment of autoimmune and inflammatory conditions. In addition, IL-10 antagonists—perhaps anti-IL-10 or anti-IL-10R Mabs—may find application in treatment of SLE and a number of infectious diseases.

What important issues remain to be addressed about IL-10's function? First, our understanding of IL-10R structure and signaling is not complete. That certain cells (e.g. monocytes, B cells) respond comparably to cIL-10 and vIL-10 whereas others are comparatively insensitive to vIL-10 suggests differences in IL-10R subunit composition or its signal transduction machinery in the former. Furthermore, the molecular basis for the different effects of IL-10 on different cell types remains to be clarified. Why IL-10 generally inhibits monocyte/macrophage and CD4⁺ T cell function, yet stimulates development of B cells and CD8⁺ T cells despite outwardly similar signaling responses in all cells is not understood.

What determines which of IL-10's activities will dominate in an immune response? As discussed, studies of IL-10 in vivo in models of autoimmunity, cancer, and transplantation have revealed that IL-10 can effect very different outcomes

depending on timing, dose, and location of expression; in some scenarios the expected immunosuppressive activities are observed, while in others IL-10 enhances immune or inflammatory responses. The cellular mechanisms underlying these phenomena are unclear, and their elucidation is of particular importance for the successful use of IL-10 in the clinic. Valuable understanding in this area may come from further studies of IL-10's effects on DC and renewed efforts to understand its activity on other hemopoietic cells.

Understanding the role of IL-10 in differentiation and function of T regulatory cells—in their various manifestations—is crucial for attaining a complete understanding of these cells and their *in vivo* significance in immune tolerance. The most helpful advance in this area would be an improved method of growing and maintaining such cells *in vitro*. The potential utility of these cells in treating autoimmune disorders and in organ transplantation cannot be ignored.

Finally, the clinical potential of IL-10 requires further evaluation. It is possible that IL-10 or anti-IL-10 may synergize with existing suboptimal therapies (e.g., cyclosporine, steroids, anti-microbials) to effect a superior therapeutic outcome with fewer undesirable side effects. Moreover, because of the restricted bioactivity profile of vIL-10, the viral cytokine or a modified hIL-10 with impaired pleiotropic activities (88) may in fact be the preferred therapeutic entity in a number of IL-10 protein or gene therapy applications.

In this area, the emerging field of pharmacogenomics may offer the ability to determine in advance which patient subsets are most likely to respond to IL-10 or anti-IL-10 therapy. A foundation for this already exists in knowledge derived from IL-10 promoter genotype studies. It is also plausible that similar studies of the IL-10R1 and/or IL-10R2 loci may reveal polymorphisms that correlate with the ability of patients to respond to such therapies.

We are confident that the second decade of research on IL-10 will be as productive as the first.

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