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Interleukin-10 Therapy—Review of a New Approach

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***Abstract*——Interleukin (IL)-10 is an important immunoregulatory cytokine produced by many cell populations. Its main biological function seems to be the limitation and termination of inflammatory responses and the regulation of differentiation and proliferation of several immune cells such as T cells, B cells, natural killer cells, antigen-presenting cells, mast cells, and granulocytes. However, very recent data suggest IL-10 also mediates immunostimulatory properties that help to eliminate infectious and noninfectious particles with limited inflammation. Numerous investigations, including expression analyses in patients, in vitro and animal experiments suggest a major impact of IL-10 in inflammatory, malignant, and autoimmune diseases. So IL-10 overexpression was found in certain tumors as melanoma and several lymphomas and is considered to promote further tumor development. Systemic IL-10 release is a powerful tool of the central nervous system to prevent hyperinflammatory processes by activation of the neuro-endocrine axis following acute stress reactions. In contrast, a relative IL-10 deficiency has been observed and is regarded to be of pathophysiological relevance in certain inflammatory disorders characterized by a type 1 cytokine pattern such as psoriasis. Recombinant human IL-10 has been produced and is currently being tested in clinical trials. This includes rheumatoid arthritis, inflammatory bowel disease, psoriasis, organ transplantation, and chronic hepatitis C. The results are heterogeneous. They give new insight into the immunobiology of IL-10 and suggest that the IL-10/IL-10 receptor system may become a new therapeutic target.**

I. Introduction

Cytokines have been in the focus of scientific interest for more than a decade now. Analyzing their expression has enabled a better understanding of the pathogenesis of various diseases. Moreover, they are now far beyond the stage when they were of interest for pathophysiological research; some cytokine therapies are already used as part of clinical practice, ranging from early exploratory trials to well established therapies that have already received approval (Asadullah et al., 2002a,b).

Mosmann and coworkers (Fiorentino et al., 1989) first described a cytokine that is produced by T helper 2 (Th2[1]) cell clones and inhibits interferon (IFN)-γ synthesis in Th1 cell clones (Fiorentino et al., 1989). Today this "cytokine synthesis inhibiting factor (CSIF)" is known as interleukin (IL)-10, and although we also know that several immune cells produce IL-10, macrophages are the major source. Investigations during the last decade showed that this cytokine is of crucial importance for immunoregulation and led to its use in first clinical trials.

[1]Abbreviations: Th, T helper; APC, antigen-presenting cells; ATF-1, activating transcription factor-1; CBCL, cutaneous B cell lymphomas; CD, Crohn's disease; CMV, cytomegalovirus; CREB-1, cAMP response element binding protein-1; CRF, cytokine receptor family; CSIF, cytokine synthesis-inhibiting factor; CTCL, cutaneous T cell lymphoma; CTL, cytotoxic T cell lysis; DC, dendritic cells; EAE, experimental allergic encephalomyelitis; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIV, human immunodeficiency virus; HO, heme oxygenase; IFN, interferon; Ig, immunoglobulin; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric-oxide synthase; IP, inducible protein; kb, kilobase(s); KC, keratinocytes; LPS, lipopolysaccharide; mAb, monoclonal antibody; Mϕ, macrophages; MF, mycosis fungoides; MHC, major histocompatibility complex; MIG, monokine induced by IFN-γ; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NHL, non-Hodgkin's lymphoma; NK cells, natural killer cells; PASI, psoriasis area and severity index; PBMC, peripheral blood mononuclear cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SOCS, suppressor of cytokine synthesis; SSc, systemic sclerosis; STAT, signal transducer and activator of transcription; TAP, transporter associated with antigen processing; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor.

II. Interleukin-10

A. Interleukin-10 and Interleukin-10 Homologs

The human cytokine is a homodimer with a molecular mass of 37 kDa. Each monomer consists of 160 amino acids with a molecular mass of 18.5 kDa. Murine and human IL-10 exhibit a homology of about 80%. There are several viral IL-10 homologs: Epstein-Barr virus (BCRF1) (Hsu et al., 1990), herpes virus type 2 (Rode et al., 1994), cytomegalovirus (Kotenko et al., 2000; Spencer, 2002), and Orf virus (Fleming et al., 1997), with the EBV-derived BCRF1 being the most studied homolog.

The structure of human IL-10 and BCRF1 (ebvIL-10) was studied by X-ray crystal-structure-analysis (Zdanov et al., 1995, 1997) (Fig. 1). Apart from marginal differences predominantly in the N-terminal part of the molecule, the structures of hIL-10 and ebvIL-10 are strikingly similar; the two identical intertwining polypeptide chains of 160 (hIL-10) or 145 (ebvIL-10) amino acids are rotated by 180° to each other, forming two domains oriented in a V-shaped structure. Each domain contains six helices, four (A–D) from one monomer and two (E + F) from the other (Spits et al., 1992; Moore et al., 2001). Such a topology has been described first for the interferon-γ homodimer (Ealick et al., 1991)—a cytokine with many biological properties antagonistic to those of IL-10.

The capability for IL-10 production has been demonstrated for various cell populations; in addition to certain T cell subsets (Th2, Tc2, Tr1), also monocytes, macrophages, and several other cells may synthesize IL-10 (Table 1). Whether human keratinocytes really produce IL-10 like their murine counterparts is subject to contrary discussions (Enk and Katz, 1992; Kang et al., 1994; Enk et al., 1995; Grewe et al., 1995; Teunissen et al., 1997). The major source of IL-10 in vivo seems to be macrophages.

Five new human molecules structurally related to IL-10 have been discovered (Jiang et al., 1995; Gallagher et al., 2000; Dumoutier et al., 2000a,b,c; Knappe et al., 2000; Blumberg et al., 2001). They are called IL-19, IL-20, IL-22, IL-24 (mda-7), and IL-26 (AK155). Similar to IL-10, they are α-helical proteins with similar cysteine localizations, whose amino acid sequences are about 30% identical. Interestingly, in the human genome, the encoding genes are located in two clusters, one comprising the genes for IL-10, IL-19, IL-20, and IL-24 (mda-7) on chromosome 1q31-32, whereas the second cluster comprising the genes encoding IL-26 (AK155) and IL-22 is located on human chromosome 12q15 near the IFN-γ gene (12q14) (Dumoutier et al., 2000b; Blumberg et al., 2001) (Fig. 2). Taking into account the clear structural relation between the new IL-10 homologs and IL-10, all of these six molecules should be considered as (IL-10) family members.

In contrast to the extensively studied IL-10 (as described below and recently reviewed by Moore et al., 2001), the knowledge of the biology of the new IL-10 homologs is still fragmentary. The first functional data exists for IL-20, IL-22, and IL-24 (mda-7) (Fickenscher et al., 2002). Overexpression of IL-20 in transgenic mice induced neonatal lethality, psoriasis-like skin abnormalities, lack of adipose tissue, and elevated apoptosis of thymic lymphocytes (Blumberg et al., 2001). It has been suggested that IL-22 plays a role in inflammatory processes through the observation that it induces acute phase-reactant production in a hepatoma cell line and in

TABLE 1
Cellular sources of IL-10 (Asadullah et al., 1999b)

Cell Population	Reference
T helper 2 cells	Fiorentino et al., 1989
Monocytes	De Waal Malefyt et al., 1991a
Macrophages	Spits and De Waal Malefyt, 1992
B cells	Pistoia, 1997
Eosinophils	Nakajima et al., 1996
Mast cells	Lin and Befus, 1997
Keratinocytes (?)	Enk and Katz, 1992; Teunissen et al., 1997

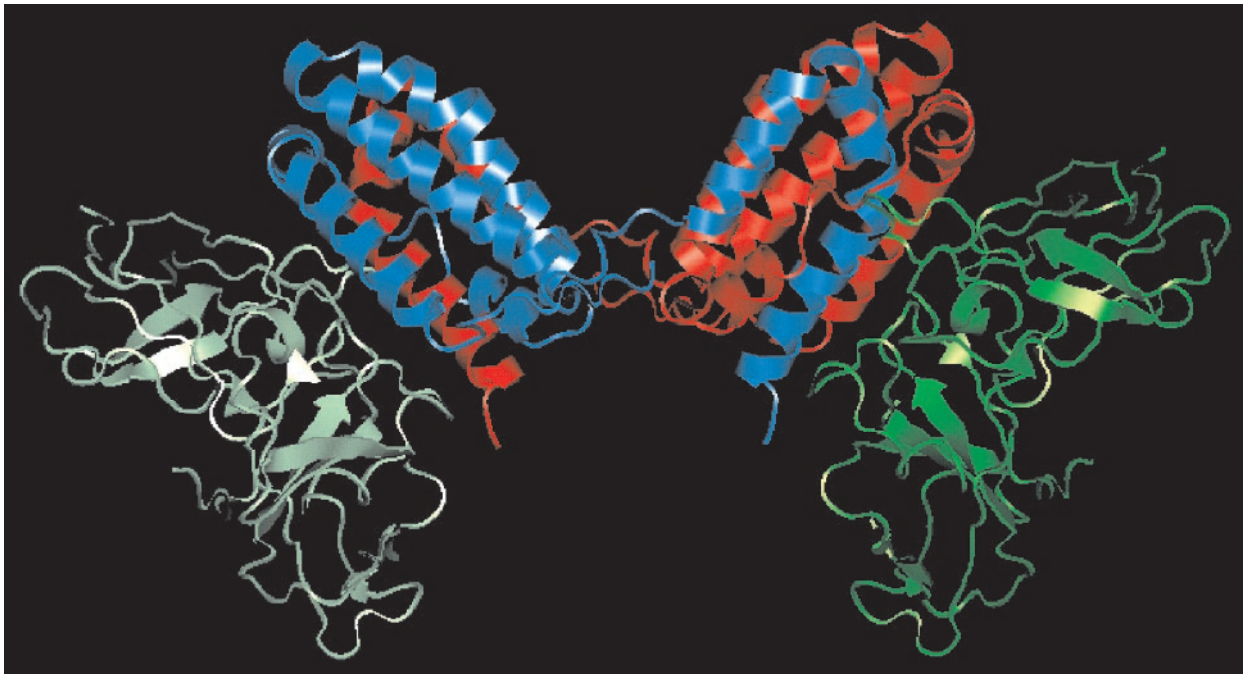

FIG. 1. Three-dimensional structure of hIL-10 (figure reproduced from a review by Asadullah et al., 2000a initially developed by Zdanov et al., 1995, 1997 and reprinted with permission from Ashley Publications Ltd., London).

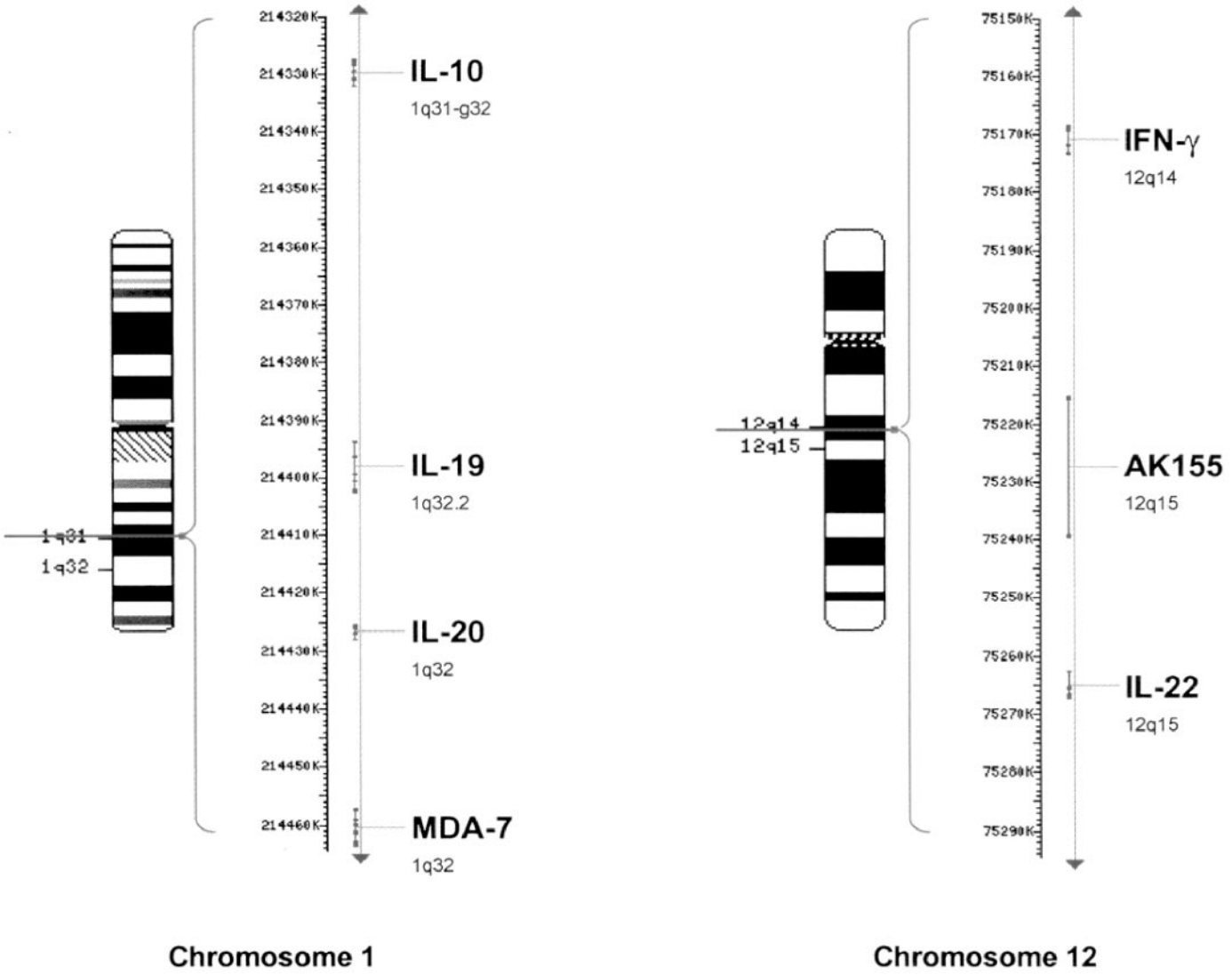

FIG. 2. Chromosomal location of IL-10 and homologs cytokines. The genomic localization of the IL-10 family genes. AK155, Andre Knappe, MDA-7, melanoma differentiation-associated gene-7 (figure modified from Volk et al., 2001).

vivo (Dumoutier et al., 2000b). Overexpression of mda-7 via adenoviral gene transfer induced growth inhibition in various tumor types (Jiang et al., 1996). Interestingly, the IL-24 (mda-7) mouse counterpart, called FISP, was postulated to be a Th2-specific protein (Schaefer et al., 2001). No function is known for IL-19 and IL-26 (AK155) to date. Table 2 summarizes the most important properties known so far (Volk et al., 2001).

We recently investigated the expression of five new human IL-10-related molecules and their receptors in blood mononuclear cells (Wolk et al., 2002). IL-19 and IL-20 were found to be preferentially expressed in monocytes. IL-22 and IL-26 (AK155) expression was exclusively detected in NK and T cells, especially upon T1 polarization. IL-24 (mda-7) expression was restricted to monocytes and T cells. Secretion of these molecules by lymphocytes was predominantly linked to cellular activation. Regarding T cells, IL-26 was primarily produced by memory cells, and its expression was independent of costimulation. This data suggests that immune cells are a major source of the new IL-10 family members (Wolk et al., 2002).

B. Interleukin-10 Promoter and Interleukin-10 Polymorphisms

The human IL-10 gene is located on chromosome 1 and encodes for 5 exons (5.1 kb) (Spits and De Waal Malefyt, 1992). The IL-10 promoter is highly polymorphic with two informative microsatellites, IL10.G and IL10.R, 1.2 kb and 4 kb upstream of the transcription start site (Eskdale and Gallagher, 1995; Eskdale et al., 1996) and three frequent point mutations −1082(G/A), −819(C/T), and −592(C/A) (Eskdale et al., 1997a; Turner et al., 1997a; Hurme et al., 1998). Recently, several new single-nucleotide polymorphisms have been defined in the human IL-10 locus. A correlation of particular microsatellite polymorphisms with lipopolysaccharide (LPS)-induced IL-10 secretion by PBMC in vitro

TABLE 2
Properties of IL-10 homolog (Volk et al., 2001)

IL-10 Homologs	Cellular Source	Biological Effects		Receptor
		In Vivo	In Vitro	
IL-19	Activated monocytes (LPS or GM-CSF)	?	No effects on cytokine synthesis by PBMC ?	?
IL-20	LPS-stimulated PBMC monocytes (?)	Overexpression in mice causes retarding of growth and development, skin abnormalities, and neonatal lethality	Enhancement of IL-10-induced expression of inflammation-related genes (HaCaT)	IL-20Rα IL-20Rβ
IL-22	Activated T cells (Th1 ?), IL-9-stimulated mast cells, mesangium cells	Application in adult mice induces acute phase response and basophilia in proximal renal tubules, autocrine factor for mesangium cells	Induction of acute phase response (hepatoma cell lines), inhibition of IL-4 production from Th2 cells, activates Stat3 in hepatocytes but not macrophages	IL-22Rα IL-10Rβ
AK155	T cell lines (CD4+ and CD8+) herpesvirus saimiri-infected T cells, activated monocytes (?)	?	?	?
MDA-7	Melanoma cells, skin fibroblasts, activated PBMC (LPS or PHA)	Antitumor effects ?	Irreversible growth arrest of tumor (induction of apoptosis or differentiation) inhibition of angiogenesis induction of Th1 type cytokines in PBMC (?)	?

AK, Andrea Knappe; PHA, phytohemagglutinin.

(presumably mostly from monocytes) was reported (Eskdale et al., 1998); the −1082(G) allele was associated with higher ConA-induced IL-10 production (likely both T cells and monocytes) (Turner et al., 1997a).

C. Regulation of Interleukin-10 Secretion

The IL-10 promoter contains several transcription factor-responsive elements (Platzer et al., 1994). Thus macrophages, the major source of IL-10, are stimulated to produce IL-10 by several endogenous and exogenous factors such as endotoxin (via Toll-like receptor 4, NF-κB dependent), tumor necrosis factor (TNF)-α (via TNF receptor p55, NF-κB-dependent), catecholamines, and cAMP-elevating drugs (both via protein kinase A, CREB-1/ATF-1 dependent) (Platzer et al., 1995, 1999, 2000; Meisel et al., 1996; Woichiechowsky et al., 1998; Riese et al., 2000).

In particular, the stress axis plays a significant role in regulating IL-10 expression in vivo. Inflammation of the central nervous system (particularly local IL-1 release following trauma, neurosurgery, or increase of intrabrain pressure) or indirect activation of the stress axis by endotoxemia/bacteremia triggers the release of catecholamines that up-regulate IL-10 production in macrophages, particularly in the liver (Barsig et al., 1995; Jilg et al., 1996; Woichiechowsky et al., 1998). Blocking the stress axis increases the susceptibility to endotoxemia-mediated shock. So the cross-talk between the central nervous system and (liver) macrophages controls systemic inflammation whereby the cAMP/protein kinase A/CREB-1/ATF-1 signaling pathway seems to play an essential role in inducing IL-10. On the other hand, systemic release of TNF-α also induces IL-10 via a negative feedback by using a NF-κB-dependent pathway (Barsig et al., 1995; Meisel et al., 1996). Recent data suggests that the p38 mitogen-activated kinase pathway also regulates the human IL-10 promoter via the activation of sp1 transcription factor (Ma et al., 2001).

III. Interleukin-10 Receptors and Signaling

A. Interleukin-10 Receptors and Other Cytokine Receptor Family Type 2 Members

IL-10 activity is mediated by its specific cell surface receptor complex, which is expressed on a variety of cells, in particular immune cells. Only a few copies of the IL-10R are expressed on the surface of the cells (Carson et al., 1995; Jurlander et al., 1997). The expression is variable, but so far only a few regulating factors are known. Endotoxin increases the expression of IL-10R on fibroblasts (Weber-Nordt et al., 1994). After T cell stimulation with anti-CD3-antibodies or phorbol ester, a decrease of IL-10R gene expression has been found (Liu et al., 1994). It has been demonstrated that dermatological therapeutic agents such as glucocorticoids, vitamin D_3, and calcipotriol significantly increase IL-10R expression (Michel et al., 1997a,b). The IL-10 receptor is composed of two different chains, α (Ho et al., 1993) and β (CRFB4) (Kotenko et al., 1997), both members of the class II cytokine receptor family. The interaction of hIL-10R with hIL-10 has been characterized recently and seems to be highly complex (Ho et al., 1993; Tan et al., 1993; Reineke et al., 1998, 1999). The IL-10Rβ chain is essential for IL-10-mediated effects and CRFB4-deficient mice display the same phenotype as IL-10 deficient mice (Spencer et al., 1998). Interestingly, for cells that only express IL-10Rβ, no IL-10/IL-10R complexes are formed suggesting that only IL-10/IL-10Rα complexes interact

with the β-chain. Only in cells expressing both the IL-10Rα and β chains is the characteristic STAT transcription factor activation pattern for IL-10 signaling observed (Kotenko et al., 1997; Spencer et al., 1998).

As for IL-10, all the receptors of the new molecules from the IL-10 family known so far belong to the cytokine receptor family type 2 (CRF2) (Kotenko and Pestka, 2000). They are generally transmembrane glycoproteins whose extracellular domains consist of about 210 amino acids comprising two tandem fibronectin type III domains and having several conserved amino acid positions important for the secondary structure. More recently, it has been discovered that some of the human IL-10 homologs share single receptor chains and even whole receptor complexes (Dumoutier et al., 2000c, 2001; Xie et al., 2000; Kotenko et al., 2001). One receptor from the family is soluble (Gruenberg et al., 2001). Overall, the interaction of IL-10 homologs with their receptors is quite complex (Fig. 3) and so far only partially understood. Although the predicted helical structure of these homodimeric molecules is conserved, certain receptor-binding residues are variable and define the interaction with specific heterodimers of different CRF2. This leads, through the activation of STAT factors, to diverse biological effects.

We recently investigated the expression of the receptors for the five new human IL-10-related molecules in blood mononuclear cells (Wolk et al., 2002). In contrast to the high expression of receptors for IL-10 homologs in different tissues and cell lines, immune cells (monocytes, NK, B, and T cells) showed only expression of IL-10R1, IL-10R2, and IL-20R2. In these cells, IL-20R2 might be part of a still unknown receptor complex. Immune cells, therefore, may represent a major source but a minor target of the new IL-10 family members (Fig. 3).

B. Interleukin-10 Receptor Polymorphisms

Polymorphisms within the human IL-10 receptor cDNA gene sequence have been described (Tanaka et al., 1997). However, their biological relevance is not clear so far.

C. Interleukin-10 Receptor Signaling

IL-10/IL-10R interaction in immune cells results in transcriptional activation of several hundred genes, some of them are more than 50-fold up-regulated. IL-10 down-regulates expression of far fewer genes (M. Jung, R. Sabat, J. Krätschmar, K. Wolk, C. Schönbein, S. Schütt, M. Freidrich, W. D. Asadullah, H. D. Volk, and G. Grütz, submitted). There is only limited knowledge, however, regarding the IL-10 intracellular signal transduction pathway to date. The IL-10/IL-10R interaction activates the tyrosine kinases Jak1 and Tyk2, which are associated with the IL-1R1 and IL-10R2, respectively (Moore et al., 2001). The receptor engagement and tyrosine phosphorylation activates the cytoplasmically localized inactive transcription factors STAT 1, 3, and 5, resulting in translocation and gene activation (Finbloom et al., 1995). The evidence for the key role of these signaling molecules for the inhibitory effects of IL-10 have been excellently reviewed recently (Moore et al., 2001).

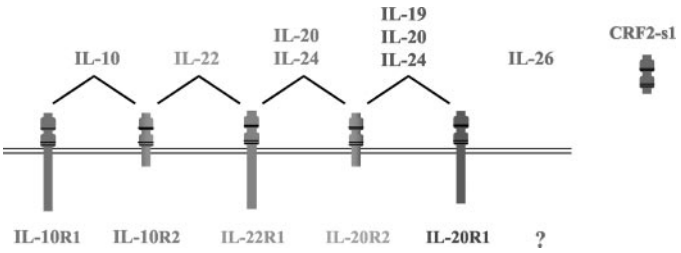

FIG. 3. Ligand/receptor binding of the IL-10 family molecules. All the receptors of the IL-10 family known to date belong to the CRF2. As shown, some of the human IL-10 homologs share single receptor chains and even whole receptor complexes.

How does IL-10 signaling result in the inhibition of immune functions? IL-10 controls inflammatory processes by suppressing the expression of proinflammatory cytokines, chemokines, adhesion molecules, as well as antigen-presenting and costimulatory molecules in monocytes/macrophages, neutrophils, and T cells (Moore et al., 2001). As all of these inflammatory proteins are transcriptionally controlled by NF-κB it was suggested that IL-10 may exert a significant part of its anti-inflammatory properties by inhibiting this transcription factor. In fact, a number of studies were able to demonstrate that IL-10 blocks nuclear translocation of the classic NF-κB p65/p50 heterodimer in monocytes/macrophages (Wang et al., 1995; Clarke et al., 1998). It has been recently shown that IL-10 inhibits NF-κB activity through dual mechanisms: 1) it blocks NF-κB nuclear translocation by inhibiting IKK activity; and 2) IL-10 blocks DNA-binding of NF-κB already present in the nucleus (Fig. 4). Since the inhibition of nuclear NF-κB could not be explained by an increase of nuclear levels of its inhibitor IκB (Schottelius et al., 1999), the mechanisms underlying this observation needs to be further investigated. Our recent unpublished findings suggest that IL-10 exerts its anti-inflammatory activity, in part, by a selective induction of p50 nuclear translocation while blocking translocation of the classical p65-p50 heterodimer (F. Driessler, R. Sabat, K. Asadullah, and A. J. G. Schottelius, submitted).

Recent reports (Ito et al., 1999; Yamaoka et al., 1999; Moore et al., 2001) demonstrated that IL-10 inhibits IFN-induced gene transcription (e.g., IP-10, ISG-54), which correlated with the IL-10-mediated inhibition of IFN-induced STAT1 phosphorylation. Moreover, IL-10 inhibition can be overcome by increasing IFN concentrations suggesting competitive interaction between the two cytokine pathways. This interaction at the STAT1 activation level results in inhibition of IFN-mediated antiviral effects by IL-10 (Ichikawa et al., 2002).

IL-10 induces the suppressor of cytokine synthesis (SOCS)-3 probably via a STAT3-dependent pathway

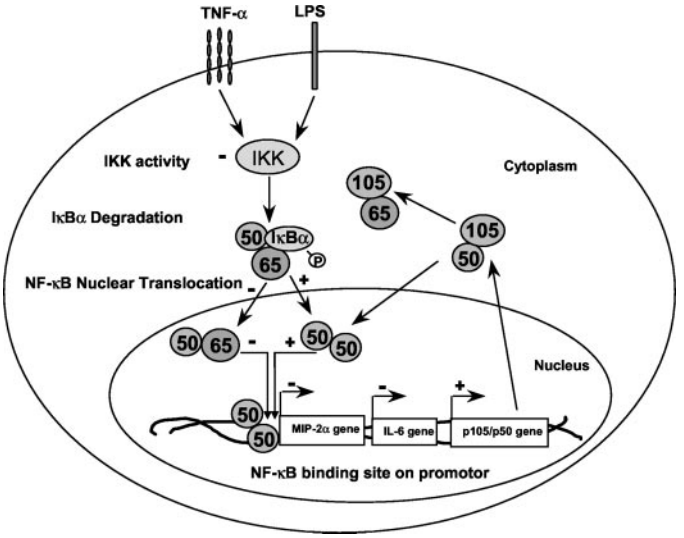

FIG. 4. Scheme representing the molecular mechanisms used by IL-10 to inhibit NF-κB activity. In the absence of an activating stimulus such as TNF-α, IL-10 specifically induces the nuclear translocation of repressive p50/p50 homodimers, which compete with proinflammatory p65/p50 heterodimers for DNA binding to NF-κB promoter sites on inflammatory genes such as IL-6 or MIP-2α. In the presence of a stimulus such as TNF-α, IL-10 can suppress nuclear translocation and DNA binding of p65/p50 heterodimers by inhibiting IKK activity and thus delaying degradation of IκBα. Conserved levels of IκBα will sequester p65 in the cytoplasm, whereas p105/p50 expression is up-regulated and p50 is free to translocate to the nucleus to form homodimers. Up-regulated p105 may also additionally sequester p65 in the cytoplasm. In the absence of the p105/p50 gene, IL-10 loses its ability to suppress constitutive NF-κB activity. Upon activation of p105/p50-deficient cells, p65 may recruit a different Rel protein to form transcriptionally active heterodimers, which can still be inhibited by IL-10 (modified from Schottelius et al., 1999).

(Cassatella et al., 1999; Ito et al., 1999; Moore et al., 2001). There is indirect (Donnelly et al., 1999) and more direct (Berlato et al., 2002) evidence that SOCS-3 plays a key role as mediator of the inhibitory effects of IL-10 on macrophage activation. Very recently, it was shown (Shen et al., 2000) that the IL-10-mediated attenuation of IFN-activated STAT1 is also dependent on SOCS-2 and SOCS-3.

Recent data suggest that IL-10 induces heme oxygenase-1 (HO-1), a heat-shock protein, in murine macrophages via a p38 mitogen-activated protein kinase-dependent pathway (Lee and Chau, 2002). This stress protein degrades heme to carbon monoxide, free iron (that induces ferritin), and biliverdin/bilirubin (Buelow et al., 2002) and plays an essential role in controlling tissue homeostasis in inflammation by inhibiting proinflammatory cytokine synthesis and inducing antiapoptotic processes. Blocking HO-1 by zinc protoporphyrin attenuated the IL-10-mediated protection against endotoxin-induced septic shock in mice, suggesting HO-1 might be an important downstream effector of IL-10 (Lee and Chau, 2002). Induction of HO-1 by cobalt protoporphyrin is associated with upregulation of SOCS-3 and STAT3 supporting this connection (K. Kotsch, R. Buelow, U. Janssen, and H. D. Volk, submitted).

IV. Immunobiology of Interleukin-10

A. Effects of Interleukin-10 on Immune Cells in Vitro

Antigen-presenting cells and lymphocytes are the primary targets of IL-10. Direct effects on these populations explains the major immunological impact of this cytokine, including the regulation of the Th1/Th2 balance (Fig. 5). Th1 cells are known to be essential for effective cell-mediated immunity [cytotoxic T cell lysis (CTL), cell-mediated inflammation, complement/Fcγ-R binding antibodies] in particular against intracellular organisms, whereas a Th2 (or type 2) cytokine pattern is especially responsible for effective production of IgE, IgA, and noncomplement/Fc-R binding IgG in particular for neutralizing microorganisms and their toxins and for mucosal immunity (Romagnani, 1995). IL-10 promotes the development of a type 2 cytokine pattern by inhibiting the IFN-γ production of T lymphocytes particularly via the suppression of IL-12 synthesis in accessory cells. According to this, IL-10 costimulates the proliferation and differentiation of B cells, which is important in the adequate defense against intestinal parasites, neutralization of bacterial toxins, and in local mucosa defense (Romagnani, 1995). Moreover, IL-10 suppresses proinflammatory cytokine production and the antigen-presenting capacity of monocytes/macrophages and dendritic cells (De Waal Malefyt et al., 1991a,b; Fiorentino et al., 1991a,b; Romagnani, 1995). Therefore, IL-10 represents a substantial suppressor of the cellular immunity (Spits and De Waal Malefyt, 1992). Important effects of IL-10 on immune cells are summarized in Table 3 and have recently been reviewed by Moore et al., 2001.

1. Effects on Myeloid Antigen-Presenting Cells. Peripheral blood monocytes are very sensitive to IL-10

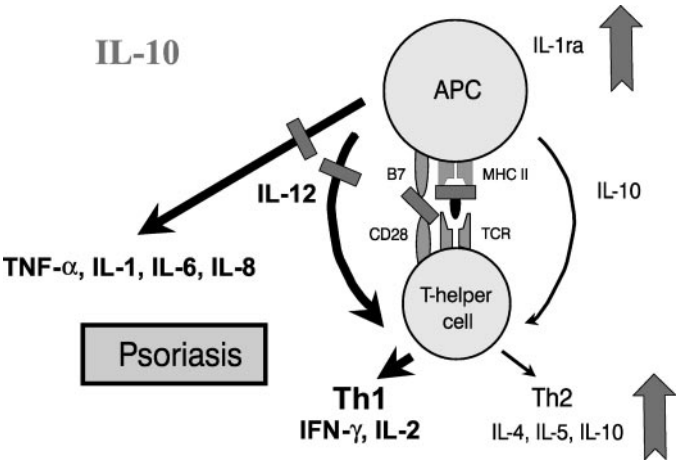

FIG. 5. Effects of IL-10 on the Th1/Th2 dysbalance. An immune deviation toward a type 1 cytokine pattern is a typical finding in several indications such as psoriasis, rheumatoid arthritis, inflammatory bowel disease, transplant rejection, and multiple sclerosis. IL-10 reverses the Th1 cytokine pattern present. It promotes the development of a type 2 cytokine pattern by inhibiting the IFN-γ production of T lymphocytes particularly via the suppression of IL-12 synthesis in accessory cells. Moreover, it inhibits MHC class II and costimulatory molecule expression (Asadullah et al., 2002a; reprinted with permission from Ashley Publications Ltd., London).

TABLE 3
Effect of IL-10 on immune cells (Asadullah et al., 1999b)

Cell Population	Suppression	Induction	Reference
Langerhans cells	Antigen presentation		Enk et al., 1993
Dermal dendritic cells	CD86 expression, antigen presentation		Mitra et al., 1995
Monocytes/macrophages	TNF-α, IL-1, 6, 8, 12 production, expression of MHC class II, CD86, CD54, CD40, antigen presentation	IL-1RA production Soluble TNF receptors	De Waal Malefyt et al., 1991a; Fiorentino et al., 1991b; D'Andrea et al., 1993; Jenkins et al., 1994; Hart et al., 1996
Eosinophils	IL-8, GM-CSF liberation		Takanaski et al., 1994, Nakajima et al., 1996
Neutrophils	TNF-α, IL-1, IL-8 production	IL-1RA production	Cassatella et al., 1994; Jenkins, 1994
Mast cells	TNF-α production	Growth Antigen-induced histamine liberation	Lin and Befus, 1997 Thompson-Snipes et al., 1991
T cells	IL-2 and IFN-γ production, mitogen-induced proliferation		Matsuda et al., 1994
NK cells		Cytotoxicity	Carson et al., 1995
B cells		Growth, IgE synthesis	Uejima et al., 1996, Pistoia, 1997
Keratinocytes	TNF-α, IL-6 secretion capacity (?)		Bécherel et al., 1995; Seifert et al., 2000, 2002
Endothelial cells	No effects	E-Selectin expression	Vora et al., 1996

presence. These cells are not a finely differentiated population. After their 24- to 48-h residence in the circulation, they migrate into the stromal tissues where, depending on the micromilieu, they develop into more specialized cell populations, into either macrophages (Mϕ) or type 1 dendritic cells (DC1) (Randolph et al., 1998). IL-10 is able to prevent monocyte differentiation into DC1, which are the most important antigen-presenting cells (APC) especially for primary immune responses (Buelens et al., 1997; Allavena et al., 1998; Banchereau and Steinman, 1998). During DC1 development, the influence of IL-10 on these cells decreases. This is associated with a decrease of cellular IL-10Rα expression (R. Sabat, unpublished). In contrast, IL-10 supports monocyte maturation to Mϕ, and the sensitivity of Mϕ to IL-10 is comparable to that of monocytes (Allavena et al., 1998; R. Sabat, unpublished). The functions of monocytes and Mϕ that are regulated by IL-10 can be divided into three groups: 1) production of soluble immunomediators regulating inflammation and tissue repair; 2) antigen presentation; and 3) phagocytosis. In general, IL-10 inhibits all those activities that favor the inflammatory or specific cellular immune response and enhances those activities that are associated with the induction of tolerance in adaptive immunity as well as with scavenger function. More concretely, IL-10 inhibits the production of proinflammatory mediators by monocytes and Mϕ, such as endotoxin- and IFN-γ-induced release of IL-1β, IL-6, IL-8, G-CSF, GM-CSF, and TNF-α (de Waal Malefyt et al., 1991a; Fiorentino et al., 1991a). In addition, it enhances the production of anti-inflammatory mediators such as IL-1RA and soluble TNF-α receptors (Jenkins et al., 1994; Joyce et al., 1994; Hart et al., 1996). IL-10 inhibits the capacity of monocytes and Mϕ to present antigen to T cells. This is realized by down-regulation of constitutive and IFN-γ-induced cell surface levels of MHC class II, of costimulatory molecules such as CD86 and of some adhesion molecules such as CD58 (de Waal Malefyt et al., 1991b; Willemset al., 1994; Creery et al., 1996). Moreover, IL-10 inhibits the monocytic production of IL-12, an essential mediator for the development of specific cellular immune defense (D'Andrea et al., 1993). Beside these suppressive activities, IL-10 favors the phagocytic activity of monocytes and Mϕ (Buchwald et al., 1999). This is mediated via up-regulation of specific receptors that are essential for the uptake of opsonized and nonopsonized microorganisms. Indeed, IL-10-treated monocytes and Mϕ display an enhanced expression of IgG-Fc receptors (CD16, CD32, and CD64) as well as scavenger receptors (CD163 and CD14) (te Velde et al., 1992; Spittler et al., 1995; Calzada-Wack et al., 1996; Ritter et al., 1999). Interestingly, IL-10 simultaneously diminishes the killing of ingested microorganisms (Roilides et al., 1998). The up-regulated expression of scavenger receptors seems to be responsible for the observation that IL-10-treated monocytes and Mϕ more strongly ingest apoptotic cells (W. D. Döcke and R. Sabat, unpublished), whereas the chemotaxis of monocytes is only marginally impaired by IL-10 (Vicioso et al., 1998).

2. Effects on T Cells. Besides the dominating indirect impact via the APC (Fig. 5), IL-10 also exerts some direct effects on T cells. In particular, inhibitory effects have been described on $CD4^+$ T cells. IL-10 inhibits the proliferation as well as the cytokine synthesis of these cells. Concerning the latter, it affects their IL-2 and IFN-γ as well as their IL-4 and IL-5 production, which has been induced by various stimuli (Del Prete et al., 1993; Groux et al., 1996). At least in the human system, IL-10, therefore, seems to inhibit both the Th1-type and the Th2-type responses, although the effect on Th1 cells appears to be stronger (Asadullah et al., 1998). Whereas naive $CD4^+$ T cells are targeted by IL-10, activated and memory T cells seem to be rather insensitive toward this cytokine. This might be related to the down-regulation of IL-10Rα upon T cell activation (Liu et al., 1994). However, we observed a similar SOCS-3 induction in activated and resting T cells following IL-10 incubation,

making a functional receptor down-regulation less likely (M. Schroeder, unpublished). The presence of IL-10 during the activation of $CD4^+$ T cells results in the development of a regulatory phenotype of these cells (Groux et al., 1997; Zeller et al., 1999; Levings et al., 2001a,b). It is characterized by weak proliferation, absence of IL-2 production, and a specific cytokine profile (IL-10+, IFN-g+, IL-4−, IL-5−) after repeated stimulation. Typically these cells also have the capacity to transfer this phenotype to other T cells with the same antigen specificity. This transfer may not be dependent on soluble mediators but on cell surface molecules (Jonuleit et al., 2000). Whether the influence of IL-10 on $CD4^+$ T cells or on APC is more important in vivo or the generation of such regulatory cells remains to be clarified. In vitro, both pathways have been demonstrated. IL-10 does not exert potent direct inhibitory effects on $CD8^+$ T cells. It can even activate $CD8^+$ T cells under certain conditions (Groux et al., 1998; Santin et al., 2000).

3. Effects on Natural Killer Cells. The effect of IL-10 on NK cells is mainly stimulatory. IL-10 favors the cytotoxic activity of these cells. It increases the IL-2-induced production of cytokines such as IFN-γ, GM-CSF, and TNF-α. Furthermore, it amplifies the IL-2-induced proliferation of the CD56-bright NK cell subpopulation (Carson et al., 1995). Moreover, IL-10 augments the ability of IL-18 to stimulate NK cells (Cai et al., 1999).

4. Effects on Other Immune Cells. IL-10 has various but weak stimulatory effects on B cells. It prevents apoptosis and enhances the proliferation and differentiation toward plasma cells as well as the IgM synthesis (Levy and Brouet, 1994; Rousset et al., 1995). It also plays a role in the Ig switch. In combination with IL-4, it induces IgG4 but inhibits IgE production; in combination with TGF-β, IL-10 induces IgA1 and IgA2 secretion (Defrance et al., 1992; Jeannin et al., 1998).

Very similar to monocytes and Mϕ, in granulocytes IL-10 inhibits the production of proinflammatory (TNF-α, IL-1β) and induces the production of anti-inflammatory (IL-1RA) mediators. Moreover, it inhibits the release of various chemokines by neutrophils (Cassatella et al., 1993; Kasama et al., 1994). The synthesis of cyclooxygenase-2 as well as the production of prostaglandin E2 is also inhibited by IL-10 (Niiro et al., 1997). Another effect of IL-10 is the inhibition of LPS-induced synthesis of proinflammatory mediators in eosinophils and mast cells (Takanaski et al., 1994; Arock et al., 1996). In combination with IL-3 and IL-4, however, IL-10 favors the growth of mast cells (Lin and Befus, 1997).

5. Effects on Epithelial Cells. It has been shown that several epithelial cells express the IL-10R. IL-10 exerts direct effects on these cells (Bourreille et al., 1999; Denning et al., 2000; Parry et al., 2001). The capability of IL-10 to target keratinocytes (KC) is still a matter of debate. When we analyzed the biological effects of IL-10 on KC in vitro, we did not find any evidence for IL-10 effects on KC proliferation, cytokine formation, and expression of surface molecules with impact on immunoregulation. No effects on unstimulated or stimulated KC were observed in primary human KC or on cultured HaCaT cells (Seifert et al., 2000). These results are in line with other observations (Chatelain et al.,1998) showing that IL-10 inhibits intercellular adhesion molecule-1 (ICAM-1) expression on Langerhans cells but not on KC, but do not support some earlier observations regarding a certain in vitro effect of IL-10 in KC. So it was reported that IL-10 inhibits the cytokine synthesis of TNF-α and IL-6 (Bécherel et al., 1995) as well as proliferation (Michel et al., 1997) of KC. This discrepancy might result from impure primary KC cultures (for example contamination with fibroblasts), other culture conditions, different IL-10 proteins used (LPS contamination?), or differences in the experimental proceedings, but overall the reasons remain unclear (Seifert et al., 2000). Recently, we investigated further the direct effects of IL-10 on keratinocytes and addressed the reason for potential IL-10 unresponsiveness using the keratinocyte-like cell line HaCaT as well as primary foreskin keratinocytes. Using real time reverse transcription-polymerase chain reaction, we demonstrated that IL-10 is neither able to induce its typical early gene product SOCS-3 nor to modulate the IFN-γ-induced expression of SOCS-1 and -3. Although flow cytometric analyses showed binding of biotin-labeled IL-10 to HaCaT cells, blocking experiments indicated that this resulted from unspecific binding, which may explain discrepancies to some earlier observations (Michel et al., 1997a,b). Moreover, scattered plot analyses excluded specific binding to primary KC and HaCaT cells. Finally, real-time mRNA analyses demonstrated that the absence of any specific binding results from the lack of IL-10R1 (α-chain) expression, whereas the IL-10R2 (β-chain) is constitutively expressed. This indicates that IL-10 unresponsiveness of keratinocytes could be explained by a lack of IL-10R1 expression and suggest that any IL-10 effects on these cells observed in vivo are indirectly mediated (Seifert et al., 2003).

There is some evidence that IL-10 regulates collagen and DNA synthesis in activated hepatic stellate cells (Mathurin et al., 2002). Taken together, IL-10 is a pluripotent cytokine with potent effects on numerous cell populations, in particular circulating and resident immune cells, as well as epithelial and some other parenchymal cells. Whereas initial data after its discovery suggested that IL-10 mainly mediates suppressive functions, more recent data showed stimulatory properties on certain cell populations, too. Recent data suggests that the effects of IL-10 are quite complex and still considering IL-10 just as immunosuppressive and anti-inflammatory (as it was done in the past) might be an oversimplification. Considering IL-10 as immunoregulatory instead of immunosuppressive is supported by recent in vivo data.

B. Effects of Interleukin-10 in Animals/Animal Models

The data from investigations of IL-10 effects on immune cells suggests that the major physiological importance of IL-10 seems to be the limitation of inflammation, the prevention of uncontrolled nonadequate immunologic reactions, as well as the support of the humoral (Th2) immune responses (De Waal Malefyt et al., 1991a,b; Romagnani, 1995). This hypothesis was confirmed by experimental research in animals, including analyses of IL-10 knockout mice as well as by the effects of IL-10 observed in several inflammatory, autoimmune, and tumor models.

1. Interleukin-10 Knockout Mice. IL-10-deficient mice develop lethal inflammation of the intestine, which can be stopped by application of IL-10 (Kuhn et al., 1993). Interestingly, IL-$10^{-/-}$ mice kept under germ-free conditions do not develop enterocolitis, which suggests that in the absence of the immunomodulatory effects of IL-10, an unrestricted intestinal inflammatory response develops toward normal enteric antigens (Rennick et al., 2000).

2. Inflammation and Autoimmune Models. The observations in the IL-$10^{-/-}$ mice were the rationale for administering IL-10 in several animal models for colitis. The results of these studies clearly showed prevention of intestinal inflammation by IL-10, mainly by down-regulation of an intestinal proinflammatory Th1-like response. However, systemic IL-10 administration was successful only when administered before the initiation of colitis but was ineffective at reversing any established inflammation (Powrie et al., 1993; Herfarth et al., 1996, 1998; Barbara et al., 2000).

Effects of IL-10 application have been investigated in various other inflammatory animal models, too. It turned out that treatment with IL-10 is beneficial in models of experimental autoimmune encephalomyelitis (Rott et al., 1994), pancreatitis (Van Laethem et al., 1995), diabetes mellitus (Pennline et al., 1994), and experimental endotoxemia (Gerard et al., 1993). IL-10 was also effective in various animal models of arthritis, in reducing inflammation, in cellular infiltrates, and in joint destruction (Persson et al., 1996; Tanaka et al., 1996).

However, some of the data are conflicting. For examples, studies have shown both inhibition and exacerbation of experimental allergic encephalomyelitis (EAE) after systemic IL-10 administration. Different therapeutic outcomes are also dependent on the mode of delivery of IL-10 by gene therapeutic vectors (Broberg et al., 2001; Croxford et al., 2001; Cua et al., 2001). Thus the action of IL-10 may differ depending on the local microenvironment, the disease stage, and the IL-10 concentration.

The majority of experimental data suggests the IL-10 application might be beneficial in several inflammatory and organ-restricted autoimmune diseases. With regard to systemic autoimmune diseases a different picture is emerging. For example, anti-IL-10 mAb treatment of SCID mice injected with PBMC from systemic lupus erythematosus (SLE) patients strongly inhibits autoantibody production in vivo (Llorente et al., 1995); also, treatment of New Zealand black/white mice (mice that spontaneously develop a severe autoimmune disease that closely resembles SLE) with anti-IL-10 mAb substantially delayed onset of autoimmunity (Ishida et al., 1994). This may indicate that neutralizing IL-10 might be a new therapeutic option here. In contrast to the organ-specific autoimmunopathies, SLE is thought to be more a "B cell disease". The different pathogenesis might explain the opposite effects of IL-10.

3. Tumor Models. Several animal experiments have been performed to analyze the role of IL-10 on tumor development. The data are complex, showing diverse effects regarding the influence of IL-10 on cancer. Dependent on the experimental model, IL-10 seems to favor or inhibit the existence and progression of tumors (Sabat and Asadullah, 2002).

IL-10 is able to favor tumor growth both directly by affecting the tumor cells and indirectly by inhibition of immune cells. IL-10 can convert tumor cells to a CTL-resistant phenotype. Kiessling and coauthors reported an approximately 50% reduction of MHC class I expression in human melanoma cells after IL-10 treatment. This pretreatment resulted in a dose-dependent, and up to 100% inhibition of autologous CTL-mediated, tumor-specific lysis (Matsuda et al., 1994). This effect is mediated by reduced expression of the so-called transporter associated with antigen processing (TAP)-1 and -2, which results in reduced translocation of peptides to the endoplasmic reticulum and, therefore, in diminished MHC class I peptide loading and cell surface levels (Salazar-Onfray et al., 1997). However, the down-regulation of MHC class I expression results in higher sensitivity of these cells toward NK cell activity (Salazar-Onfray et al., 1995; and see below). The consequence of IL-10 presence and thereby the resulting inhibition of the antitumor immune reaction might be the uncontrolled development of cancers. This has been demonstrated in transgenic mice expressing IL-10 under control of the IL-2 promoter. These animals are unable to limit the growth of immunogenic tumors. However, administration of anti-IL-10 antibodies restored the anticancer response (Hagenbaugh et al., 1997).

The direct negative effect of IL-10 on tumor survival has been described by the Fulton group. They observed that the IL-10 gene transfer in murine mammary tumor cells was associated with increased expression of the inducible isoform of nitric-oxide synthase (iNOS). The activity of this enzyme was elevated as well. This can result in elevated levels of nitric oxide in transfected tumor cells (Kundu et al., 1998). Nitric oxide is known to show potent antitumor activity.

IL-10 can inhibit the generation of new vessels within the tumor both directly by acting on the tumor cells and indirectly by influencing infiltrating immune cells. IL-10 induced the tissue inhibitor of metalloproteinase 2 (TIMP-2) in primary human prostate cancer cells. Simultaneously, it reduced the secretion of matrix metalloproteinase (MMP)-2 and MMP-9 from these cells. The consequence was the inhibition of microvessel formation (Stearns et al., 1999). Interestingly, TGF-β induced the expression of MMP-2, and this induction was prevented by IL-10. When primary human prostate cancer cells either expressing TGF-β or IL-10 were implanted in SCID mice, TGF-β-promoted tumor growth, angiogenesis, and metastasis. In contrast, IL-10 reduced growth rates, angiogenesis, and metastasis. More importantly, none of the mice bearing TGF-β-expressing tumor cells survived compared with 80% of those expressing IL-10 (Stearns et al., 1999). IL-10 can also inhibit the angiogenesis by inhibiting tumor-resident macrophages. Bar-Eli and coauthors (Huang et al., 1996, 1999) reported that the transplantation of human melanoma cells that had been transfected with the murine IL-10 cDNA into nude mice resulted in fewer lung metastases and significant inhibition of tumor growth. The authors suggested that this was due to inhibition of angiogenesis by IL-10. They referred to the fact that IL-10 down-regulated the production of vascular endothelial growth factor in the tumor-associated macrophages. Other factors involved in neovascularization such as IL-1β, TNF-α, and IL-6 were also inhibited (Huang et al., 1996, 1999). Velu and coauthors (Gerard et al., 1996) demonstrated a loss of tumorigenicity of melanoma cells injected into syngeneic mice after the previous retroviral transfection of these cells with IL-10 cDNA. Host T cells and NK cells might be involved in the observed tumor eradication because IL-10-producing tumor cells grew in nude mice and in $CD8^+$ T or NK cell-depleted mice (Gerard et al., 1996). Similar observations have been reported by the Fulton group. They described that injection of a murine mammalian tumor cell line in syngeneic mice resulted in progressive tumor growth and death from pulmonary metastases. In contrast, transfection of IL-10 cDNA in these cell lines resulted in complete inhibition of growth and metastatic disease. Interestingly, the antimetastatic activity of IL-10 is observed also in T cell-deficient mice but is lost when NK cell activity is suppressed (Kundu and Fulton, 1997).

4. Experimental Models of Infections. It is well recognized that IL-10 can inhibit protective immune response to infections (Moore et al., 2001). It has been shown that the trauma-, burn-, and major surgery-induced immunodepression, which predispose to infectious complications, is related to IL-10 overexpression (Ayala et al., 1994; Woiciechowsky, 1998; Kobayashi et al., 2001). Prolonged IL-10 expression increases the risk for infectious complications, whereas neutralizing IL-10 >12 h post trauma reduces the immunodepression and infection-related mortality (Song et al., 1999).

Overexpression of IL-10 or other type 2 cytokines also modifies the immune response to intracellular bacteria and parasites as well as the susceptibility of mice to these infections (Yamakami et al., 2002).

On the other hand, IL-10 has also protective effects in infection because it prevents an uncontrolled inflammatory response to infectious triggers. IL-10-deficient mice show a prolonged inflammatory response to acute Pseudomonas challenge resulting in neutrophil accumulation in the lung. This observation suggests that IL-10 deficiency might contribute to prolonged inflammatory responses early in cystic fibrosis, a lung disease that is characterized by a neutrophilic infiltrate that is excessive relative to the burden of infection (Chmiel et al., 2002). Overexpression of IL-10 prevents mice from endotoxin or bacteria-induced septic shock whereas lack of IL-10 increases the susceptibility to toxin-related shock (Moore et al., 2001; Oberholzer et al., 2002). IL-10 also protects against experimental group B streptococcal arthritis (Puliti et al., 2002). Similar protective properties of IL-10 were observed for gastrointestinal helminth infections (Schopf et al., 2002).

C. Interleukin-10 and Interleukin-10 Receptor Expression in Diseases

Its considerable anti-inflammatory effects and ability to act as a main suppressor of cellular immunity (Spits and De Waal Malefyt, 1992) raises the question of the IL-10 expression under pathophysiological conditions. Both overexpression (e.g., in lymphoma) as well as IL-10 deficency were found (e.g., in inflammatory bowel disease, psoriasis) and seems to have a pathophysiological significance (Schreiber et al., 1995). Numerous studies have investigated the expression and suggested the importance of IL-10 dysregulation in different entities.

1. Expression in Malignant Diseases.

a. Melanoma. Krüger-Kraskagakes et al. (1994) could demonstrate significant IL-10 mRNA expression in melanoma and melanoma metastases but not in healthy skin. Moreover, they found IL-10 mRNA and the biologically active protein in 3 of 13 melanoma cell lines. This suggests that melanoma cells themselves are contributing at least in part to the IL-10 overexpression in melanoma lesions. Similar results were reported by Dummer et al. (1996b) who also demonstrated IL-10 production by a high percentage of melanoma metastases and corresponding cell lines. This may be of particular pathogenetic importance, since IL-10 functions as autocrine growth factor for malignant melanoma and reduces the expression of HLA class I and II on melanoma cells (Yue et al., 1997).

b. Carcinoma. There are reports on the overexpression of IL-10 in basal cell and squamous cell carcinoma (Kim et al., 1995). Cytotoxic T cell lines recognizing these tumors proliferated in the presence of the tumor

cells only when IL-10 was neutralized by monoclonal antibodies. On the other hand, the intralesional injection of IFN-α resulted in a tumor regression that was associated with the down-regulation of IL-10 mRNA expression. IL-10, therefore, seems to be an important mediator in evading the T cell-mediated immune response in these cutaneous malignancies (Kim et al., 1995). The Strieter group described increased levels of IL-10 protein in tissue homogenates of human bronchogenic carcinomas compared with normal lung tissues. Staining of these tumors illustrated primary localization of IL-10 protein to cancer cells. Furthermore, IL-10 protein was present in supernatants of several unstimulated human bronchogenic cell lines (Smith et al., 1994).

Interestingly, a correlation between IL-10 and vascular endothelial growth factor expression in esophageal cancer was demonstrated suggesting a relation between IL-10 and tumor-promoting angiogenic factor gene expression (Nagata et al., 2002).

c. Lymphoma. Tumor cells from B, T, and NK cell lymphoma are able to produce biologically active IL-10 (Kitabayashi et al., 1995; Masood et al., 1995; Sjoberg et al., 1996; Beatty et al., 1997; Boulland et al., 1998; Jones et al., 1999). As early as 1993, Favrot and coauthors (Blay et al., 1993) investigated IL-10 serum levels using an ELISA, which detects both viral and human IL-10 in patients with active non-Hodgkin's lymphoma (NHL) and healthy volunteers. They described the detection of IL-10 in serum from about 50% of these patients but none of the control blood donors. IL-10 was detectable with a similar frequency in all subtypes of NHL and in all clinical stages, as well as in both EBV-seropositive and EBV-seronegative patients (Blay et al., 1993). One year later the Papa group (Stasi et al., 1994a) demonstrated similar results obtained in patients with aggressive non-Hodgkin's lymphoma. In the following years these observations were extended to Hodgkin's disease and other lymphoma species, and due to improved sensitivity of ELISA systems, it was possible to demonstrate that lymphoma patients had significantly higher serum levels of IL-10 than healthy volunteers (Cortes et al., 1995; Cortes and Kurzrock, 1997; Sarris et al., 1999; Bohlen et al., 2000; Vassilakopoulos et al., 2001; Fayad et al., 2001). An elevated local expression of IL-10 was detected in various cutaneous T cell lymphoma entities (CTCL). Dummer et al. (1996a) showed IL-10 production by malignant T cells in Sézary syndrome, a leukemic type of cutaneous T cell lymphoma. We demonstrated cutaneous IL-10 mRNA overexpression in mycosis fungoides (MF) lesions (Asadullah et al., 1996). Increasing IL-10 gene expression correlated with the tumor progression. An increased cutaneous IL-10 mRNA expression was also found in $CD30^+$ pleomorphic T cell lymphomas (Asadullah et al., 1996; Yagi et al., 1996) and cutaneous B cell lymphomas (CBCL) (Asadullah et al., 2000b). The IL-10 overexpression in CTCL might contribute to a number of immunological abnormalities well known in these patients. These include eosinophilia and elevated IgE and IgA levels (Edelson, 1980). We recently observed a stage-dependent decrease in T cell activation of antigen expression suggesting impairment of tumor surveillance in advanced MF stages (Asadullah et al., 1997a). Such findings might result from the IL-10 overexpression that also might be responsible for the development of a systemic type 2 cytokine pattern in CTCL (Dummer et al., 1993).

d. Prognostic Value of Interleukin-10 Overexpression. In different lymphomas, increased IL-10 production has been reported and a negative prognostic meaning of increased IL-10 plasma levels is being discussed (Blay et al., 1993; Stasi et al., 1994a,b; Cortes et al., 1995). Elevated IL-10 serum levels have been also described as a negative prognostic factor for responsiveness toward treatment, as well as the disease-free and overall survival by patients with melanoma and solid tumors, particularly with lung, gastrointestinal, and renal cell cancer. Several groups including ours reported on increased circulating IL-10 serum levels in gastric, colon, and renal-cell cancer patients (Ordemann et al., 2002). IL-10 serum levels commonly returned to normal in radically resected patients. Persistently elevated IL-10 serum levels after surgery predicted tumor recurrence (Galizia et al., 2002a,b; Uwatoko et al., 2002). Moreover, a further significant increase in IL-10 serum levels has been observed in nonresponders after chemotherapy (Wojciechowska-Lacka et al., 1996; De Vita et al., 1999, 2000a,b; Nemunaitis et al., 2001).

In summary, there are several lines of evidence that IL-10 overexpression in different malignancies might contribute to tumor development, in particular, by suppressing the antitumor immune response (Matsuda et al., 1994). Moreover, IL-10 might even be a tumor cell growth factor in certain tumors such as B cell lymphoma and melanoma.

2. Autoimmune and Inflammatory Diseases. IL-10 has been investigated in several immune disorders with identified autoantigen. This includes lupus erythematosus, systemic sclerosis, and bullous diseases. Overall enhanced IL-10 levels were observed and seem to be of pathophysiological relevance. Several investigations pointed to the major role of IL-10 in chronic inflammatory disorders characterized by the predominance of a type 1 cytokine pattern. These included psoriasis, inflammatory bowel disease such as Crohn's diseases, multiple sclerosis, rheumatoid arthritis, transplant rejection, and allergic contact dermatitis. So in contrast to several malignant and autoimmune diseases, a relative deficiency rather than an overexpression is considered to be of pathophysiological relevance here.

a. Systemic Lupus Erythematosus. IL-10 functions as a potent B cell stimulator that enhances activation, proliferation, and differentiation of B cells. With regard to B cell activation, IL-10 might play a critical role in SLE, since this systemic autoimmune disease is charac-

terized by high autoantibody production and by decreased cellular immune responses. In SLE, high levels of autoantibodies generate immune complexes causing tissue damage. Therefore, expression of this cytokine was investigated. Compared with healthy individuals, levels of IL-10 in SLE patients are significantly higher and there is a correlation of IL-10 levels with the clinical disease activity (Park et al., 1998). Depletion of IL-10 by anti-IL-10 mAb in vitro treatment of SLE patient-derived PBMC significantly decreased autoantibody production (Llorente et al., 1995). Together with the data from animal models described above, this data suggests that IL-10 is harmful in systemic lupus and that IL-10 antagonists may be beneficial in the treatment of human SLE (Llorente et al., 1999).

b. Systemic Sclerosis. Increased IL-10 serum levels (significant in diffuse SSc, not significant in limited SSc) in patients compared with levels in healthy controls has been found. Although the role of IL-10 in SSc is not known yet, it is suggested that IL-10 may contribute to the development of SSc (Hasegawa et al., 1997).

c. Bullous Pemphigoid. Titers of IL-10 in blister fluids of patients were significantly higher than in suction blisters from control probands (Schmidt et al., 1996; Giacalone et al., 1998). Apart from this correlation, the role of IL-10 in bullous pemphigoid is not understood yet.

d. Psoriasis. We have recently demonstrated that the cutaneous IL-10 mRNA expression in psoriasis was significantly lower than in atopic dermatitis or cutaneous T cell lymphoma. The level of IL-10 mRNA expression did not differ from healthy skin, even though numerous proinflammatory cytokines are overexpressed. This indicates a relative IL-10 deficiency in psoriasis (Asadullah et al., 1998). These results are supported by immunohistochemical findings of low cutaneous IL-10 protein expression (Nickoloff et al., 1994) and by quantification of IL-10 protein in blister fluids (Mussi et al., 1994). Accordingly, it has also been shown that T cells involved in psoriasis vulgaris belong to the Th1 subset (Schlaak et al., 1994).

e. Rheumatoid Arthritis. A number of published studies have shown a correlative relationship between IL-10 and RA. This includes studies carried out to detect IL-10 in the serum, synovial fluid, or synovial explants of patients (Jenkins et al., 1994; Cush et al., 1995; Al-Janadi et al., 1996). Several ex vivo studies show that IL-10 can effectively block the production of the proinflammatory cytokines TNF-α, IL-1, and IL-8 by snivel macrophages and synoviocytes. IL-10 has been correlated with an increased autoantibody production, serum factor, and B cell activation in RA patients (Chomarat et al., 1995; Hart et al., 1995, 1996). These findings indicate that it might be difficult to predict the response of a human patient population to IL-10, despite the promising findings in animal models of arthritis (Narula, 2000).

f. Allergic Contact Dermatitis and Other Non-Atopic Eczemas. Important clues for the role of IL-10 in contact dermatitis were demonstrated by in vivo experiments. Allergic contact dermatitis represents a classic type 1 cytokine-dominated immune reaction, suggesting only low levels of the type 2 cytokine IL-10. Kondo and Schwarz demonstrated that the application of IL-10 blocks the effector phase in allergic contact hypersensitivity reactions (epicutaneous application) (Kondo et al., 1994; Schwarz et al., 1994). Consequently, it might be speculated that therapeutic IL-10 application in allergic contact dermatitis would be beneficial.

The expression of IL-10 in other eczematic non-atopic skin diseases might represent an important counter-regulatory, i.e., protective mechanism in stopping overwhelming inflammatory reactions. This hypothesis is strengthened by the observation that therapeutic UV radiation, effective in treating several inflammatory dermatoses, enhances IL-10 production. Kang et al. (1994) showed that skin-infiltrating macrophages are the main source of epidermal IL-10 production after UV exposure. This IL-10 seems to be responsible for the fast disappearance (resolution) of UV-induced erythema within a couple of days seen for example in solar dermatitis (Kang et al., 1994).

g. Chronic Inflammatory Bowel Diseases. The gastrointestinal tract serves as a barrier between the host and several foreign antigens and pathogens that are contained within its lumen. The mucosa-associated immune system must balance two opposing functions: the development of an immune response to pathogens while maintaining tolerance to antigens derived from food and "natural" microbial flora. The regulation of this balance is very complex but cytokines seem to play a key role. Mice deficient in the immunoregulatory cytokines IL-10 or TGF-β develop an imbalance of this system resulting in severe inflammatory disease and death by uncontrolled inflammation. Local release of IL-10 by genetically modified bacteria, intestinal cells, or T cells prevents chronic ileocolitis in these mice (Kuhn et al., 1993; Lindsay and Hodgson, 2001).

Transfer of T cells depleted of $CD4^+25^+$ regulatory T cells into immunodeficient SCID mice induces chronic inflammatory bowel disease as well. Enriched IL-10-expressing regulatory T cells can prevent the disease (Lindsay and Hodgson, 2001).

h. Multiple Sclerosis. In several experimental models of EAE, a protective effect of IL-10 has been described. In vitro generation of IL-10 producing regulatory $CD4^+25^+$ T cells is induced by a combination of vitamin D and dexamethasone. The regulatory function of these cells that in vitro inhibit both Th1- and Th2-inducing cytokines was demonstrated in vivo by their ability to prevent EAE, when targeted to the site of inflammation, and this function was shown to be IL-10-dependent (Barrat et al., 2002).

Local delivery of IL-10 in the brain using gene transfer methods also improved the EAE disease, although the kind of delivery system seems to be important (Croxford et al., 2001; Cua et al., 2001). Intranasal or mucosal delivery of IL-10 with or without coapplication of autoantigen was also sufficient to prevent EAE (Massey et al., 2002)

In most models, however, IL-10 was active in preventing EAE whereas its efficiency in ongoing or established EAE was less clear (Link and Xiao, 2001).

Interestingly, IFN-β application, the best established therapeutic approach in multiple sclerosis in patients, modulates the IL-10/IL-12 cytokine circuit resulting in dominance of IL-10 (Tuohy et al., 2000).

i. Transplantation. The role of IL-10 in transplantation is poorly understood. Because of its anti-inflammatory properties and its association with regulatory T cells, IL-10 should have some benefit on graft survival. In fact, IL-10 inhibits ischemia/reperfusion injury (Deng et al., 2001), prolongs allograft survival (Feng et al., 1999; Zuo et al., 2001), and is essential for the action of regulatory T cells mediating tolerance at least in some transplant models (Hara et al., 2001). In addition, IL-10 prevents several side effects of OKT3 mAb-mediated cytokine release (Moore et al., 2001).

On the other hand, in several transplant models, particularly across strong MHC barriers, IL-10 did not improve graft survival (T. Ritter, unpublished). Moreover, intragraft up-regulation of IL-10 showed a strong correlation to acute and chronic rejection of human kidney transplant, much stronger than proinflammatory cytokines such as TNF-α, IFN-γ, IL-2, etc. (Ode-Hakim et al., 1996; Suthanthiran and Strom, 1998). Tacrolimus is much more potent in preventing chronic rejection than cyclosporin A. A major risk factor of chronic rejection is incomplete reversal of acute rejection. Ongoing acute allograft rejection was found to be rescued by tacrolimus but not by cyclosporin A at the equivalent dose. Tacrolimus but not cyclosporin A inhibited intragraft IL-10 and perforin expression as well as $CD8^+$ T cell infiltration. However, both drugs inhibited other immune cells ($CD4^+$, $ED2^+$ macrophages) and cytokines (IL-1β, IL-2, IL-4, IL-6, IL-12, IFN-γ, and TGF-β). The inability of cyclosporin A to overcome ongoing allograft rejection could be addressed by cotreating recipients with neutralizing anti-IL-10 antibody. These data suggest that intragraft IL-10 production might be a critical factor in persistent rejection resulting in chronic graft injury (Jiang et al., 2002).

The main problem in allogeneic bone marrow transplant patients is the development of graft-versus-host disease. Increased IL-10 production before allogeneic bone marrow transplant correlated with a subsequent low incidence of graft-versus-host disease and transplant related mortality as compared with low IL-10 production (Baker et al., 1999; Holler et al., 2000).

3. Expression in Atopic Disorders. IL-10 overexpression is considered to be responsible for the immune deviation into a type 2 direction a hallmark of atopic disorders such as atopic dermatitis and allergic asthma. Consequently, IL-10 is speculated to be harmful here and a potential target for neutralization. However, IL-10 with its obvious anti-inflammatory capacities and its overexpression might in fact also contribute to the limitation of inflammation (as counter-regulation). Indeed, it has therefore even been postulated that it might therapeutically be applied even in the treatment of allergic inflammation (Pretolani and Goldman, 1997), but IL-10 treatment of a pre-existing type 2 cytokine pattern may have only limited effect, or may even worsen the course of the disease.

a. Atopic Dermatitis. In atopic dermatitis, Ohmen et al. (1995) reported a marked overexpression of IL-10 mRNA, predominantly of monocytic origin but possibly also from skin-infiltrating Th2 cells. We found similar results in our atopic patients (Asadullah et al., 1996). The cutaneous overexpression of IL-10 reflects the general immunological imbalance in atopic dermatitis. According to current knowledge, type 2 cytokine (IL-4, IL-5, IL-10)-producing allergen-specific T cells are considered to be crucial in atopic dermatitis. In fact, such allergen-specific activated T cells were isolated (Renz et al., 1992; Van Reijsen et al., 1992). The type 2 cytokine pattern in atopic dermatitis (Bos et al., 1992; Chan et al., 1993; Romagnani, 1995) explains the atopy-associated eosinophilia and hyper-IgE phenomenon, findings considered to be of pathophysiological importance for this disease. IL-10, however, is of considerable importance in the regulation of the type 1/type 2 balance as outlined before. Moreover, the persistently elevated cutaneous IL-10 expression might also be responsible for the lasting suppression of the skin immune system, which might contribute to the increased incidence of cutaneous infections in patients with atopic eczema (Braun-Falco et al., 1995). Infiltrating macrophages also contribute to the high IL-10 expression in atopic dermatitis. It is possible, therefore, that IL-10 production in atopy also exerts counter-regulatory effects.

b. Allergic Asthma. In animal models of asthma, IL-10 was shown to be capable of inhibiting allergen-induced airway inflammation and nonspecific airway responsiveness (Tournoy et al., 2000). IL-10 gene transfer to the airway abrogated both the cellular and physiological recall response in vivo. However, IL-10 did not prevent expansion and activation of T cells (Stampfli et al., 1999). In addition, studies in gene-deficient mice suggest IL-10 is necessary for the expression of airway hyperresponsiveness but not pulmonary inflammation after allergic sensitization (Makela et al., 2000). These data suggest the complexity of IL-10 in the pathogenesis of asthma (Barnes, 2002).

A relative underproduction of IL-10 from alveolar macrophages and in sputum of atopic asthmatics has

been reported in patients (Takanashi et al., 1999; Chung, 2001). During classic specific immunotherapy that has been proved to be clinically effective, the Th2-dominated immune response is modified toward a Th1 response leading to a decline in allergen-specific IgE and an increase in allergen-specific IgG production. Most importantly, however, production of IL-10 is also induced leading to T cell anergy (Bellinghausen et al., 2001). A randomized, double-blind trial of the effect of glucocorticoid, antileukotriene, and β-agonist treatment in children with asthma demonstrated that triamcinolone and montelukast treatment increased the serum IL-10 levels but decreased eosinophil counts and that all clinical parameters improved; treatment with formoterol had no significant effects on these parameters. Thus, the positive effects of triamcinolone and montelukast on asthma might be related to increasing IL-10 serum levels (Stelmach et al., 2002).

4. Expression in Infection. Because IL-10 expresses potent immunomodulatory properties it can modulate the course of infections. The main target of IL-10 is macrophages, and these cells play a central role in infections, as a target for pathogens and in the activation of both specific and innate immune response. Certain viruses induce production of host IL-10 by macrophages, whereas other viruses encode their own viral IL-10 homologs. As already suggested (see *Section II.A.*), several DNA viruses such as herpes viruses (e.g., EBV, CMV, primate CMVs, equine herpesvirus 2, herpesvirus samiri) and pox viruses (e.g., parapoxvirus orf) encode for their own IL-10. Other viruses such as respiratory syncytial virus, human rhinovirus-14, and parainfluenza virus 3 have developed strategies to induce cellular IL-10 in host macrophages. The exact molecular mechanisms by which these viruses cause increased IL-10 secretion have not been determined. However, it is apparent that expression of viral IL-10 homologs or induction of cellular IL-10 by viruses that target macrophages leads to suppression of the localized and perhaps also generalized inflammatory response (Kotenko et al., 2000; Moore et al., 2001; Redpath et al., 2001; Spencer et al., 2002).

On the other hand, cellular IL-10 can activate several viruses by triggering promoters encoding essential viral proteins; e.g., the early promoter of human papilloma virus type 16 (Arany et al., 2002) and the immediate early promoter of human CMV (Kline et al., 1998; K. Pioch, C. Priemer, C. Liebenthal, D. H. Krüger, H. D. Volk, and S. Prösch, submitted). Additionally, specific intracellular bacteria, including several mycobacteria and Listeria monocytogenes, can replicate in macrophages while inducing cellular IL-10 (Redpath et al., 2001; Demangel et al., 2002).

As in experimental models, trauma, burn, and major surgery induces increased production of IL-10. Stress mediators seem to play an important role in regulating IL-10 (Woiciechowsky et al., 1998). Recent data from our group shows that blocking sympathetic activation after major surgery by high epidural anesthesia significantly reduces the postoperative IL-10 release (Volk et al., 2003). Several studies report on an association between IL-10 release, immunodepression, and decreased resistance to infections (Lyons et al., 1997; van Dissel et al., 1998; Opal and Huber, 2000; Volk et al., 2000; Muehlstedt et al., 2002; Spiess et al., 2002).

D. Interleukin-10 and Interleukin-10 Receptor Polymorphisms and Diseases

Genetic markers in cytokine genes are becoming widely used in studies of immune-mediated disease, and it is becoming apparent that they can be markers of disease susceptibility as well as of disease severity (Bidwell et al., 1999). Since inadequate expression of IL-10 seems to be of pathophysiological relevance in several diseases and the expression levels seem to have a genetic background (as described above), linkage analyses of IL-10 promoter haplotypes to diseases have been performed. Possible linkage of IL-10 promoter haplotypes to disease susceptibility or severity has been reported (Moore et al., 2001).

The strongest association seems to be established for SLE, where it has been suggested that high IL-10 expression (Llorente et al., 1995, 1997), and the corresponding IL-10 alleles (Eskadale et al., 1997b), play a causative or aggravating role (Lazarus et al., 1997; Gonzalez-Amaro et al., 1998; Rood et al., 1999). The IL10.G microsatellite showed significant allele skewing in patients versus controls. This has been observed in patients from the United Kingdom (Eskdale et al., 1997a), Mexico (Mehrian et al., 1998), and Italy (D'Alfonso et al., 2000). Both in the UK and Italian study the same allele was associated with SLE (IL10.G13). To what extent high IL-10 expression actually contributes to or is just a consequence of the disease is not really understood. Healthy relatives of lupus erythematosus patients also exhibit elevated IL-10 expression (Llorente et al., 1997; Grondal et al., 1999), suggesting that high IL-10 levels may predispose to disease and precede onset. Another 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 (Mehrian et al., 1998). One of the lupus susceptibility loci in the New Zealand mouse is near IL-10 on chromosome 1 (Kono et al., 1994), and an IL-10 promoter polymorphism in this strain has been noted (Morse et al., 1999). By contrast, the IL-10 receptor genotype does not determine susceptibility to SLE (Nakashima et al., 1999).

When the two known polymorphic microsatellite markers in the human IL-10 promoter IL10.G and IL10.R were investigated in psoriasis patients, no difference was noted in comparison to the control group. Also, no difference in allele distribution was observed when the psoriasis patients were stratified according to age of onset. However, a clear differential distribution was re-

vealed when patients were grouped according to whether they had a positive family history of psoriasis. In this case, allele IL10.G13 was positively associated with familial psoriasis, and this was also true when younger patients were considered; patients with age-of-onset less than 40 were 3-fold more likely to have a psoriatic family background if they carried this allele. Thus, it appears that the IL-10 locus contributes to the genetic background in familial psoriasis (Asadullah et al., 2001a).

There is only some preliminary evidence for a relationship between genetic IL-10 secretion predisposition and infectious disease. Genetic predisposition to high IL-10 expression has been reported to be associated with a higher rate of mortality in meningococcal disease (Westendrop et al., 1997). Moreover, chronically infected hepatitis C patients who are genetically predisposed to high IL-10 production were reportedly less likely to benefit from IFN-α therapy (Edwards-Smith et al., 1999). An association between IL-10 polymorphism and recurrence of hepatitis C in liver transplant patients has also been reported (Tambur et al., 2001).

Some groups found an association between IL-10 polymorphism and severity of, but not susceptibility to, asthma (Zhang 2002). Several reports suggest that genetic factors in the IL-10 gene may modify the incidence and outcome of tumors (McCarron et al., 2002; Wu et al., 2002).

IL-10.G microsatellites mark promoter haplotypes associated with protection against the development of reactive arthritis (Kaluza et al., 2001). In female rheumatoid arthritis patients followed up for >12 years, the mean increase in radiographic damage score during the first 6 years was significantly lower in the IL-10 high responder group expressing the −1082 GG genotype (Huizinga et al., 2000). In addition, IL-10 microsatellite polymorphisms also influences the susceptibility to rheumatoid arthritis (Eskdale et al., 1998).

A significant association between IL-10 polymorphisms and the outcome of organ and bone marrow allografts has also been reported although different results were found between distinct transplant populations (Turner, 1997b; Takahashi, 2000; Asderakis et al., 2001; Hahn et al., 2001; McShane, 2002).

Although it has been shown that genetic relationships between cytokine alleles and secretion may vary in patient groups compared with normal groups, the possibility must be considered that the dysregulation of IL-10 seen in psoriasis (Asadullah et al., 1998) and other diseases and the association between an IL-10 locus gene marker and the disease investigated are complimentary rather than related. Of course, this allele may well be of importance in alternative pathways of IL-10 regulation, but if IL10.G13 is not associated with differential IL-10 secretion then it is likely that this allele is associated with both psoriasis and SLE, through linkage disequilibrium with a new functional element yet to be defined. Recently, several new single-nucleotide polymorphisms have been defined in the human IL-10 locus, but none of these was specifically linked to IL10.G13. Furthermore, the complex haplotypic nature of the IL-10 locus (Eskdale et al., 1999) placed the IL10.G13 on at least two frequent haplotypes. Both these observations support the hypothesis that any functional element linked to this allele may in fact lie outside the IL-10 locus per se. If true, this would implicate IL-10 as a disease-modifying gene in psoriasis (and probably other immune diseases) rather than a disease-causing gene.

V. Interleukin-10 As a Therapeutic Agent

The powerful immunomodulatory properties of IL-10 and the promising results from IL-10 delivery on the course of several inflammatory diseases in experimental models induced the interest on clinical application of IL-10. To our knowledge, so far human recombined IL-10 (ilodecakin/Tenovil; Schering-Plough Research, Kenilworth, NJ) has been tested in healthy volunteers, patients with Crohn's disease, rheumatoid arthritis, psoriasis, hepatitis C infection, HIV infection, and for the inhibition of therapy associated cytokine releases in organ transplantation and Jarisch-Herxheimer reaction.

A. Phase I Trials in Healthy Volunteers

In phase I clinical trials, safety, tolerance, pharmacokinetics, pharmacodynamics, immunological, and hematological effects of single or multiple doses of IL-10 administered by intravenous (i.v.) or subcutaneous (s.c.) route have been investigated in various settings on healthy volunteers (Chernoff et al., 1995; Huhn et al., 1996, 1997). The first administration of human recombined IL-10 in human was performed in 1995 (Chernoff et al., 1995). Overall, these studies showed that IL-10 is well tolerated without serious side effects at doses up to 25 μg/kg; mild to moderate flu-like symptoms were observed in a fraction of recipients at doses up to 100 μg/kg (Moore et al., 2001).

Single i.v. or s.c. 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 i.v. dose of IL-10 in healthy volunteers (Fuchs et al., 1996; Huhn et al., 1999). In addition to transient neutrophilia, lymphocytopenia, and monocytosis, a delayed decrease in platelet

counts was observed following a single s.c. dose of IL-10 (Huhn et al., 1997).

Pharmacokinetic parameters of IL-10 were determined following i.v. or s.c. administration of doses ranging from 0.1 to 100 μg/kg (recently reviewed by Moore et al., 2001). Following i.v. administration, IL-10 serum levels initially declined fairly rapidly but yielded a less steep terminal phase with a $t_{1/2}$ of 2 to 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 (Andersen et al., 1999). 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 to 6.5 h post injection. The slower absorption of IL-10 following s.c. versus i.v. administration led to prolonged but lower AUC with a mean terminal $t_{1/2}$ of 2.7 to 4.5 h and so resulted in a prolonged immunosuppressive effect. Mean exposure parameters were also linearly related to dosage (Radwanski et al., 1998). Production of neutralizing antibodies was not observed in any of the studies. Coadministration of IL-10 and prednisolone did not result in pharmacokinetic alterations of either drug. In addition, IL-10 administration did not significantly alter cytochrome P450-mediated drug metabolism (Gorski et al., 2000).

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 proliferate responses and IFN-γ production following phytohemagglutinin stimulation of PBMC, indicating that IL-10 retains immunomodulatory activity when administered in vivo. The doses required to effect 50% maximum inhibition (IC_{50}) of TNF and IL-1β production and a maximum fraction of inhibition (I_{max}) indicated that IL-10 inhibited production of proinflammatory mediators in vivo at concentrations similar to those used in vitro experiments (Radwanski et al., 1998). Similarly, i.v. administration of 25 μg/kg IL-10-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 (Pajkrt et al., 1997a). 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 Mip1α, Mip1β, and MCP1 (Pajkrt et al., 1997b; Olszyna et al., 2000). Delay in administration of IL-10 for 1 h only reduced IL-6 and Mip1β 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.

Taken together, IL-10 application induces a number of immunological changes and is well tolerated. Some clinical trials have been accompanied by a reversible decline in platelet counts and hemoglobin levels. Recently, it was confirmed in healthy probands that IL-10 decreases both parameters. No significant change was observed in the bone marrow cellularity or myeloid/erythroid ratio or in the number of megakaryocytes. A decrease was observed in the number of megakaryocyte colony-forming units after administration of IL-10 compared with those receiving placebo. No differences were observed in granulocyte-macrophage, mixed lineage or erythroid burst-forming colonies suggesting IL-10 selectively targets platelet production (Sosman et al., 2000). The mild anemia might be related to changes in iron homeostasis (see below; Tilg et al., 2002a).

B. Prevention of Cytokine Release in Transplant Patients and Jarisch-Herxheimer Reaction

The effects of IL-10 on systemic production of proinflammatory cytokines in organ transplant patients who received anti-T cell therapy as induction therapy were investigated. OKT3 monoclonal antibody is a powerful T cell-targeting immunosuppressive agent, but it stimulates a dramatic cytokine release by triggering almost all T cells. This results in severe side effects that are particularly related to systemic TNF-α, IL-1β, IL-2, and IFN-γ release. 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 (Wissing et al., 1997; Moore et al., 2001).

By contrast, 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 (Cooper et al., 2000).

C. Therapy of Crohn's Disease

Based on the successful experimental findings in animal models of intestinal inflammation, IL-10 therapy was introduced as a potential new anti-inflammatory therapy in Crohn's disease (CD). Indeed the first therapeutic administration was reported in patients successfully treated with IL-10 for steroid-refractory Crohn's disease (Van Deventer et al., 1997).

Several large multicenter trials were performed, testing multiple IL-10 dosages in patients with mild/moderate or therapy refractory CD, as well as in patients undergoing curative ileal or ileocolonic resection to prevent endoscopic postoperative occurrence by systemic administration (Fedorak et al., 2000; Schreiber et al., 2000; Colombel et al., 2001) Overall the data indicates that IL-10 therapy is safe and well tolerated. However,

IL-10 treatment did not result in significantly higher remission rates or clinical improvement compared with placebo treatment.

In another trial, IL-10 was not used for treatment of acute Crohn's disease but for prevention of postoperative recurrence of Chorines disease. At 12 weeks after curative ileal or ileocolonic resection and primary anastomosis, the incidence of severe endoscopic recurrence was similar in the IL-10 and placebo-treated groups (Colombel et al., 2001). Thus the clinical results are overall unsatisfying.

Several explanations for the disappointment with this therapeutic strategy are discussed (Herfarth and Schölmerich, 2002).

1. With the administered dose of IL-10 in the clinical trials, the ultimate local IL-10 concentrations in the intestine could be too low to result in downregulation of inflammation. Increasing the dose of systemically administered IL-10 is limited due to side effects (for example, anemia, headache).
2. IL-10 administration is only successful in preventing and not treating an established disease, as was suggested by the results of the animal experiments.
3. Administration of IL-10 alone fails to effectively suppress the dysregulation of the wide variety of proinflammatory mediators that are involved in the perpetuation of chronic intestinal inflammation.
4. The immunostimulatory properties of IL-10 on B cells and on IFN-γ production by $CD4^+$, $CD8^+$, and/or natural killer cells counterbalance its immunosuppressive properties.
5. Very recently, data has been presented which may explain, at least in part, the dilemma of IL-10 therapy in CD. Tilg et al. (2002a) have investigated the influence of subcutaneous administration of various doses of human recombinant IL-10 on lymphocytic IFN-γ production and LPS-induced TNF secretion by macrophages in whole blood assays as well as on serum neopterin and nitrite/nitrate levels. The study was conducted using samples from two multicenter therapeutic trials in patients with steroid-dependent chronic active CD and patients with mild to moderately active CD.

In patients treated with the highest dose of IL-10 (20 μg/kg), the study described a significant increase in neopterin, which is produced by human monocytes/macrophages in response to IFN-γ, as well as an increase in phytohemagglutinin-induced IFN-γ production compared with pretreatment levels. Furthermore, LPS-induced TNF-α production was dose dependently downregulated by IL-10. Neither the elevation in neopterin or IFN-γ nor suppression of TNF correlated with the clinical response of the patients, which may also reflect the divergence of the clinical (Crohn's disease activity index) and immunological (for example, proinflammatory mediators) readouts in trials employing cytokine or anticytokine strategies.

The immunopotentiating effects of IL-10 found by Tilg et al. (2002a) are corroborated by a study in healthy volunteers subjected to experimental endotoxemia (Lauw et al., 2000). Systemic IL-10 treatment enhanced endotoxin (LPS)-induced IFN-γ release as well as the IFN-γ-dependent chemokines, IFN-γ-inducible protein 10 (IP-10), and monokine induced by IFN-γ (MIG). The stimulatory effects were most pronounced when IL-10 administration was performed 1 h after the LPS challenge.

Patients receiving higher doses of IL-10 developed anemia and presented with a dose-dependent increase of ferritin and soluble transferrin receptor levels, an indicator of iron restriction to erythroid progenitor cells. Hyperferritinemia may result from direct stimulation of ferritin translation by IL-10 in activated monocytic cells (Tilg et al., 2002b).

All in all the clinical results of IL-10 therapy in Crohn's disease have been unsatisfying. Therefore it is very unlikely that this cytokine will be approved for therapy in this inflammatory bowel disease.

D. Therapy of Rheumatoid Arthritis

Limited data regarding the effects of IL-10 in rheumatoid arthritis are available (Moore et al., 2001). Only a limited efficacy but a good safety profile was observed when IL-10 was administered for 28 days to RA patients (Keystone et al., 1998). A combination of IL-10 and methotrexate in a multicenter, placebo-controlled, dose-escalating study in RA patients was described where 8 μg/kg q.i.d. or 8 μg/kg 3 times per week produced an ACR20 response in 50% of patients compared with 63% at a dose of 20 μg/kg 3 times per week and 10% with placebo. Similarly, ACR50 was achieved in 13% (8 μg/kg q.i.d.) and in 25 and 13% (8 and 20 μg/kg 3 times per week, respectively). A decrease in platelet count and hemoglobin were noted. Taken together, the clinical data from RA patients has been rather discouraging, showing only marginal activity of the drug (Narula, 2000).

Overall the role of IL-10 in rheumatoid arthritis remains unclear both from a clinical as well as from a theoretical point of view. On the one hand, there are the known anti-inflammatory properties of IL-10 and effects in various animal models of arthritis; on the other hand, there is the known correlation between IL-10 and an increased autoantibody production, serum factor, and B cell activation in RA patients (Narula, 2000). It has to be further determined whether IL-10 in combination with other therapies such as low dose steroid or therapeutic anti-TNF monoclonal antibodies (Maini and Taylor, 2000) may benefit a significant patient population (Moore et al., 2001). All in all, however, it seems unlikely that IL-10 will become an approved therapy in rheumatoid arthritis.

E. Therapy of Psoriasis

Therapeutic effects of recombinant human (rh)IL-10 (Schering Plough Research) in psoriatic patients has been studied in seven trials to date (Table 4). In our pilot trial starting in 1997, daily injections of 8 μg of rhIL-10/kg body weight directly under a psoriatic plaque over a 24-day period led to complete clearance of the plaque in one of two patients (Asadullah et al., 1998). Moreover, some systemic antipsoriatic effects were observed in all three patients treated in this pilot trial (subcutaneous injections under nonlesional skin in the third patient).

In a second trial (open-label phase II), ten psoriatic patients received subcutaneously rhIL-10 over a 7-week period in a dosage of 8 μg/kg daily ($n = 5$) or 20 μg/kg three times per week ($n = 5$), respectively (Asadullah et al., 1999a). Patients were followed up for an additional 7 weeks. The treatment was well tolerated. We found antipsoriatic effects in 9 of 10 patients resulting in a significant decrease of the psoriasis area and severity index (PASI) by 55.3 $\pm$ 11.5% (mean $\pm$ S.E.M., $p < 0.02$). The antipsoriatic effect was confirmed by histological examination. Heterogeneity in the effectiveness was found among the patients but seemed to be independent of the dosage regime (Asadullah et al., 1999a) (Fig. 6). Similar clinical effectiveness of IL-10 application has recently been reported by Reich et al. (1998). In this open-label phase II trial, ten patients were treated subcutaneously with 4 μg/kg rhIL-10 daily. The mean of the disease activity score PASI decreased by 67.9% after 6 weeks of treatment and was associated with improvement of histological parameters (Reich et al., 2001). The clinical response was associated with a significant decrease of cutaneous cell infiltration and the lesional expression of type 1 cytokines (IFN-γ, TNF), IL-17, IL-8, and IL-8 receptor CXCR2. There was some evidence that genetic factors are involved in the response to IL-10 (Reich et al., 2001).

In a recent study (Kimball et al., 2002), 28 patients with moderate-to-severe psoriasis received rhIL-10 (20 μg/kg) or placebo subcutaneously three times weekly for 12 weeks in a randomized, double-blind manner. Remarkably, treatment with rhIL-10 resulted in only temporary clinical improvement after 6 and 8 weeks, despite sustained systemic decreases in proinflammatory and type 1 cytokine production.

The effect of IL-10 in psoriatic arthritis patients has been investigated by McInnes et al. (2001). IL-10 was given s.c. for 28 consecutive days in a double-blind, placebo-controlled study including 29 patients (0, 1, 5, or 10 μg/kg). Modest, but significant, clinical improvement in skin but not articular disease activity scores with only minor adverse effects was observed.

Recently, we investigated the effects of long-term IL-10 application on the immune system and duration of psoriasis remission (Friedrich et al., 2002). We performed a placebo-controlled, double-blind, phase II trial using IL-10 in patients with chronic plaque psoriasis in remission. Patients received subcutaneous injections with either IL-10 (10 μg/kg body weight; $n = 7$) or placebo ($n = 10$) three times per week until relapse or

TABLE 4
IL-10 therapy in psoriasis: published results from clinical trials

Study	Design, patients, and interventions	Outcome and Remarks	Reference
Pilot study in exacerbated psoriasis vulgaris	Open label, not placebo controlled; three patients with moderate to severe psoriasis; 8 μg/kg/day, s.c. over a 24-day period	Safe, clinical, and histological confirmed improvement	Asadullah et al., 1998
Pilot study in exacerbated psoriasis vulgaris	Open label, not placebo controlled, ten patients with moderate to severe psoriasis; 4 μg/kg/day s.c. over 42 days	Safe, good to moderate response, histological confirmed; significant mean decrease in PASI by 40% after 3 weeks and 68% after 6 weeks. These patients are a subgroup of the study by Reich et al. (2001).	Reich et al., 1998
Phase II in exacerbated psoriasis vulgaris	Open label, not placebo controlled, ten patients with moderate to severe psoriasis; 8 μg/kg daily ($n = 5$) or 20 μg/kg three times per week ($n = 5$) s.c. over 49 days	Safe, good to moderate response, histological confirmed, significant mean decrease in PASI by 55% after 7 weeks	Asadullah et al., 1999
Phase II in exacerbated psoriasis vulgaris	Open label, not placebo-controlled, 15 patients with moderate to severe disease; 4 μg/kg/day, s.c. over 42 days	Safe, good to moderate response, histological confirmed; 14 patients evaluated, mean decrease in PASI by 50% after 4 weeks and 59% after 6 weeks.	Reich et al., 2001
Phase II in psoriatic arthritis	Placebo-controlled, double-blind, 29 patients with psoriatic arthritis, dose escalating with 1, 5, or 10 μg/kg, s.c. daily for 28 days	Well tolerated, significant clinical improvement in skin (>30%) PASI reduction: 50% in IL-10 group (10 μg/kg) versus 10% in placebo after 4 weeks. No decrease in articular disease activity.	McInnes et al., 2001
Phase II in exacerbated psoriasis vulgaris	Randomized, double-blind, placebo-controlled, 28 patients with moderate to severe psoriasis; 20 μg/kg three times per week for 12 weeks	Modest trend towards improvement after 6 and 8 weeks (mean decrease in PASI by 31% and 35% in IL-10 group versus 7% and 13% in placebo group, respectively), but no significant difference at week 12 (17% versus 13% in placebo group).	Kimball et al., 2002
Phase II in psoriasis vulgaris in remission	Placebo-controlled, double-blind, 17 patients with moderate to severe psoriasis in remission; 10 μg/kg; IL-10 ($n = 7$) or placebo ($n = 10$) three times per week for 4 months	Well tolerated; 90% relapse in the placebo group versus 28% in the IL-10 treated group; significant prolongation of relapse-free interval (101 days versus 66 in placebo).	Friedrich et al., 2002

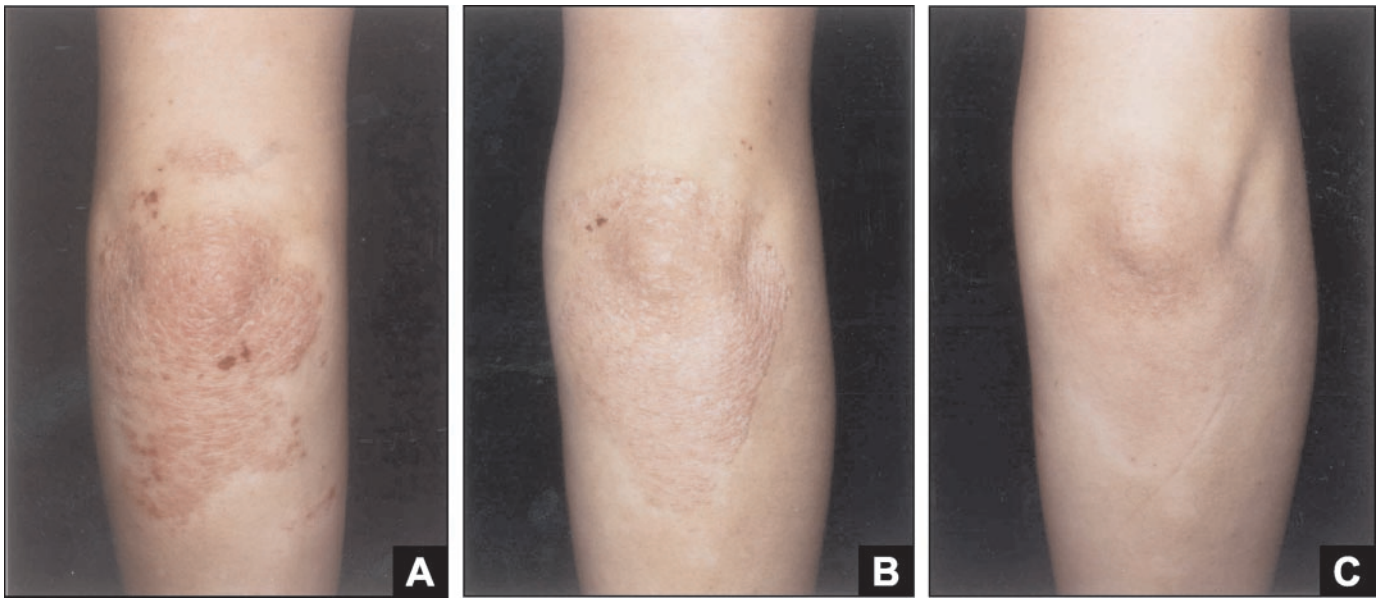

FIG. 6. Clinical effects of short course IL-10 therapy in established psoriasis. Example of a patient showing good response toward IL-10 therapy. Typical skin lesions before (A), during (B, day 15), and at the end (C, day 50) of therapy are shown. The patient received IL-10 injections in a dosage of 20 μg/kg three times per week. (Copyright 1999, American Medical Association; Asadullah et al., 1999).

study termination after 4 months. The treatment was well tolerated. In the placebo group almost all patients (90%) showed a relapse during the observation period. In contrast to this, only two of seven patients (28.6%) relapsed in the IL-10-treated group. Kaplan-Meier analysis revealed a significantly lower relapse incidence in the IL-10 group than in the placebo group ($p = 0.02$). The mean relapse-free interval time was 101.6 ± 12.6 days in the IL-10 group compared with 66.4 ± 10.4 days in the placebo group (Fig. 7).

It is likely that IL-10 exerts its antipsoriatic activity by effects on different cell populations including T cells and APCs as well as their mutual interaction. Psoriasis is a T cell-dependent (auto)immune disease (Valdimarsson et al., 1985), probably initiated by presentation of so far unknown "psoriasis-related antigens" by specialized cutaneous APCs (Mitra et al., 1995; Weinstein, 1996; Norris et al., 1997). IL-10 is able to suppress the APC activity of monocytes/macrophages and the development of dendritic cells. In fact, depressed monocytic HLA-DR and CD86 expression as well as TNF-α and IL-12 secretion capacities were observed by us during IL-10 therapy. Moreover, IL-10 led to a lasting type 1/type 2 shift (increasing proportion of IL-4, IL-5, and IL-10 producing T cells, selective increase in IgE serum levels). A significant negative correlation was demonstrated between the IL-4 secretion capacity and PASI score that was found in our long-term trial. The physiological significance of these findings was reflected by the depressed DTH reaction to recall antigens during IL-10 therapy (Asadullah et al., 1999a). Interestingly, IL-10 therapy led to a decrease in cutaneous IL-8 and an increase in IL-4 expression, both of which might contribute to the antipsoriatic effect (Asadullah et al., 2001b; Reich et al., 2001). Direct effects of IL-10 on keratinocytes are unlikely to have contributed to the clinical response, since the IL-10 unresponsiveness of keratinocytes has been demonstrated by us recently (see above).

Overall, IL-10 therapy seems to be well tolerated and immunologically effective in psoriasis. Determination of definitive clinical efficacy, however, awaits phase III studies. Moreover, the effects of IL-10 on the skin immune system has to be investigated in more detail.

F. Therapy of Viral Infections—Chronic Hepatitis C and Human Immunodeficiency Virus

It has been shown that TNF and other inflammatory mediators promote the replication of HIV. This was the rationale for investigating the effects of IL-10 on viral load and CD4 counts in HIV infected patients who did not fully respond to antiretroviral treatment. The lack of a demonstrable virological and immunological benefit with 4 weeks of IL-10 treatment does not support the development of this therapy for treatment of HIV infection (Angel et al., 2000).

Considerable progress has been made in the field of hepatitis C virus since its discovery about 10 years ago but a major effort needs to be made to control hepatitis C virus-related liver disease. Despite new therapeutic options (modified interferons, antiviral drugs) the long-term outcome of hepatitis C is still unsatisfactory (Boyer and Marcillin, 2000). There are several reports on an association between IL-10 polymorphisms and the course of hepatitis C infection (see above). Moreover, IL-10 is able to express antifibrotic properties in experimental models of liver cirrhosis (Boyer and Marcillin, 2000). Recently, it was shown that IL-10, although it has no apparent antiviral activity, normalizes serum ALT

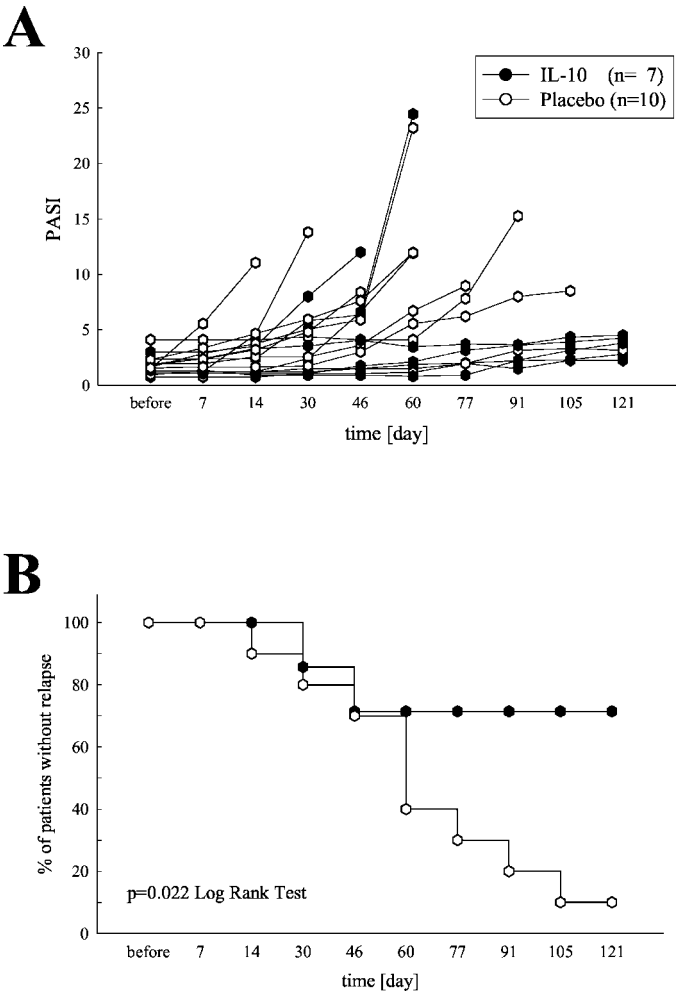

FIG. 7. Clinical effects of IL-10 therapy (Asadullah et al., 2002a). A, individual courses of psoriatic disease. The patients dropped out of the analysis when fulfilling the criteria for psoriasis relapse. B, Kaplan-Meier analysis of relapse-risk. Reprinted with permission from Blackwell Publishing, Oxford, UK.

levels, improves liver histology, and reduces liver fibrosis in a large proportion of patients (63–86%) receiving treatment (Dharancy et al., 2000; Nelson et al., 2000; Schuppan and Hahn, 2000).

VI. Prospects of Interleukin-10/Interleukin-10 Receptor As a Therapeutic Target

Application of IL-10 in humans seems to be safe and immunologically active. Indeed the majority of studies indicate that IL-10 seems to reverse a pre-existing Th1/Th2 imbalance (Fig. 5). Since such an immune deviation is based on the current pathophysiological understanding in several indications, characterized by inflammation with a type 1 cytokine pattern, IL-10 should be a promising approach there.

The clinical effects of recombinant IL-10, however, has been quite heterogeneous in different entities. Whereas almost no effect was seen in rheumatoid arthritis, significant response was observed in psoriasis. The clinical studies published to date clearly indicate some but overall no really relevant advantage of systemic IL-10 therapy compared with placebo in active and postoperative CD. Results of Tilg et al. (2002a) indicate that higher doses of systemically administered IL-10 (which were also used in the clinical trials) may be detrimental rather than helpful in CD. This may also be true for other indications. Nevertheless, the concept of rebalancing the intestinal immunological homeostasis with IL-10 is still very compelling and applying IL-10 locally in high concentrations may result in strong immunosuppression and circumvent the systemic side effects (Herfarth and Schölmerich, 2002). We do not know whether high IL-10 concentrations also have immunostimulatory properties, e.g., in the intestine or the skin. Furthermore IL-10 prevented intestinal inflammation in animal studies but could never completely cure an established disease, indicating that IL-10 therapy in CD would succeed in preventing relapses rather than abolishing acute or chronic inflammation. The recent results from IL-10 therapy in psoriasis (Friedrich et al., 2002) seems to support this hypothesis. So it might very well be that IL-10 is much more effective in a (primary or secondary) prophylactic than in a therapeutic approach. Theoretically, this can be explained by the observation that IL-10 is powerful in preventing proinflammatory effects of macrophages and differentiation of dendritic cells but less effective in targeting T cells, particularly memory/effector T cells, and mature dendritic cells. Additionally, IL-10 supports the generation of regulatory T cells (Levings et al., 2001a; Roncarolo et al., 2001). So IL-10 may be more effective in preventing undesired immune reactions than in treating them.

Another problem is the adequate delivery of IL-10 to the site of action. Taking into account the adverse effects of high-dose IL-10 and its low half-life in vivo, local delivery may probably be the more promising approach in several diseases. Gene therapy by using viral vectors has several disadvantages for application in humans. Recently, an approach of local IL-10 therapy, which could also be used for long-term therapy, has been described. Steidler et al. (2000) demonstrated that intragastric administration of a genetically engineered IL-10 secreting *Lactobacillus lactis* caused a significant reduction in colitis in two different mouse models. Therefore, with dietary supplementation it may be possible to deliver high concentrations of IL-10 within the gut, thus preventing the recurrence of CD. However, this study has just proved a therapeutic principle, and there is still a long way to go before such a concept can be evaluated in clinical studies for chronic inflammatory bowel disease (Herfarth and Schölmerich, 2002). Topical application at least from a theoretic point of view might also be possible in inflammatory skin disorders or asthma.

Even in the majority of clinical trials where IL-10 showed a clinical effect, patients with both good and no responses at all were found. The reason for this heterogeneous interindividual response is unclear. What must

be done, therefore, is to identify which patients might be suitable for IL-10 therapy. Preliminary data supports this concept (Reich et al., 2001).

If this can be done, an effective immunotherapy with few side effects might conceivably be tailored to suit individual patients. Analyzing the individual cytokine and cytokine promoter polymorphism might be helpful. Similar heterogeneity in response is observed for other new immunomodulatory treatments. For example, only 2/3 of rheumatoid arthritis patients respond to anti-TNF treatment. A similar response rate was found for psoriasis patients in response to several immunomodulatory antibodies and drugs (Asadullah et al., 2002b). Thus, it would be of interest to analyze: 1) whether the group of nonresponders is overlapping between different drugs; and 2) whether combinations might be useful to improve the results (e.g., therapy with vitamin D derivatives known to induce IL-10 receptor expression).

To predict the therapeutic effect of IL-10 in inflammatory disorders dominated by a type 2 cytokine pattern is difficult. Its anti-inflammatory activity may lead to an improvement although a further shift into the type 2 cytokine deviation might be harmful. Indeed preliminary data on IL-10 therapy in atopic dermatitis patients suggests unresponsiveness in these patients (Reich et al., personal communication). Similarly, it is hard to predict a therapeutic effect of IL-10 in malignancies, since both tumor-suppressive as well as tumor-promoting effects have been described in in vitro and in vivo models. Depending on the particular type of the tumor, it is likely that IL-10 application could be either effective (e.g., in tumors mainly controlled by NK cells) or fatal (e.g., in tumors mainly controlled by cytotoxic T cells and where IL-10 is a growth factor). Considering the immunosuppressive effects of IL-10 in general, caution in its application in tumor patients is recommended. Indeed it might very well be that targeting IL-10 by antibodies or IL-10 receptor constructs is much more appropriate in tumors, e.g., in certain lymphomas. Well defined clinical studies might be the only way to obtain the final answer.

IL-10 as a cytokine has therapeutically been used as a recombinant protein, i.e., a large molecule. Therefore it is quite expensive to produce, must be administered by injection, which is quite inconvenient for the patient, and the induction of neutralizing antibodies, which might limit their effect, has to be excluded for long-term application. Identification of molecules mediating the effects of this cytokine that are suitable for pharmacological intervention with small molecules will be, therefore, of increasing interest. Interference of complex protein-protein interaction with small molecules, however, is almost impossible. Therefore, it is unlikely that IL-10 receptor agonists suitable for oral application will be discovered. Molecules acting downstream of the cytokine receptors targeting for example certain kinases or phosphatases or signal transduction molecules might represent much better "drugable" approaches. The problem here, however, is the specificity, since the known IL-10 signal transduction molecules are shared by different cytokines. Induction of cytokine production with low molecular weight compounds may represent novel approaches. In any case, further investigations on the regulation of IL-10 expression and signaling are of major importance and may lead to better therapeutic approaches.

Whereas IL-10 application/induction seems to represent an interesting therapeutic approach in some indications, its neutralization might be promising in others. Thus, apart from in certain tumors as outlined above, IL-10 seems to play a critical role, e.g., in SLE. This systemic autoimmune disease is characterized by high autoantibody production and by decreased cellular immune responses. In SLE, high levels of autoantibodies generate immune complexes causing tissue damage. Compared with healthy individuals, levels of IL-10 in SLE patients are significantly higher, and there is a correlation of IL-10 levels with the clinical disease activity (Park et al., 1998). In experimental studies, depletion of IL-10 resulted in the following effects: 1) anti-IL-10 mAb in vitro treatment of SLE patient-derived PBMC significantly decreased autoantibody production (Llorente et al., 1995); 2) anti-IL-10 mAb treatment of SCID mice injected with PBMC from SLE patients strongly inhibit autoantibody production in vivo (Llorente et al., 1995); 3) treatment of New Zealand black/white mice—mice that spontaneously develop a severe autoimmune disease that closely resembles SLE—with anti-IL-10 mAb substantially delayed onset of autoimmunity (Ishida et al., 1994). The data suggest that IL-10 is harmful in systemic lupus and that IL-10 antagonists may be beneficial in the treatment of human SLE. In fact, beneficial effects of application of a neutralizing IL-10 antibody has been reported in a preliminary study very recently (Llorente et al., 1999). Furthermore, more investigation is necessary to support this in SLE and perhaps other indications as B cell lymphomas.

VII. Conclusions

IL-10 is a pluripotent cytokine with potent effects on numerous cell populations, in particular circulating and resident immune cells as well as epithelial cells. This makes it an important broad effector molecule in immunoregulation/host defense. Whereas soon after its discovery initial data suggested that IL-10 mainly mediates suppressive functions, more recent data showed stimulatory properties on certain cell populations also. Overall, the effects of IL-10 seem to be quite complex, and still considering IL-10 just as immunosuppressive and anti-inflammatory (as was done in the past) might be oversimplifying. Considering IL-10 as immunoregulatory instead of immunosuppressive might be more appropriate. It stimulates functions of innate immunity

(NK cell activity, noninflammatory removal of particles, cells, and microbes by stimulating phagocytosis) and of Th2-related immunity but suppresses inflammation-associated immune response (Th1, cytokine proinflammatory secretion by macrophages, modulation of Th2) both directly and indirectly.

Inadequate IL-10 expression seems to have considerable pathophysiological impact. Both overexpression (e.g., in lymphoma, SLE, intensive care unit patients) as well as IL-10 deficiency (e.g., in inflammatory bowel disease, psoriasis) are likely to have a pathophysiological significance. Therefore, neutralization of the cytokine could be a promising approach to treat diseases from the first group, whereas application of IL-10 itself could be helpful for diseases from the second group.

Some effectiveness of IL-10 application for the therapy of established, exacerbated immune diseases such as psoriasis, inflammatory bowel diseases, and rheumatoid arthritis has been suggested by several early phase II trials. Other studies, however, showed disappointing results. Further investigations, in particular multicenter placebo-controlled double-blind trials, are therefore required to better determine the therapeutic potential of this cytokine. The picture is already emerging that the potency of this treatment overall seems to be below that of other promising approaches such as the anti-TNF-α strategies. Thus, a complete disease clearance is usually a rare event after IL-10 application, suggesting a relatively low anti-inflammatory potential for this therapy. Moreover, a recent report (Lauw et al., 2000) and our recent unpublished observations suggest proinflammatory properties of IL-10. In agreement with this, we observed an increase of the sIL-2R levels in IL-10 long-term-treated patients. Therefore, we speculate that IL-10 might not be the major "breakthrough" in anti-inflammatory therapy of exacerbated disease. In contrast, impressive clinical effects with regard to prevention of psoriasis relapse, were found in a single study, reflecting the long-term immunomodulatory rather than the anti-inflammatory properties of IL-10. It might be that not anti-inflammatory but complex immunomodulatory effects might be primarily responsible for the prolongation of the disease-free interval we observed in psoriasis. Such a hypothesis is supported by recent data from animal and in vitro experiments, demonstrating that IL-10 can induce the formation of regulatory T cells with major impact on the immunoregulation (Cottrez et al., 2000; Levings et al., 2001a). Taken together, both first clinical and immunological data suggest that IL-10 application seems to be even more attractive in a secondary prophylactic (prevention of relapse) than in a therapeutic approach in psoriasis. It might be speculated that IL-10 long-term therapy could be equally effective in other entities such as inflammatory bowel diseases or rheumatoid arthritis and transplantation.

Why certain patients show a good response whereas others do not respond at all may lead to the identification of patients suitable for IL-10 therapy. A better understanding of the molecular mechanisms of IL-10-mediated effects may lead to the identification of new drug targets (either for mimicking or inhibition of IL-10 effects) that could be approached by small orally bioavailable compounds. It has to be determined whether the new IL-10 homologs might have better therapeutic potential than IL-10 itself.

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