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Biology of Interleukin-10

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Abstract

Interleukin(IL)-10 is the most important cytokine with anti-inflammatory properties aside from TGF-β and IL-35. It is produced by activated immune cells, in particular monocytes/macrophages, and subsets of T cells, like Tr1, Treg, and Th1. IL-10 acts through a transmembrane receptor complex, which is composed of IL-10R1 and IL-10R2, and regulates the functions of many different immune cells. In monocytes/macrophages, IL-10 diminishes the production of inflammatory mediators and inhibits antigen presentation, although it enhances uptake of antigens. Additionally, IL-10 plays an important role in the biology of B cells and T cells. The special physiological relevance of this cytokine lies in the prevention and limitation of over-whelming specific and unspecific immune reactions and in consequence of tissue damage. At the same time, IL-10 strengthens the “scavenger”-function and contributes to induced tolerance. This review provides an overview about the cellular sources, molecular mechanisms, effects, and the biological role of IL-10.

Introduction

In 1989, Mosmann and co-workers described a novel immune mediator that is secreted by mouse type 2 T-helper cell clones (Th2) and inhibits the synthesis of interleukin(IL)-2 and interferon(IFN)-γ in Th1 cell clones (1). Originally named "cytokine synthesis inhibitory factor" (CSIF), this mediator was accepted as "IL-10" in the everyday cytokine nomenclature. In the 21 years since its discovery, numerous groups have intensively investigated the biology of IL-10.

1. The IL-10 gene and protein

The gene encoding human IL-10 is located on chromosome 1 covering a total of 5.1 kb pairs comprising five exons (2). A large number of polymorphisms [primarily single nucleotide polymorphisms (SNPs)] have been identified in the IL-10 gene promoter. Some evidence exists that certain of these polymorphisms are associated with differential expression of IL-10 *in vitro* and a number of studies have investigated associations between IL-10 polymorphisms and various diseases (see below). The IL-10 gene encodes a 178 amino acids long protein, which is secreted after cleavage of the 18 amino acids comprising signal peptide. Between human (h) and murine (m) IL-10, there is an approximately 75% identity in the amino acid sequence. The groups of A. Wlodawer and M.R. Walter resolved the structure of hIL-10 using X-ray crystallography structure analysis (3-6). Interestingly, the structure of IL-10 is like the IFN-γ structure (7). Human IL-10 is a 35 kD homodimer that is composed of two, non-covalently bonded monomers. The homodimer has two V-oriented domains, each of which is composed of six helices: four (A-D) of one monomer and two (E' and F') of the other. Within

the monomer, two disulfide bridges exist (C30-C126 and C80-C132) that are essential for maintaining the structure and the biological activity of the cytokine (8). A detailed description of the IL-10 structure is published by A. Zdanov in this issue of CGFR. In addition to various mammalian IL-10 related molecules (see below), four viral IL-10 homologues are known. They are produced by the Epstein-Barr virus, the equine Herpes type 2 virus, the Orf virus (parapoxvirus ovis), and the Cytomegalovirus (reviewed in (9)). With the exception of Cytomegalovirus' IL-10, the similarity of the viral and cellular IL-10s with respect to the amino acid sequence is very high. For instance, the sequence of the Epstein-Barr virus' IL-10 (BCRF1) is 83% identical to that of hIL-10. This, apart from marginal differences predominantly in the N-terminal part, results in very similar protein structures (10). The expression of virus IL-10s appears during the lytic phase of virus infection. Virus IL-10s are suggested to act *via* the same receptor as cellular IL-10 does. When compared to hIL-10, however, an approximately 1000-fold lower efficiency is observed for many effects (11). Unfortunately, most anti-hIL-10 antibodies and ELISA cannot discriminate between hIL-10 and Epstein-Barr virus derived IL-10. Recently, novel human molecules with structural similarity to IL-10 have also been identified. These are now combined in the so-called IL-10 family comprising IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26 (12). Interestingly, their sequence relation is not reflected by a shared biological function [reviewed in (9, 13, 14)]. A detailed description of others as IL-10 members of this family is published in this issue of CGFR.

2. Cellular sources of IL-10

Today it is known that the ability to synthesize IL-10 not limited to certain T cell subsets, but is a characteristic of almost all leukocytes (15). Very important sources *in vivo* appear to be

mainly monocytes and macrophages as well as T cells (16-19). Moreover, dendritic cells, B cells, cytotoxic T cells, γδ T cells, NK cells, mast cells, as well as neutrophilic and eosinophilic granulocytes synthesize IL-10 (20-28). Which of these cells in defined situations are mainly responsible for the presence of IL-10 is dependent on the kind of stimulus, type of affected tissue, and time point in an immune process [see below and reviewed in (29)].

Monocytes and macrophages secrete IL-10 after activation with various endogenous as well as exogenous mediators such as bacterial lipopolysaccharide (LPS) [*via* toll-like receptor (TLR) 4-, TRAF3-, NF-κB p50/p50-, and ERK-dependent)] and catecholamines (*via* protein kinase A, CREB-1/ATF-1 dependent) by induction of IL-10 gene transcription (20, 21, 23-28, 30-34). Monocytes and macrophages also secrete IL-10 during clearance of apoptotic cells in a process that is dependent on CD36 and p38 mitogen-activated protein (MAP) kinase (35). In addition to the transcriptional level, Sharma *et al*. recently suggested that IL-10 expression is also regulated on the posttranscriptional level by microRNAs (36).

T cells secrete IL-10 predominantly following T cell receptor triggering and the activation of ERK1 and ERK2 MAP kinases (37). Furthermore, IL-10 secretion correlated with the expression of c-maf transcription factor (37). The antigen-primed T cells *in vivo* show a higher basal probability to transcribe IL-10 than naive T cells, although the antigen-primed T cells still demonstrate mostly mono-allelic IL-10 expression (38). Among antigen-primed T cells, Th2 cells were originally believed to be the principal source of IL-10. In these cells, IRF4 furthers the IL-10 expression (39). However, today it is clear that Th1 cells produce at least same amounts of IL-10 as Th2 cells (37, 40-43). In these cells IL-12 augments IL-10 production by increasing phosphatidylinositol-3 kinase activity, which leads to inactivation of the constitutively active serine/threonine kinase glycogen synthase kinase-3beta and enhances c-jun levels (44). Stimulation of Th1 cells with IL-27 elevates IL-10 production and slowly enhances IFN-γ expression (45, 46). In 1997 so-called type 1 regulatory T cells (Tr1) were identified as a subset of CD4+ cells that produces high levels of IL-10, low levels of IL-2 and

no IL-4 (47). Tr1 cells are Foxp3- cells that are characterized by a) a weak proliferation and nearly selective synthesis of IL-10 and b) their ability to suppress the function of antigen-presenting cells (APC) and antigen-specific effector T cells *via* a cytokine-dependent mechanism. They develop from the naïve T cells under the influence of IL-27 (46, 48-50) that induces the aryl hydrocarbon receptor (AHR). AHR binds c-maf and they synergistically activate the *Il10* and *Il21* promoters as well as induce generation of Tr1 cells (51, 52). The novel cytokine IL-21 [reviewed in (53)] up-regulates the c-maf expression and enhances IL-10 secretion (50, 54). The expression of c-maf can be also induced by transforming growth factor (TGF)-β/IL-6 (55). Tr1 like cells can also differentiate from Th1 cells (56, 57). IL-10 is additionally produced by naturally occurring T regulatory cells (Treg) (58). Treg cells are mostly CD25+ and are generated in the thymus, but also peripherally in response to tolerogenic stimuli. The development of Treg is dependent on TGF-β, all-trans retinoid acid, TCR signaling, and the engagement of common γ-chain cytokine receptors [(59) and reviewed in (60)]. TGF-β induces the expression of Foxp3 and IL-10, however, all-trans retinoid acids favor Foxp3 expression and inhibit IL-10 (61). IL-2, by means of signal transducer and activator of transcription (STAT)5, enhances IL-10 production and is an important activator of Treg suppressive activity (62, 63). During infection or inflammation Treg can migrate from blood to inflamed tissues where they are activated and inhibit the migration of dendritic cells and the cytokine production in antigen-specific T cells. Then Treg can itself migrate to draining lymph nodes and inhibit the activation and proliferation of antigen-specific T cells (64, 65). In mice, Foxp3 is a specific marker of Treg, however, in humans it is not always linked to regulatory function. Lastly, the very recently discovered Th17 and Th22 cells can also produce IL-10 [(66), reviewed in (60, 67) and R. Sabat, unpublished]. Interestingly, IL-27 reduces the RORγt expression and inhibits development of Th17 cells (46, 68). However, in stable Th17 cells IL-27 together with IL-23 can induces IL-10 secretion without exerting a negative influence on IL-17 expression (68). In summary,

each currently known Th population can produce IL-10, although in slightly different amounts (**Figure 1**). Very recently, it was even postulated that many memory T cells secrete IL-10 under steady-state conditions and first after recognition of a relevant antigen revealing their specific phenotype (69).

IL-10 production can be inhibited by IL-4, IFN-γ, and IL-23 (70, 71). Additionally, IL-10 is self-inhibiting (21, 72).

3. The IL-10 receptor

IL-10´s pleiotropic activities are mediated by a specific cell surface receptor complex. The IL-10 receptor (IL-10R) is composed of two different chains, IL-10R1 and IL-10R2 (**Figure 2**). Both chains belong to the class II cytokine receptor family (CRF2). CRF2 members are usually transmembrane glycoproteins, whose extracellular domains typically consist of about 210 amino acids forming two fibronectin type III domains and have several conserved amino acid positions that are important for their secondary structure. In contrast, their intracellular domains vary in length and do not demonstrate striking sequence similarity (reviewed in (73)). The Moore group cloned the mIL-10R1 in 1993 (74). A year later, the same group published the sequence of the hIL-10R1, which was 60% identical and 73% similar on the amino acid level to the murine chain (75). The IL-10R1 is a 90 – 110 kD, glycosylated protein, and the encoding gene is located on chromosome 11 (75, 76). Interestingly, polymorphisms within the human IL-10R1 gene have been described (77, 78). More recently, a protein known since 1993 as CRF2-4 was identified as the IL-10R2 (79). The gene for this chain can be found on human chromosome 21. The affinity of IL-10 to the IL-10R complex is markedly higher (50-250 pM) than to the isolated IL-10R1 (500-620 pM). Binding of IL-10 to its receptor complex consists of two steps (**Figure 2**). IL-10 first binds to IL-10R1. The IL-10

/ IL-10R1 interaction changes the cytokine conformation allowing the association of the IL-10 / IL-10R1 complex with IL-10R2 (80-82). IL-10R2 alone is unable to bind IL-10 (81, 83). The molecular basis of the interaction between human IL-10 and IL-10R1 has been characterized in detail (3, 84). An IL-10 epitope that becomes available after its conformational change has been proposed to represent the binding site for IL-10R2 (81-83, 85). IL-10R1 is mainly found on immune cells. Its expression is generally low, varying between 100 and 800 molecules per cell [(86, 87), and R. Sabat, unpublished]. Interestingly, monocytes and macrophages exhibit the highest IL-10R expression [(15, 88, 89) and R. Sabat, unpublished]. The expression is adjustable, but only few regulating factors are known so far. The activation of monocytes with LPS strengthens both the mRNA expression of IL-10R1 (2 hours) and IL-10R2 (18 hours) in these cells (88, 90). IL-10R1 is expressed at higher levels on CD4+ memory than on naïve T cells (91) and the expression of both components of the IL-10R complex decreases following stimulation in T cells as well as in B and NK cells (88, 90). In the case of T cells, this is dependent on the strength of cellular activation (88, 90). Very low levels of IL-10R1 expression have also been described for a few non-immune cells (92, 93). Here, cellular activation enhances its expression. The IL-10R1 expression levels correlate with the strengths of the effects of IL-10 on immune cells (94, 95). In contrast to IL-10R1, IL-10R2 is widely and strongly expressed in most cells and tissues (81, 88, 90). The stimulation of tissue cells with IFN-γ or TNF-α leads to increased mRNA expression of IL-10R2 (88, 90, 96). While IL-10R1 is specific for the IL-10 receptor complex, IL-10R2 is simultaneously part of the receptor complexes of other ligands. In fact, its role was recently demonstrated in transmitting the effects of the newly discovered cytokines IL-22, IL-26, IL-28, and IL-29 (97-100). This explains the broad expression of IL-10R2 in a series of cell types, which express IL-10R2 but not IL-10R1. We recently demonstrated for IL-22 and IL-10 that this IL-10R2 sharing does not appear to be associated with binding competition for IL-10R2 and mutual limitation of the biological effects of the different mediators (81). Given the fact that there is

apparently no co-expression of IL-22R1 and IL-10R1 in any cell type (81, 90), the reason for the lacking interference is likely the nonexistent binding between either cytokine and IL-10R2 in the absence of the R1 chain for the competing cytokine (81).

IL-10 mainly uses the Janus kinase family members and STAT transcription factors to mediate its effects, principally like IFNs (101). In fact, the binding of IL-10 to its receptor activates two members of the Janus kinase family: Jak1 (associated with the IL-10R1) and Tyk2 (associated with the IL-10R2) (**Figure 2**) (102). Afterwards, two tyrosines (Tyr 446 and Tyr 496) of IL-10R1 are phosphorylated by these kinases, to which the transcription factor STAT3 binds and becomes phosphorylated in its SH2 domain (102, 103). Additionally, STAT1 and, in certain cell types, STAT5 molecules are activated in IL-10-treated cells (102, 104). These transcription factors build homo- and hetero-dimers that migrate into the cell nucleus and bind to the STAT binding elements of various promoters in order to induce transcription of the corresponding genes. In contrast to earlier studies, there is emerging evidence that, instead of STAT molecule dimerization induced by SH2 tyrosine phosphorylation, the STAT molecules are already present as dimers in the cytoplasm and will undergo a conformational switch upon activation by the Janus kinases (105-108). The suppressor of cytokine signaling 3 (SOCS3) is one of the genes whose expression is induced by IL-10. SOCS3 belongs to a protein family that binds Janus kinases and inhibits their activity (109). SOCS3 induction appears to be responsible for the termination of IL-10 effects (110).

In addition to the two IL-10R1 tyrosines described above, another region of IL-10R1 is essential for inhibiting the production of inflammatory mediators, specifically a region near the C-terminus of the chain that contains two serines (111). Despite intensive research, many aspects of the IL-10 signal cascade (i.e. the role of other kinases such as phosphatidylinositol-3 kinase or p70 S6 kinase) that are activated after IL-10-treatment are still unclear (112). The

intracellular part of IL-10R1 also contains a region, which, when removed from the cell, makes it 100 times more sensitive to IL-10. Which mediators play a role in this is still unclear (113).

4. Biological effects of IL-10

The biological effects of IL-10 are incredibly multifaceted and were intensively investigated in the last years. In doing this, the effects on various cell populations including thymocytes, T cells, B cells, NK cells, monocytes, mast cells, as well as neutrophilic and eosinophilic granulocytes were illuminated. According to the latest knowledge, it appears that above all monocytes/macrophages are the main target cells of the inhibitory IL-10 effects. Interestingly, the IL-10R signaling in monocytes causes transcriptional activation of several hundred genes: In our recent gene chip analysis, we found the expression of about 1,600 genes up-regulated and of about 1,300 genes down-regulated (114). IL-10 influences three important functions of the monocytes/macrophages: the release of immune mediators, antigen presentation, and phagocytosis. Simply said, it suppresses all functions of monocytes/macrophages that are responsible for a positive role of these cells in both innate and specific immunity. At the same time, it enhances the inhibitory, tolerance inducing, and 'scavenger' functions of these cells. In fact, IL-10 inhibits the release of pro-inflammatory mediators from monocytes/macrophages and therefore inhibits the LPS- and IFN-γ-induced secretion of TNF-α, IL-1β, IL-6, IL-8, G-CSF, and GM-CSF (72, 115). Additionally, it enhances the release of anti-inflammatory mediators such as IL-1 receptor antagonist and soluble TNF-α receptors (116-118). Thereby, IL-10 drastically reduces the production of important mediators that mostly play a role in innate immunity [reviewed in (119)]. Furthermore, IL-10 inhibits antigen presentation of monocytes/macrophages. It reduces the constitutive as well as the IFN-γ-

induced cell surface expression of major histocompatibility complex class II (MHC II) molecules and of co-stimulating (i.e. CD86) and adhesion (i.e. CD54) molecules (120-122). Moreover, IL-10 inhibits the synthesis of IL-12 (123). Thereby, IL-10 inhibits the development of Th1 immunity. The direct inhibitory influence on APCs is then indirectly enhanced by repression of CD4+ T cells. For example, IL-10 initiated inhibition of IL-12 synthesis in APCs results in reduced IFN-γ production in T cells. Further, IL-10 itself reduces IFN-γ production in Th1 cells (see below). An IFN-γ deficit then amplifies the deactivation of APCs (124). IL-10 reduces also the secretion of IL-23 by macrophages, which is essential for the existence of Th17 cellular immunity (125). As mentioned above, IL-10 enhances the phagocytosis of monocytes/macrophages (126). It increases the expression of various receptors that are responsible for the uptake of opsonized and non-opsonized microorganisms. IL-10-treated monocytes demonstrate an enhanced expression of IgG-Fc receptors (CD64, CD32, CD16) and also of molecules such as CD14, which play an important role in the uptake of non-opsonized material (127-129). Interestingly, IL-10 concurrently inhibits the killing of microorganisms that have been taken up (130). This increased phagocytosis of pathogens could, however, enhance the risk for an attack by complement activity. A recent paper described a new function of IL-10 in protecting human monocytes and macrophages from this kind of complement lysis (131). IL-10 has an inhibitory influence on the chemotaxis of monocytes, although it is very weak (132). It also significantly influences the further differentiation of monocytes because it enhances the final differentiation of these cells into macrophages (127, 133) or even into inhibitory APCs (134) and at the same time inhibits the appearance of myeloid dendritic cells (133). The function of plasmacytoid dendritic cells [reviewed in (135)] is only minimally influenced by IL-10; for example it slightly inhibits the production of type I IFNs in these cells (136, 137).

IL-10 also acts directly on T cells, independent of its inhibitory effect on APCs. IL-10 inhibits both the proliferation and the cytokine synthesis of CD4+ T cells, including the production of IL-2, IFN-γ by Th1 as well as IL-4 and IL-5 by Th2 (41, 138). Interestingly, IL-10 is not able to suppress the IL-17 production in Th17 cells (139). In addition, IL-10 apparently has no direct inhibitory influence on CD8+ T cells (140). Upon CD4+ T cell activation *in vitro,* the presence of IL-10 causes these cells to develop a regulatory phenotype (47, 138). In this manner, Tr1 cells arise that secrete IL-10 and suppress antigen-specific effector T cell responses *via* a cytokine-dependent mechanism. Although the *in vitro* formation of Tr1 is caused by both the pre-treatment of APCs with IL-10 and the presence of IL-10 in the APC-independent stimulation of CD4+ T cells and other regimens (see below), it appears that the effects of IL-10 on APCs play a more important role in the development of Tr1 than a direct influence on CD4+ T cells. Additionally, the presence of IL-27 and co-engagement of complement receptor CD46 during activation can also promote the differentiation of naïve T cells to Tr1 (48, 50, 141). It is believed that in contrast to Tr1 cells, IL-10 is generally not so important for the *in vitro* suppressive activity of Treg [reviewed in (142)]. However, in 2008 Ito *et al.* described two subsets of Treg cells in the human thymus and periphery defined by the expression of ICOS (143). Whereas the ICOS+ Treg cells use IL-10 to suppress DC function and TGF-β to suppress T cell function, the ICOS- Treg cells used TGF-β only. Furthermore, Collison *et al.* recently postulated that the contact between Treg and other T cells is important for the induction of IL-35 and the active state of Treg although the inhibiting activity of Treg is IL-35- and IL-10-dependent (144). However, Treg-produced IL-10 only slowly limits immune responses in the colon and the lung *in vivo* (145).

Similar to monocytes, in neutrophilic granulocytes IL-10 inhibits the release of pro-inflammatory mediators. Thereby, it inhibits the production of TNF-α and IL-1β that are induced by LPS or by phagocytosis of bacteria (146). Additionally, it inhibits the secretion of various chemokines attracting neutrophilic granulocytes (147). The synthesis of

cyclooxygenase-2 and the resulting production of prostaglandin E2 are also inhibited by IL-10 (148). In eosinophilic granulocytes, IL-10 inhibits the LPS-induced synthesis of numerous pro-inflammatory mediators such as TNF-α, GM-CSF, CXCL8 (149). Furthermore, the LPS-caused increase of vitality in both neutrophilic and eosinophilic granulocytes is diminished by IL-10 (149, 150).

IL-10 together with IL-4 suppresses the mast cell development induced by IL-3 and stem cell factor (SCF) (26). Furthermore, an incubation of mast cells with IL-10 inhibits the spontaneous and antigen-induced TNF-α, GM-CSF, and nitric oxide production in these cells (151, 152). IL-10 also diminishes the expression of IgE receptor and its signaling molecules like Syk, Fyn, and Akt (153). Consistent with these observations, IL-10 overexpression reduces the IgE-mediated anaphylactic response *in vivo* (153).

Notably, IL-10 also has important non-inhibitory functions on several immune cells. Thus, it prevents the apoptosis of B cells, enhances their proliferation, differentiation, and MHC II expression in addition to playing a positive role in immunoglobulin class switching (154-157). Moreover, IL-10 stimulates the cytotoxic activity of the NK cells (86). Additionally, it increases the IL-2-induced production of cytokines such as IFN-γ, GM-CSF, and TNF-α in these cells. It also increases the IL-2-induced proliferation of the CD56-bright subpopulation of NK cells (86).

The human cytokine is also biologically active in the mouse, although mIL-10 has no effects on the function of human cells (75). The Epstein Barr virus-encoded IL-10 homolog BCRF1 has a spectrum of immunological effects similar to that of the human cytokine. However, a series of positive effects cannot be detected. For example, the expression of MHC II on murine B cells was not increased by BCRF1 (155, 158). Additionally, a 1000-fold higher concentration of viral IL-10 is necessary in comparison to human IL-10 in order to produce most effects such as the inhibition of the IL-2 release. This is probably due to a lower affinity

of viral IL-10 to IL-10R1. Furthermore, it seems that in contrast to hIL-10 virus IL-10s bind different IL-10R1 variants with different affinities (159).

5. Molecular basis of IL-10's immunosuppressive effects

The exact molecular bases of immunosuppressive affects of IL-10 on APCs (the inhibition of cytokine production and antigen presentation) and T cells (the suppression of cytokine production and proliferation) are still a matter of debate despite a long research activity in this field.

There is however general agreement that STAT3 activation by IL-10 receptor engagement is essential for the anti-inflammatory effects of IL-10 in cells of myeloid origin. This was demonstrated most convincingly in STAT3 deficient mice (160) and confirmed by several *in vitro* studies (161, 162). Most interestingly, there is evidence also from patients with hyper-IgE syndrome, harboring a dominant negative STAT3-mutation, who show a defective IL-10 inhibition of LPS induced TNF-α (163). Whether STAT3 activation accounts also for direct inhibitory effects on T cells remains to be demonstrated, in particular because cytokines driving pro-inflammatory Th17 induction as IL-6 and IL-23 act also mainly *via* activation of STAT3. This is reflected by the fact that hyper-IgE syndrome patients with STAT3 mutations have also a strongly reduced Th17 population (164).

New protein synthesis induced by STAT3 activation seems to be necessary for the anti-inflammatory effects of IL-10 in myeloid cells although anti-inflammatory effects independent of new protein synthesis have been described in neutrophils (165). This prompted several studies on identifying genes which are induced by IL-10 by gene profiling (114, 166, 167). However, from these studies no clear candidate has emerged which would be a key

mediator of anti-inflammatory effects of IL-10. It appears that some IL-10 induced genes would rather lead to effect specific inhibition as discussed in more detail below.

Monocytic cells (monocytes, macrophages, dendritic cells) produce several pro-inflammatory mediators after the recognition of pathogens e.g. by means of TLR family members. Engaged TLRs trigger a signal transduction cascade *via* several adaptor molecules of which MyD88 is the most common one used. This leads to the activation of the transcription factor NF-κB and several MAP kinases (p38, ERK, JNK) [reviewed in (168-170)]. IL-10 in turn is known to inhibit the TLR-triggered production of pro-inflammatory mediators (see above). There are contrasting reports whether IL-10 would interfere with TLR induced signaling events [reviewed in (171)]. Of the IL-10-induced gene expression SOCS3 seemed to be the most promising candidate particularly since deficiency of its kinsman SOCS1 (which itself does not seem to be clearly induced by IL-10) augmented the LPS response and mortality due to an interference with the Myd88 independent pathway and inhibition of type I IFN (172-174). However, SOCS3-deficient mice exhibited a normal capacity of IL-10 to inhibit TNF-α production (175-177). Some phosphatases, which deactivate specific MAP kinases (e.g. DUSP1/MKP1), have been reported to be regulated by IL-10 (178) and were also shown to be negative regulators of LPS-signaling (179-182). However, formal proof that genetic deficiencies of these phosphatases would abrogate the inhibitory capacity of IL-10 is still lacking (180) or even disproved for TNF-α regulation (179). Some recent papers suggested that translation of MyD88 (183) or ubiquitination and thereby degradation of MyD88 dependent signaling molecules (IRAK-1, IRAK-4 and TRAF6) (184) might be regulated by IL-10. Another level of regulation of TLR signaling could arise from the fact that IL-10 inhibits miR-155 induction by TLRs (185). This microRNA targets the phosphatase SHIP1 (186) and therefore SHIP1 levels are elevated by a decreased SHIP1 translation which has been shown in another context to affect TLR signaling events (187).

Murray *et al.* claimed that the anti-inflammatory effects of IL-10 in murine macrophages are mainly mediated at the level of transcriptional activation of TNF-α gene (188). There have been several mechanisms suggested by which such a transcriptional repression of pro-inflammatory cytokines could be realized. First, IL-10 was suggested to induce nuclear translocation and DNA binding of the transcriptionally inactive p50/p50 homodimers of NF-κB leading to reduced transcription of NF-κB dependent gene expression (189). However, Cao *et al.* demonstrated that p50/p50 homodimers are not transcriptionally inactive and specifically induce the expression of IL-10 (190). Therefore the possibility arises that these inhibitory effects of p50/p50 homodimers could result from an autocrine IL-10 feedback loop, which would down-regulate cytokine expression *via* an alternative mechanism.

From gene expression profiling, several factors emerged which have been described to repress NF-κB activity [Bcl-3 (191), IKBNS (192), Abin3 (193), ETV3, and SBNO2 (194)]. However, formal proof that absence of these factors would abrogate the IL-10 inhibitory effect was provided only so far for Bcl-3. Interestingly, Bcl-3 and IKBNS might mediate the above mentioned recruitment of p50/p50 homodimers, but only to specific cytokine promoters. Whereas Bcl-3 regulates TNF-α and IL-23p19 but not IL-6 expression (191, 195), IKBNS is affecting only IL-6 and IL-12/IL-23p40 but not TNF-α transcription. On the other hand, the IL-10 induced gene B-ATF, which can repress AP-1 activity does apparently neither affect TNF-α nor IL-6 expression (171).

There have been several reports supporting the idea that there is a post-transcriptional element in the inhibitory capacity of IL-10 (196-199). However, this may be dependent on the timing of the IL-10 challenge (200). Many cytokines and growth factors contain AU-rich elements (AREs) which are targeted by ARE-binding proteins regulating thereby mRNA-stability and translation. The TLR activated p38 MAPK pathway has been shown to regulate mRNA-decay of TNF-α *via* inactivation of TTP by MK2 mediated phosphorylation [(reviewed in (201)].

Some publications suggest that IL-10 would interfere with this pathway either by interfering with p38 MAPK signalling (199, 202) or by regulating the expression of the ARE-binding proteins TTP (203) or HuR (202, 204).

As mentioned above, IL-10 is thought to be responsible for the inhibition of Th1 as well as Th2 and Th17 immunity. Some of the negative effects of IL-10 on T cell activation are the result of the immunosuppressive effects on APCs. The IL-10-induced inhibition of antigen presentation causes a down-regulation of Th1 as well as Th2 and Th17 responses. Interestingly, Koppelman *et al.* (205) demonstrated that, in IL-10-treated monocytes, mature peptide-bound MHC II molecules accumulate in intracellular vesicles and are prevented from reaching the cell membrane. The Steimle group recently explained this phenomenon (206). They found that IL-10 induces the membrane-associated RING-CH (MARCH) 1 - a member of the ubiquitin ligase family in human primary monocytes. MARCH1 down-regulates the surface expression of MHC II molecules in transfected cells. Furthermore, they found ubiquitinated forms of MHC II molecules both in IL-10-treated monocytes and in cells transfected with MARCH1. The knockdown of MARCH1 by means of siRNA reverses IL-10-induced MHC II down-regulation in primary monocytes.

In addition to antigen presentation, cytokine production, which would favor the development of Th1 cells, is reduced greatly as discussed above. Interestingly, even the IFN-γ production in pre-activated T cells is indirectly inhibited by IL-10 *via* its down-regulating effect on the APC IL-12 and IL-18 production (207). In addition to the indirect influence on T cell activation, there have been some reports about a direct inhibition of CD4+ T ells when stimulated by low numbers of triggered T cell receptors (208, 209). It has been proposed that this would be mainly due to an inhibitory affect of IL-10 on the CD28 co-stimulatory pathway, namely a reduced CD28 tyrosine phosphorylation and thereby reduced recruitment of phosphatidylinositol 3-kinase p85 (209). However, our own observations demonstrated that

IL-10 can also inhibit T cell receptor-induced IFN-γ production in CD28-negative T cells suggesting an additional mechanism independent of CD28 signaling (139).

6. Role of IL-10 in immune-mediated diseases

There are numerous investigations that describe an important role of IL-10 in the pathogenesis of various diseases. These diseases can be subdivided into:

a) Diseases with relative or absolute IL-10 over-production and

b) Diseases with a relative or absolute IL-10 deficiency.

In diseases with an IL-10 over-production, undesired immunosuppressive effects of IL-10 and the growth of some tumors can be observed. Lupus erythematosus, EBV-associated lymphomas in particular, and skin malignomas such as melanoma belong to this group of diseases (210-212). Furthermore, an elevated production of IL-10 during infections causes unfavorable progress. For example, a genetically dependent increased production of IL-10 is strongly associates with active lesions of cutaneous leishmaniasis (213). IL-10 also plays a decisive role in the formation of immune paralysis, a temporary immunodeficiency occurring after trauma, major surgery, burns, or shock, and which has a high risk of bacterial/mycological infections with lethal outcomes (214-219). It seems that macrophage-derived IL-10 is also jointly responsible for age-associated immune deficiency (220).

In diseases with a relative or absolute IL-10 deficiency, a persistent immune activation exists. This is the case in chronic-inflammatory bowel diseases (e.g. Crohn’s disease), psoriasis, rheumatoid arthritis, and after organ transplantation (221-224).

The IL-10 promoter was found to have discrete SNPs in different individuals, similar to promoters of other cytokines [(225) and reviewed in (226, 227)]. Interestingly, the

transcription factor Sp1 was shown to bind to one of these SNPs and to enhance IL-10 transcription in response to LPS (228). However, it should be noted that the association of SNPs in the IL-10 promoter and the amount of secreted IL-10 is dependent on many facts i.e. cell type, stimulation time, kind of stimulus (191, 229). Nevertheless, correlations between certain haplotypes of the IL-10 and IL-10R1 genes and the occurrence and/or course of various diseases were described (230-235). In fact, in Lupus erythematosus, not only was the correlation statistically significant between the haplotype and the occurrence of disease, but also between the type of antibody and the severity of the clinical condition (230, 232, 236). Additionally, an increased incidence of certain variations of the IL-10 promoter is described in differing courses of the EBV-infection (237). Furthermore, an IL-10 'higher producing' haplotype was found to be significantly associated with a reduced risk of developing melanoma (234). Also, the immune reaction against transplants appears to be influenced by polymorphisms in the promoter region of various cytokines. After heart transplantations, those recipients defined by their promoter type to be "TNF-α high/ IL-10 low"- producers are more often confronted with organ rejection (235). In the first six months after kidney transplantations, however, those defined as "TNF-α high/ IL-10 high"-producers had most frequent multiple rejection episodes, whereas "TNF-α low/ IL-10 low" producer genotype was protective (238). This slowly discrepancy makes it clear that the role of IL-10 promoter polymorphisms in the pathogenesis of certain diseases have to be further investigated.

7. Biological relevance of IL-10

The biological relevance of IL-10 is better understandable if the timeline of released cytokines after cell activation is kept in mind. IL-10 is first produced after the pro-inflammatory mediators. Thereby, it has a special physiological significance in limiting and preventing an

excessive immune response and limit collateral damage. Concurrently, it strengthens the "scavenger" functions of the immune system which is important after a conflict with antigens, and it contributes to the peripheral tolerance during antigen persistence.

Its relevance can be seen in both IL-10 deficient (**Table 1**) and IL-10 over-expressing animals (239). Such IL-10 deficient mice, when bred under normal conditions, develop lethal intestinal inflammation as a sign of an excessive immune reaction to the intestinal antigens of otherwise commensal bacteria (240). This inflammation can be reduced by a sterile environment and the application of IL-10 or Treg (240). Notably, IL-10 produced by macrophages is necessary for the Treg mediated prevention of colitis induced by transferred CD4+CD45RB+ T cells (16, 59). In fact, in IL-10(-/-)Rag1(-/-) mice, Treg cells fails to maintain Foxp3 expression and regulatory activity. Consequently, IL-10R1-deficient Treg cells also failed to maintain Foxp3 expression, which suggests that IL-10 released from myeloid cells acts in a paracrine manner on Treg cells to maintain Foxp3 expression (16). Together with the observation that IL-10-deficient Tregs have slight defects in controlling intestinal immune responses (145), this points to a crucial role for IL-10 in the maintenance of gut homeostasis and tolerance to commensal bacteria in the mouse. In the human, IL-10 appears to have a similar role since patients with defective IL-10R expression also develop a severe form of IBD (241). The second very impressive example is systemic endotoxemia (LPS shock). Mice deficient in IL-10 production following application of modest LPS doses showed an uncontrolled TNF-α secretion and high mortality rate (242). Subsequent studies with cell-specific IL-10- and IL-10R1-deficient animals clearly demonstrated that in this model protective IL-10 is produced by macrophages and/or neutrophils and acts on these cells in an autocrine loop (17, 19, 243). Furthermore, this anti-inflammatory and immunosuppressive role of IL-10 is seen in many local and systemic inflammatory processes and some infections (22, 25, 40, 43, 244-253). For example, Langerhans cell-derived IL-10 is required for suppression of hapten-specific CD4 and CD8 T cells and optimal inhibition of

contact-hypersensitivity in mice (249). IL-10-producing Th1 cells were shown to prevent immunopathology upon infection with intracellular pathogens, such as the protozoan Leishmania major during chronic cutaneous leishmaniasis (40) and the protozoan Toxoplasma gondii during systemic infection (43). In the murine model of listeriosis, after TCR-mediated interactions with Listeria-elicited macrophages by means of IL-10, γδ T cells control the expansion and TNF-α secretion from CD8+ T cell as well as protect the animals against liver injury (25). Furthermore, IL-10 produced by B cells suppresses pathogenic inflammation in experimental autoimmune encephalomyelitis (EAE) (22) and decreases virus-specific CD8+ T cell responses during murine cytomegalovirus infection in the spleen (252).

On the other hand, organisms whose APCs or other cells produce an increased amount of IL-10 are not able to control both various infections and tumor growth [(239, 254-261) and reviewed in (262)]. For example, Th1 cell-derived IL-10 mainly inhibits Th17 cells and is responsible for the death of mice that were challenged with high doses of influenza (260). IL-10 produced by NK cells inhibits protective immunity in mice models of visceral leishmaniasis (259).

The knowledge regarding IL-10 effects forces us to think about modulation of IL-10 activity as a potential therapy for chronic infection (by decrease of IL-10 activity) or chronic inflammatory diseases (by enhancement of IL-10 activity). We could hope for enhanced clearance of pathogens as a result of inhibition of IL-10 effects, however, we also have to anticipate higher TNF-α, IFN-γ, and IL-17 levels, more distinct inflammation, and severe immunopathology. The inhibition of IL-10 effects may be achieved by means of application of anti-IL-10 or anti-IL-10R1 antibodies as well as by induction of autoantibodies [reviewed in (263)]. The fact that IL-10 mediates the therapeutic effects of some immunosuppressive therapies such as extracorporeal photopheresis (264) supports the reasons for using IL-10 as an immunosuppressive drug. However, before that we have to clear up how strong the inhibitory influence of IL-10 actually is on Th17 cells, Th22 cells, myeloid DCs, and

plasmacytoid DCs as well as how important IL-10 is for the development of Tr1 cells *in vivo*. Can we hope that by means of IL-10 application in patients we can generate Tr1 cells?

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Table 1

Model	**Phenotype IL-10 knockout (mouse)**	**References**
Inflammatory bowel disease	spontaneous inflammatory bowel disease	(16, 240)
LPS inflammation	uncontrolled production of TNF-α high mortality rate	(17, 19, 242, 243)
Collagen-induced arthritis	more susceptible more severe course of the disease	(244, 250)
Experimental autoimmune encephalomyelitis	more severe course of the disease	(244)
OVA-induced asthma	reduced immunopathology	(265)
Influenza infection	enhanced clearance of pathogens improved survival	(260, 266)
Cytomegalovirus infection	enhanced clearance of pathogens severe inflammation	(267)
Chlamydia pneumoniae infection	enhanced clearance of pathogens severe inflammation	(268, 269)
Toxoplasma gondii infection	lethal inflammatory response	(17, 43, 270, 271)
Leishmania major infection	enhanced clearance of pathogens severe immunopathology	(40, 255, 257, 272)
Mycobacterium tuberculosis / bovis infection	enhanced clearance of pathogens severe immunopathology	(248, 273)
Systemic *Escherichia coli* infection	enhanced clearance of pathogens severe immunopathology	(274)

Figure legends

Figure 1: CD4+ T cells as IL-10 sources.

Figure 2: IL-10 – IL-10 receptor interaction.

The cellular IL-10 receptor is a complex composed of the CRF2 members IL-10R1 and IL-10R2. IL-10 first binds IL-10R1. This interaction apparently leads to a conformation change of the cytokine creating a binding site for IL-10R2. The close proximity of both receptor components leads to the reciprocal activation of the receptor-associated Janus kinases Jak1 (associated with IL-10R1) and Tyk2 (associated with IL-10R1). Following the tyrosine phosphorylation of the cytoplasmatic part of IL-10R1, STAT3 molecules are bound and phosphorylated by the Janus kinases. Additionally, STAT1 and, in certain cell types, STAT5 molecules are activated. STAT homo- or heterodimers immigrate into the nucleus where they bind to the STAT binding elements of various promoters in order to induce transcription of the corresponding genes.

Figure 3: Interference of IL-10 with LPS induced gene expression.

The engagement of the TLR4 receptor complex by LPS induces pro-inflammatory responses (e.g. expression of TNF-α) mainly via the Myd88-dependent pathway (depicted in green colours) which triggers cytokine gene transcription via NF-κB and p38 MAPK. The MAPK p38 also controls TNF-α mRNA stability and translation via MK2 which deactivates the AU-rich element binding protein Tristetraprolin (TTP/zfp36) by phosphorylation. IL-10-induced STAT3 activation is essential to induce the expression of several genes that have been

implicated in the inhibition of LPS responses (depicted in red). Abin-3, which is active only in human cells, has been described to interfere with NF-κB activation and thereby prevents translocation of the activating p65/p50 heterodimers into the nucleus. DUSP-1/MKP-1 inhibits p38 MAPK activation and thereby might prevent deactivation of TTP/ZFP36 which then can initiate degradation of cytokine mRNAs via binding to AU-rich elements in their 3´UTR. The IκB-family members bcl-3 and IKBNS might favor the transport of p50 into the nucleus and guide by an unknown mechanism the binding of transcriptionally inactive p50/p50 homodimers to NF-κB-sites of specific promoters. Thereby the binding of transcriptionally activating p65/p50 heterodimers at these sites NF-κB-sites is prevented.

Figure 1

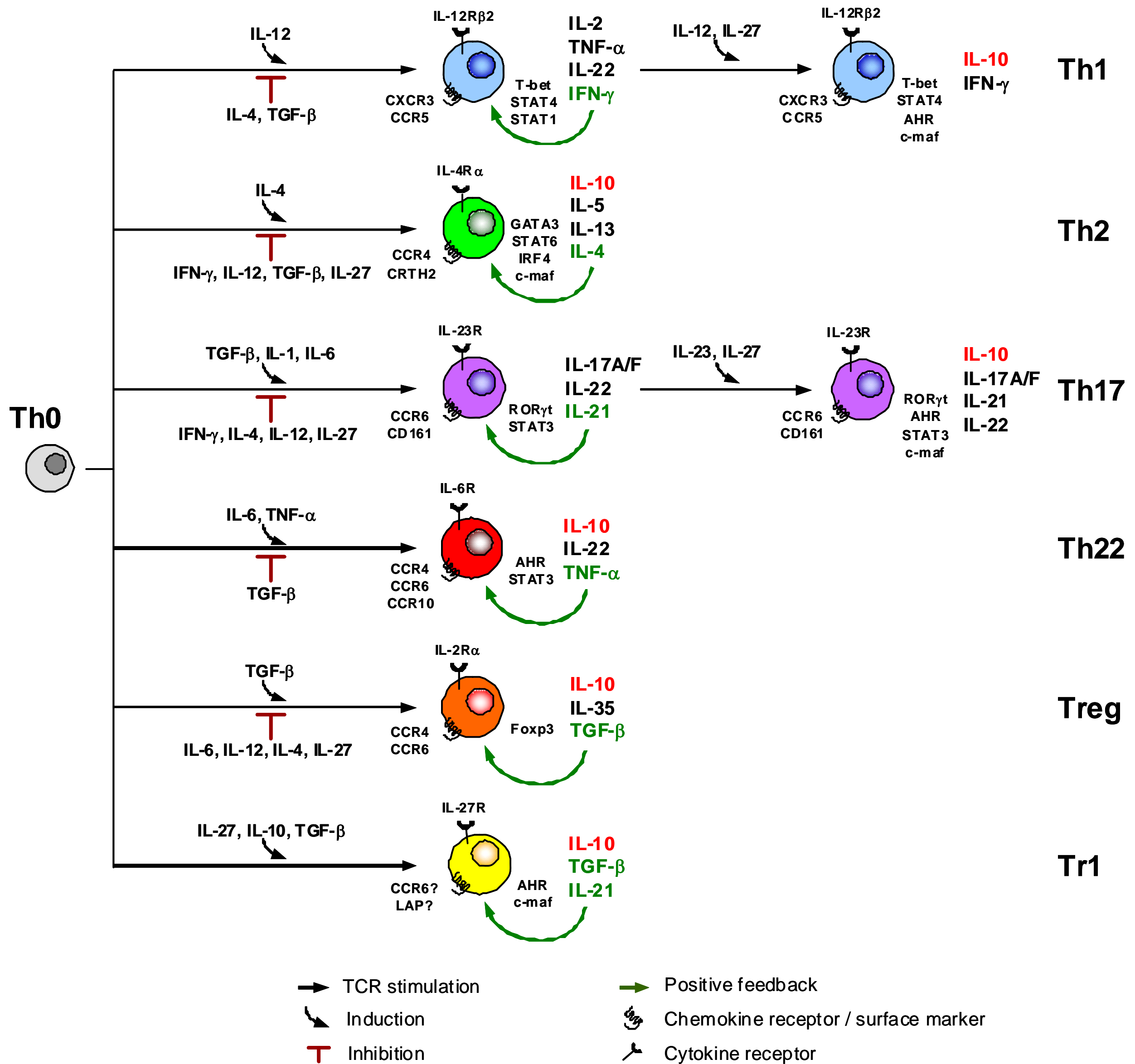

Figure 2

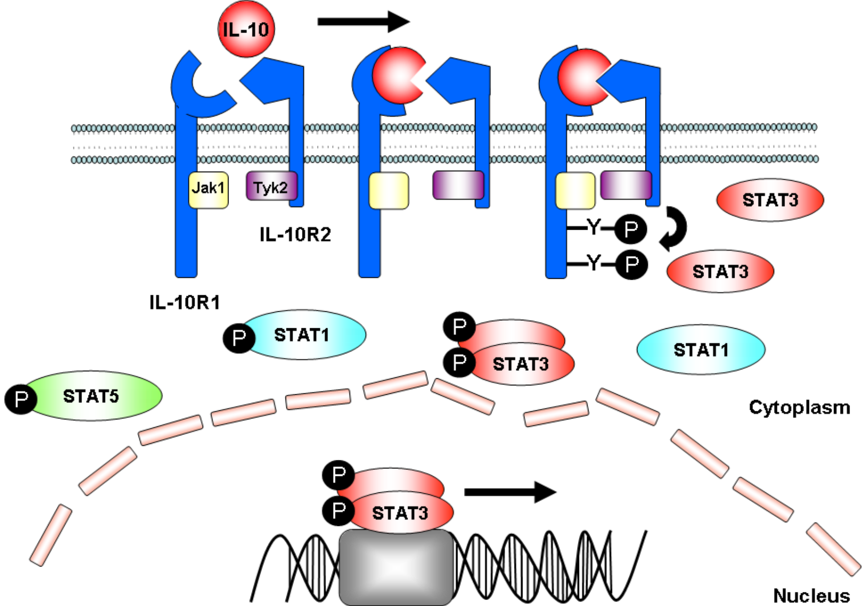

Figure 3