The dual role of IL-10

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Classification of cytokines as pro- versus anti-inflammatory might not apply to the pleiotropic effects of interleukin-10 (IL-10). Several reports suggest that IL-10 enhances the function of natural killer cells, which leads, through pathogen destruction, to increased antigen availability. In addition, by inhibiting the maturation of antigen-presenting cells (APCs), IL-10 preserves their ability for antigen uptake while simultaneously hampering their migration to draining lymph nodes. This review suggests that this ‘antigen-loading’ phase might constitute an important component of the innate immune reaction to a pathogen. Additional proinflammatory stimuli might subsequently lead to maturation of ‘loaded’ APCs that could migrate to draining lymph nodes or recruit and activate adaptive immune effectors locally.

Traditionally, cytokines have been classified as pro- versus anti-inflammatory based on global effects in animal models or direct effects on individual immune-cell populations. This simple dichotomy might not fully describe the pleiotropic role that several cytokines, such as interleukin-10 (IL-10), have during the early immune response. Indeed, the function of a given cytokine is determined by its tissue levels, the nature of the target cell and activating signal, the timing and sequence of cytokine exposure and, more generally, the experimental model tested, as recently discussed for a wide range of cytokines [1]. This review postulates that several cytokines cooperate through different pathways during the early phases of the innate immune response and thereby amplify the signal conveyed by an exogenous or endogenous insult. Stimulation of antigen-presenting cells (APCs) with lipopolysaccharide (LPS) induces IL-10 release, which is further increased by the presence of damaged cells [2–4]. In these early phases, IL-10 expression is coordinated with that of other innate immune genes that have potent proinflammatory and chemoattractant properties [3,4] and only at a later stage are genes that regulate the adaptive immune response induced [3]. In the early phase of the immune response, APCs might adopt measures conducive to the induction of the cognitive phase of the immune response (Fig. 1).

As the recruitment of immune cells progresses, APCs ‘load’ themselves with antigen in a concentrated effort to kill damaged cells by engagement of tumour necrosis factor (TNF)-family ligands to corresponding death receptors [5,6] or by activation of natural killer (NK) cells [7,8]. It is at this juncture that the pleiotropic functions of IL-10 converge into a congruent attempt to limit the damage triggered by the pathogen by contributing to its destruction while simultaneously limiting collateral damage by dampening the inflammatory process. IL-10 is a potent stimulator of NK cells [9–17], a function that might contribute to the clearance of the pathogen and facilitate antigen acquisition from dead cells for cross-priming by activated APCs, providing a link between the innate and the adaptive immune responses [8,18–20]. NK-cell activation by IL-10 could serve similar purposes because the recruitment of monocytes and macrophages induced by this cytokine (through the induction of human chemokine-4 and the scavenger receptors CD16 and CD64 Fcγ, respectively) is responsible for antibody-dependent cell-mediated cytotoxicity and phagocytosis of opsonized particles [21,22]. This ‘antigen procurement’ phase of the innate response has three potential benefits: (1) possible clearance of pathogen if the insult is limited; (2) increased antigen availability and (3) cell-damage-dependent signalling (apoptosis and/or necrosis) conducive to APC activation [9,10].

In contrast to the activation of NK cells and other effector mechanisms, IL-10 suppresses the proinflammatory functions of APCs by antagonizing expression of costimulatory molecules, the release of proinflammatory cytokines and, in general, APC maturation [4,21,23]. This function might be part of a general effort to self-contain the extent of the inflammatory process in situations when the exposure to a given insult is transitory and inconsequential. In addition, by inhibiting APC maturation, IL-10 prolongs their capability for antigen uptake while simultaneously postponing their migration to draining lymph nodes. When the pathogen is not cleared by this early response, the inflammatory process progresses, providing additional signals that lead to further APC maturation and recruitment of adaptive immune effectors [10,24,25]. IL-10 secreted by CD4⁺ T cells might have a similar role in the later phases of the immune response by extinguishing the inflammatory response when the proinflammatory stimulus induced by the pathogen is eliminated by potent antigen-specific effector mechanisms [21].

Anti-inflammatory and proinflammatory effects of IL-10

The predominant effect of IL-10 is to reduce inflammation. IL-10-knockout mice develop chronic inflammatory bowel...
disease because they cannot mitigate the immune response to intestinal flora [26]. This phenotype differs significantly from transforming growth factor-β (TGF-β)-knockout mice, which develop a widespread multi-organ autoimmune disease [27]. In transgenic models, IL-10 has a more complex role by reducing the ability of mice to mount significant T- or B-cell responses to ovalbumin, Listeria monocytogenes and Leishmania, and by preventing experimental autoimmune encephalomyelitis [28]. However, IL-10-transgenic mice demonstrate mucosal inflammation [29], accelerated development of autoimmune diabetes and increased T-cell-mediated rejection of cancer (reviewed in [1]).

Animal models suggest that IL-10 can induce NK-cell activation and facilitate target-cell destruction in a dose-dependent manner [12,13]. Administration of IL-10 to wild-type mice has variable effects. For instance, it can inhibit antigen-specific immune responses in vivo [30]. In mice and humans, IL-10 can induce long-term antigen-specific anergy in CD4+ T cells [1,21]. In humans, IL-10 has a role in inducing systemic lupus erythematosus [31], yet counteracts psoriasis [32] and Crohn’s disease [33]. During HIV infection, IL-10 sustains NK-cell cytotoxic function in vivo through induction of NK receptors [14,15]. In addition, it has recently been reported that IL-10 could have a key role in mediating autologous graft-versus-host disease [34]. Intravenous administration of IL-10 to healthy volunteers has proinflammatory effects through the release of interferon-γ (IFN-γ), IFN-γ-inducible protein (IP)-10 and increased granzyme levels [15]. These effects are counteracted by inhibition of the release of monocyte inflammatory protein-1α (MIP-1α), MIP-1β and monocyte chemotactic protein-1 (MCP-1) [35], TNF-α, IL-1β, IL-6 and IL-8 [36,37], and T-cell function [37]. In vitro evidence suggests that IL-10 inhibits APC maturation and, by downregulating their costimulatory capacity, hampers their ability to stimulate adaptive immune effector cells [21,38].

Although several inconsistencies require elucidation, it appears that the overall effect of IL-10 in mice and humans is to promote local effector mechanisms, such as NK-cell activation and the enhancement of expression of cytotoxic molecules. Concomitantly, IL-10 appears to mitigate the induction of mechanisms capable of attracting and activating adaptive immune effector cells (e.g. reduced expression of chemokines targeting T and B cells, hampered maturation of APCs) [23].

**IL-10 and experimental cancer models**

Experimentally, IL-10 consistently demonstrates antitumour properties [12,13,39–42] (Table 1). Most researchers attribute its antitumour activity to NK-cell activation [13,39], although cytotoxic T lymphocytes might be synergistically involved through maintenance of a CD8+-antitumour response [43] or tumour rejection might be mediated in the context of a systemic Th2 response [43,44]. Yet, a direct stimulatory action of IL-10 on adaptive immune effector cells remains to be convincingly demonstrated. Furthermore, IL-10 enhances the susceptibility of target cells to NK-cell lysis by reducing
the surface expression of MHC antigens [16,17]. IL-10 also increases the recruitment of macrophages and neutrophils [22] and inhibits cancer growth by hampering tumour angiogenesis and invasiveness through induction of metalloproteinase (MMP) inhibitors [22,39,40,45]. In a colon carcinoma mouse model, the transfection of tumour cells with IL-10 reduces the malignant potential in the context of a predominant Th2-type immune response [44]. IL-10-transfected cell lines derived from mouse mammary adenocarcinoma [22,46], ovarian carcinoma [47] and melanoma [11] elicit loss of tumouri-

cency and increased immunogenicity accompanied by a strong lymphocyte and antibody-dependent immune memory.

Thus, experimental models strongly support a role for IL-10 as a mediator of tumour regression. Although local administration (tumour transfectant models) predominantly inhibits tumour growth, systemic IL-10 administration has protective and/or curative effects. The mechanism(s) responsible for antitumour properties remains unclear; however, it seems that IL-10 stimulates effector functions by enhancing tumour-cell killing by NK cells and, perhaps, CD8+ T cells. This is in line with the hypothesis that the primary role of IL-10 is to induce destruction of abnormal cells with secondary beneficial effects on antigen presentation [19].

**IL-10 and human cancer**

The role of IL-10 in the context of human cancer is less clear. A negative correlation between circulating levels of IL-10 and prognosis was observed in patients with solid or haematological malignancies [21]. However, this association might reflect the bulk of IL-10-producing tumour cells in advanced stages. Overexpression of Th2-type cytokines (including IL-10) associated with depressed APC function was observed in tumours unresponsive to immunotherapy [48]. By contrast, high IL-10 levels were observed in areas of spontaneous regression of primary melanoma [49].

Information available on IL-10 production in freshly excised human tumours, including carcinomas of the ovary, breast, renal cell, lung and skin and melanoma, has recently been summarized [38]. In the tumour micro-environment, IL-10 is probably secreted by tumour cells because several human cancer cell lines constitutively produce IL-10 in vitro [38]. The biological significance of IL-10 production by tumour cells is unclear. The proliferation rate of human melanoma cell lines is enhanced by exogenous IL-10, suggesting that this cytokine might be a tumour growth factor [50]. In addition, IL-10 immune-suppressive effects could enable tumour escape from immune recognition [50–52].

However, the role that IL-10 might have in tumour escape is far from established. In the context of human papilloma virus-related cervix carcinoma, IL-10 enhances synergistically with IL-2 tumour-specific T-cell expansion and cytotoxicity by increasing the intracellular accumulation of perforin [53]. In a recent study, the treatment-induced behaviour of melanoma metastases was linked to their phenotype by serial gene expression analysis of samples obtained by fine-needle aspirates (FNA) [54]. Using this strategy, the mRNA levels were measured of genes with immune-regulatory function, such as IL-8, IL-10, TGF-β1 and TGF-β2, which are thought to be constitutively secreted by tumour cells [52]. mRNA levels were documented before and during therapy with systemic

![Table 1. Inhibitory effects of IL-10 on tumour growth in animal models (adapted from [39])](http://treimm.trends.com)

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Method of delivery</th>
<th>Role</th>
<th>Best result reported</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10-transfected hamster ovarian tumour implants</td>
<td>Local</td>
<td>Local antitumour effect</td>
<td>Inhibition of tumour growth</td>
<td>[47]</td>
</tr>
<tr>
<td>IL-10-transfected spontaneous mammary carcinoma</td>
<td>Local</td>
<td>Induction of antitumour immune response</td>
<td>Protection</td>
<td>[46]</td>
</tr>
<tr>
<td>IL-10-transfected tumour implants</td>
<td>Local</td>
<td>Induction of antitumour immune response</td>
<td>Protection</td>
<td>[42]</td>
</tr>
<tr>
<td>Various types of established (7-day) murine tumours</td>
<td>Systemic</td>
<td>Induction of antitumour immune response</td>
<td>Treatment</td>
<td>[41]</td>
</tr>
<tr>
<td>Subcutaneous implants of B16 melanoma transduced with IL-10</td>
<td>Local</td>
<td>Local antitumour effect</td>
<td>Protection</td>
<td>[11]</td>
</tr>
<tr>
<td>IL-10-transfected murine mammary cancer subcutaneous implants</td>
<td>Local</td>
<td>NK-dependent inhibition of tumour</td>
<td>Inhibition of tumour growth</td>
<td>[13]</td>
</tr>
<tr>
<td>B16 and spontaneous melanoma lung metastases</td>
<td>Systemic (i.p.)</td>
<td>NK-dependent inhibition of tumour</td>
<td>Inhibition of tumour growth</td>
<td>[12]</td>
</tr>
<tr>
<td>Breast cancer cells transfused with murine IL-10</td>
<td>Local</td>
<td>Recruitment of leukocytes</td>
<td>Inhibition of tumour growth</td>
<td>[22]</td>
</tr>
<tr>
<td>IL-10-transfected CT26 colon carcinoma-cell implants</td>
<td>Local</td>
<td>T-cell-dependent inhibition of tumour</td>
<td>Inhibition of tumour growth</td>
<td>[44]</td>
</tr>
<tr>
<td>IL-10-transfected A375 human melanoma subcutaneous and pulmonary metastases xenografts</td>
<td>Local</td>
<td>Local antitumour effect</td>
<td>Inhibition of tumour growth</td>
<td>[64]</td>
</tr>
<tr>
<td>β-Galactosidase-expressing 3-day pulmonary metastases</td>
<td>Systemic (i.p.)</td>
<td>Adjuvant to poxvirus-based vaccine</td>
<td>Treatment</td>
<td>[40]</td>
</tr>
<tr>
<td>Human prostate cancer vertebral metastases xenografts</td>
<td>Systemic (i.m.)</td>
<td>Inhibition of vasculogenesis</td>
<td>Inhibition of tumour growth</td>
<td>[45]</td>
</tr>
<tr>
<td>Ovalbumin-expressing subcutaneous implants</td>
<td>Systemic (i.p.)</td>
<td>Adjuvant to peptide-pulsed APC vaccine</td>
<td>Protection and treatment</td>
<td>[43]</td>
</tr>
</tbody>
</table>

*Abbreviations: APC, antigen-presenting cell; IL, interleukin; i.m., intramuscular; i.p., intraperitoneal; NK, natural killer.*
IL-2. Surprisingly, it was found that IL-10 mRNA was expressed at significantly higher levels in pre-treatment FNA samples obtained from immune-responsive lesions \((t\text{-test } p_{2} < 0.002)\) [55]. A follow-up study on an independent patient population confirmed this finding by identifying a positive correlation between clinical regression and IL-10 protein levels in tumour cells from FNA obtained before therapy [38]. Thus, it could be speculated that IL-10 produced by some tumours might pre-condition the tumour microenvironment to the antitumour effects of systemic IL-2 administration.

As a result of these observations and the extensive literature suggesting a role for IL-10 in NK-cell activation [9,10,12–17], the proliferative and cytotoxic activity of NK cells exposed to this cytokine in the presence or absence of IL-2 was tested. IL-10 did not affect NK-cell proliferation. However, a significant increase in the lysis of Daudi cells but not K562 cells, resulted from the combination of IL-2 and IL-10 (Fig. 2a). The enhancement of cytotoxic activity induced by IL-2 was associated with a significantly enhanced expression of perforin, granzyme, TNF-α, inducible nitric oxide synthase and IFN-γ. IL-2 also increased the expression of IL-8 but neither cytokine affected the expression of TGF-β1, TGF-β2, CD28, NK-inhibitory receptors, CD16 and CD2. Other genes analysed by cDNA arrays can be accessed at http://www.cc.nih.gov/dtm/dtm_research.htm. The data presented here do not take into account post-transcriptional regulation.

**Table 2. Selected genes with immunoregulatory properties whose mRNA levels are selectively increased on stimulation of NK cells with IL-10**

<table>
<thead>
<tr>
<th>Gene(a)</th>
<th>Putative associated function</th>
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</thead>
<tbody>
<tr>
<td>TIA-1</td>
<td>NK-cell cytotoxic function</td>
</tr>
<tr>
<td>CD69</td>
<td>NK-cell receptor</td>
</tr>
<tr>
<td>MRC OX2</td>
<td>Inducer of Th1-type immune responses</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>Chemotactic and proinflammatory properties</td>
</tr>
<tr>
<td>MxA, MxB</td>
<td>Acute inflammatory processes</td>
</tr>
<tr>
<td>Hsp70</td>
<td>Tissue damage, inflammation, antigen presentation</td>
</tr>
<tr>
<td>CD30 ligand</td>
<td>Lymphocyte survival and differentiation</td>
</tr>
<tr>
<td>ITL-α</td>
<td>Modulator of immune response through NF-κB</td>
</tr>
<tr>
<td>Lipoxin A4</td>
<td>Resolution of inflammation</td>
</tr>
<tr>
<td>Caspase-8</td>
<td>Apoptosis</td>
</tr>
</tbody>
</table>

*aAbbreviations: Hsp70, heat shock protein 70; IFN, interferon; ITL-α, inhibitor of NF-κB.*

**Fig. 2.** Effects of interleukin-2 (IL-2) and IL-10 on the cytotoxic function of natural killer (NK) cells. Peripheral blood mononuclear cells were purified by Ficoll gradient separation and cultured for 48 hours in the presence of IL-2 (300 IU ml\(^{-1}\)) and/or IL-10 (30 ng ml\(^{-1}\)). Cytotoxic activity was measured against the human chronic myelogenous leukaemia cell line K562 (a) or the human lymphoma cell line Daudi (b) with a calcein-based survival assay. Percent (%) lysis was calculated as follows at the effector to target (E/T) ratios of 5:1, 10:1 and 20:1; \(\%\) lysis = \(1 - \frac{\text{background fluorescence}}{\text{experiment fluorescence}}\) \times 100. An average of three experiments performed with NK cells from different donors is shown \(* = t\text{-test } p_{2} = 0.02\) between the treatment with IL-2 alone and the treatment with IL-2 plus IL-10.

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proteins); heat-shock protein 70; CD30 ligand], some were related to the resolution of inflammation (e.g. IKB-\(\alpha\), lipoxin A4, formyl-peptide receptor) and some had pre-apoptotic function (inhibitor of apoptosis-2, caspase-8). In general, it appeared that IL-10 activated intrinsic NK-cell activity and promoted a lipid mediator class switch to mitigate the surrounding inflammatory process [58]. The combination of IL-2 and IL-10 administration specifically induced the differential expression of 190 genes, mostly promoting inflammation and increased NK-cell migration and function [e.g. CD11c, CD151, CD27-binding protein, MMP-12, TNF receptor 1 (TNFRI), MHC class I].

On the basis of these findings and the observation that IL-10 is secreted constitutively by tumour cells, it can be hypothesized that IL-10 might pre-condition the immune responsiveness of tumours to proinflammatory stimuli. This effect might be mediated through NK-cell activation leading to tumour cell killing, antigen release and APC stimulation by damaged cells. At the same time, IL-10 inhibits classical APC maturation, which preserves their antigen-uptake function and promotes polarization towards an M2 phenotype that promotes angiogenesis, tissue remodelling and repair [23]. Finally, IL-10 inhibits recruitment and activation of adaptive immune mediators, which maintain a chronic inflammatory state within the tumour microenvironment. On addition of a secondary proinflammatory stimulus (i.e. the systemic administration of high-dose IL-2), the balance is shifted towards activation of APCs with consequent production of chemoattractants, costimulatory molecules and cytokines with proliferative effects on immune cells [57] in a situation similar to the one depicted in Fig. 1. In this case, APCs loaded with antigen act as strong immunogens for the incoming tumour-specific T cells (Fig. 4). Obviously, this proinflammatory activity is not limited to IL-2 alone because other cytokines could serve as a link between innate and adaptive antitumour immunity, as recently reviewed by Belardelli et al. [20].

**IL-10 in human trials**

There are few examples of clinical trials adopting systemic IL-10 administration. Subcutaneous administration of
IL-10 (8 μg kg⁻¹) induced modest but significant improvements in patients with psoriasis [32,59], Crohn’s disease [33], rheumatoid arthritis [60] and chronic hepatitis C infection [61]. In general, the predominant biological effect of systemic IL-10 administration was global immune suppression, decreased T-cell and macrophage infiltration, inhibition of NF-κB activation and depressed TNF-α and IL-12 expression by monocytes. In a separate study in which IL-10 was given to patients with acute myelogenous leukaemia, IL-10 induced elevated serum levels of TNF-α and IL-1β [62], an effect opposite to the in vitro observations, suggesting that these might not necessarily reflect the in vivo effects of this cytokine. Discordant with the anti-autoimmune effects of IL-10, administration of neutralizing anti-IL-10 antibodies [31] reduced symptoms in patients with SLE. Several clinical trials have been performed in healthy volunteers to address the safety and biological effects of IL-10 administration [15,36,37,63]. These studies have uniformly demonstrated that IL-10 administration at doses associated with biological activity has minimal side effects. In a recent report, intravenous administration of human recombinant IL-10 (25 μg kg⁻¹) when given 1 hours after the induction of endotoxaemia, produced proinflammatory effects by enhancing release of IFN-γ, IP-10 and other monokines induced by IFN-γ [15]. In addition, IL-10 induced activation of cytotoxic T and NK cells as reflected by increased levels of granzyme b. This finding is concordant with the observation that high levels of IL-10 during HIV infection enhance NK-cell activity [14].

Given that IL-10 has been associated with an effective anticancer immune response in animal and human models, several investigators have suggested administering IL-10 to cancer patients [12,13,40,41,64]. However, to our knowledge, no clinical trial is testing this possibility. On the basis of the previous discussion, we believe that it is unlikely that IL-10 alone will induce tumour regression. However, IL-10 might pre-condition the tumour microenvironment to concomitant therapy either with other cytokines associated with the generation of adaptive immune responses [20] or with IL-2 as suggested by our clinical findings (Fig. 4).

Conclusions
Although IL-10 is highly regarded as an immunosuppressive cytokine and this reputation has discouraged clinical investigators from using it as an anticancer agent, preclinical models as well as observations in humans suggest that it might have a facilitator role in pre-conditioning tumours to immune recognition. On the basis of extensive pre-clinical data discussed here (Table 1), together with the two consecutive studies that identified IL-10 expression in the tumour micro-environment as a classifier of immune responsiveness [38,55] and its limited toxicity when systemically administered [15,36,37,63], it is proposed that pilot clinical trials be performed under intense scrutiny to assess the true role that this cytokine might have in cancer therapy. In addition, it has become increasingly apparent that IL-10 might have a key role in...
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