Cancer Immunol Immunother (1998) 46: 239–244

REVIEW

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A review of the association between interleukin-10 and human B-cell malignancies

Received: 11 February 1998 / Accepted: 26 February 1998

Key words Interleukin-10 · Lymphoma · Epstein-Barr virus · B lymphocyte · Lymphoproliferative disorders

Introduction

Several studies have provided evidence for the role of human interleukin-10 (IL-10) in the pathogenesis of malignant B cell lymphoproliferation and lymphomas. Production of IL-10 may confer a selective advantage upon B cell malignancies by directly enhancing the survival and proliferation of tumor cells and by impairing host immune responses via its suppressive effects on macrophages and T cells. This review will outline the biological activity of IL-10, the relationship with Epstein-Barr Virus (EBV), and the experimental and clinical data that evaluate its association with B cell malignancies.

Biology of IL-10

IL-10 is a pleiotropic cytokine that was initially known as the cytokine-synthesis-inhibiting factor, and its discovery was based upon characterization of its biological activity [13]. It is a 18-kDa acid-sensitive protein comprised of 160 amino acids. Unlike murine (mu) IL-10, which is glycosylated at the N terminus, human (hu) IL-10 lacks detectable carbohydrate moieties [40]. This glycosylation, however, is not necessary for its biological activity. In its active form, huIL-10 exists as a 37-kDa non-covalently bound dimer.

The gene for IL-10 is present as a single copy in the genome and has been localized to chromosome 1 in the mouse and in humans [19]. Interestingly, both species of IL-10 exhibit a strong DNA and amino acid sequence homology to the open reading frame in the EBV genome called BCRF-1 [26]. Since huIL-10 and BCRF-1 [viral (v) IL-10] are closely related in amino acid sequence, it is postulated that EBV may have captured this mammalian gene during evolution to confer a survival advantage [27]. vIL-10 is a 17-kDa non-glycosylated polypeptide, which shares most of the functional activities with huIL-10, including receptor binding [15]. However, the specific activity of vIL-10 is three- to tenfold lower than that of huIL-10.

Production of IL-10

IL-10 is produced by monocytes, macrophages, B cells and activated T cells [16]. $CD4^+$ T cells can be separated into subsets based on a particular profile of their cytokine production following stimulation. The cytokines, in turn, dictate which response (humoral or cellular) the T cells will promote. The cell-mediated response has been referred to as the type 1 response, and the CD4 T cells that promote the type 1 response are called Th1 cells [30]. The prototypic type 1 or th1 cytokines are IL-2 and interferon γ (IFNγ). The humorally mediated response is called the type 2 response and the $CD4^+$ T cells that promote the type 2 response are called Th2 cells. The prototypic type 2 or Th2 cytokines are IL-4, IL-5, IL-6, IL-10 and IL-13 [31]. In humans, though Th2 clones are the main source of IL-10, many Thl clones will also secrete IL-10 following antigen-specific stimulation [48]. $CD45RO^+$ (memory) T cells produce tenfold higher amounts of IL-10 than do

This work was supported by grants (CA09581 and CA65670) from the National Institute of Health

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CD45RA+ (naive) T cells [48]. Human monocytes secrete IL-10 following activation with lipopolysaccharide at levels that are equivalent to those of Th2 clones [42]. IL-10 is produced in the "later phase" of monocyte/macrophage activation, consistent with its role as a monocyte/macrophage deactivator [35].

IL-10 receptor (IL-10R)

The various biological effects of IL-10 are mediated by its engagement with its cell-surface receptor. Both the murine and human receptors for IL-10 have been identified, characterized and cloned [15, 22]. There is 75% DNA sequence homology between the muIL-10R and the huIL-10R, with 60% identity between the predicted amino acid sequence. The huIL-10R gene is located on chromosome 11 and its mRNA expression has been detected in all IL-10-responsive cells (mainly hemopoietic cells). Chemical binding studies of radioiodinated huIL-10 binding to various human cell lines characterized the huIL-10R to be a 110-kDa glycoprotein. huIL-10 will bind to both muIL-10R and huIL-10R, whereas muIL-10 binds only to muIL-10R. Major differences in the N-terminal third of the muIL-10 and huIL-10 proteins may be, in part, responsible for the apparent species specificity [38].

Structural analysis reveals homology to the class II cytokine receptor family (CRF2), which includes the receptors for IFNα/β and γ [29]. Receptors belonging to the type I and II cytokine receptor families are now known to utilize the Janus kinase (JAK/signal transducers and activators of transcription (STAT) family of proteins for signal transduction [21]. Characterization of the muIL10R intracellular signaling pathway demonstrates that it activates STAT1, STAT3 and STAT5, which subsequently form multiple STAT heterocomplexes and bind to the regulatory regions of certain genes [20, 46]. Recently, the orphan receptor CRF2-4 has been shown to be a critical component of the IL-10R complex in mice but its biological function remains to be demonstrated in humans [34]. In human T cells and monocytes, the IL-10/IL-10R complex induces tyrosine phosphorylation of TYK2 and JAK1 kineses with subsequent activation of STAT1α and STAT3 [11]. STAT3 is predominantly activated over STAT1, particularly in monocytes, and the subsequent distinct homodimer/heterodimer complexes of the two STAT proteins may explain why T cells and monocytes individualize their response to IL-10. Thus, multiple and distinct signaling pathways may mediate the various pleiotropic activities of IL-10.

Effect of IL-10 on the immune system

Like most other cytokines, IL-10 exerts multiple effects on various cell lineages. A brief review of these effects is necessary to understand the interactions that may occur during the process of lymphomagenesis.

T cells

In humans, IL-10 inhibits production of IFNγ, tumor necrosis factor α (TNFα) and IL-2 by the Thl CD4+ T cell subset following activation with antigen-pulsed monocytes [14]. Similarly, human monocyte-dependent proliferation of Thl CD4+ T cells is also inhibited by IL-10 [43]. This is due in part to the ability of IL-10 to strongly downregulate constitutive and inducible expression of HLA class II molecules on monocytes [43]. IL-10 also has direct inhibitory effects on T cell proliferation, largely due to inhibition of IL-2 production [44].

Macrophage/monocytes

Experimental evidence indicates that monocytes/macrophages are the prime targets of IL-10, which has been termed the "macrophage-deactivating factor" [28]. In addition to causing de-adherence of monocytes, IL-10 also inhibits constitutive and inducible expression of MHC class II antigen following activation by lipopolysaccharide or IFNγ [43]. IL-10 has also been demonstrated to inhibit human lymphocyte production of IFNγ by suppressing IL-12 synthesis in monocytes activated with *Staphylococcus aureus* or lipopolysaccharide [9]. The production of IL-lα, IL-β, IL-6, IL-8, TNFα, granulocyte/macrophage-colony-stimulating factor and granulocyte-colony-stimulating factor by human monocytes is inhibited by IL-10 at the mRNA and protein level [42]. In fact, IL-10 inhibits the production of IL-10 itself in activated monocytes, indicating the presence of a self-regulatory negative-feedback loop [42].

Natural killer (NK) cells

NK cells can mediate spontaneous cytotoxicity against tumor cell targets, especially when stimulated with IL-2. huIL-10 can directly induce similar, albeit less, NK cytotoxic activity against tumor-resistant targets as well as enhance IL-2-induced proliferation, cytotoxicity and cytokine production [7].

B cells

IL-10 enhances the viability of B cells in vitro and augments their differentiation into antibody-secreting cells (IgM, IgG, and IgA) following activation via the CD40 antigen [32]. Furthermore, when IL-10 was provided exogenously in combination with IL-4 following CD40 activation, there was a tenfold expansion of the number of viable B cells during a 10-day culture [32]. The effects of IL-10 on B cells depend on the activation status of the B cells. Burdin et al. have provided experimental data to support an autocrine role for IL-10 in the growth and differentiation of CD40-stimulated B cells [6]. IL-10 was shown to promote apoptosis of *S. aureus*-activated B cells when IL-10 was

present during the initial activation, whereas it rescued B-cells from apoptosis if provided following *S. aureus* activation [18].

EBV and IL-10

EBV belongs to a group of DNA herpes viruses. Following primary infection, EBV tends to persist as a latent infection in human B cells. The EBV open reading frame (BCRF-l) expresses vIL-10, which has IL-10-like activity [40]. The vIL-10 gene was initially characterized as a "late" viral gene expressed during the lytic (productive) phase of EBV replication [17, 37]. However, it has also been suggested that vIL-10 is a latency gene that is critical for initiation as well as maintenance of EBV-driven B cell transformation [25]. As indicated earlier, vIL-10 shares many functions of huIL-10 and both have been demonstrated to have potent effects on the survival, growth and differentiation of human B cells [5, 27].

Finke et al. have shown that huIL-10 production can be induced in Burkitt lymphoma cells by infecting them with a non-defective EBV strain, but not with a strain that lacks EBNA-2 and LMP-1 [12]. Nagakomi et al. demonstrated that transfection of LMP-l alone is sufficient to stimulate huIL-10 gene expression and protein secretion by an EBV-negative B cell line. However, the highest levels of huIL-10 were detected in lymphoblastoid cell lines expressing all latent EBV antigens and activation markers. Thus, the EBV genome is critical for the induction of huIL-10 in immortalized B cell lines.

Recently vIL-10, as well as huIL-10, has been shown to down-regulate transport associated with antigen presentation (*TAP1*) gene expression in B lymphocytes. This results in impaired transportation of peptide antigen to the endoplasmic reticulum, their loading onto MHC class I molecules, and subsequent translocation to the cell surface [49]. Similar findings were reported when the RMA murine lymphoma cell line was transfected with IL-10 [33]. Therefore, EBV-induced IL-10 production may exert adverse effects on host immune surveillance during B cell lymphomagenesis through multiple mechanisms, (i) suppressing anti-viral activity of the immune system by inhibiting the production of monokines that normally induce IFNγ by T and NK cells [9], (ii) enhancing the survival and growth of B lymphocytes [1], (iii) suppressing EBV-specific cytotoxicity [24], and (iv) impairing cytotoxic T cell recognition of EBV-infected B cells by reducing the cell surface density of MHC class I molecules. Finke et al. proposed that, in vitro, the strong B-cell-activating effect of IL-10 may be important while in vivo the IFNγ-suppressing capacity may be critical for B cell infection and replication of EBV [12].

Experimental evidence for a role of IL-10 in EBV$^+$ and EBV$^-$ lymphomageneis

Mice with severe combined immunodeficiency (SCID) provide an excellent animal model to study human EBV lymphomagenesis. When SCID mice are injected with peripheral blood lymphocytes (PBL) from EBV-seropositive individuals, a high percentage of these mice develop fatal EBV$^+$ lymphoproliferative disease (LPD) of human B cell origin. Veronesi et al. noted that injection of human PBL depleted of CD4$^+$ T cells significantly delayed the onset of EBV-LPD in the huPBL-SCID mice, and injection of B cells alone did not lead to development of EBV-LPD [39]. This strongly suggests that CD4$^+$ T cells are required for the development of EBV-LPD in the huPBL-SCID mouse model. The cytokines produced by Th2 cells that can stimulate B cells are IL-4, IL-5, IL-6 and IL-10, and these may be involved in a paracrine pathway during lymphomagenesis in vivo [1]. huPBL-SCID mice that develop EBV-LPD were shown to have significantly higher ($P \leq 0.005$) levels of huIL-10 in the serum than control SCID mice that did not develop EBV-LPD [1]. Viral and murine IL-10 were not detected. Baiocchi et al. showed evidence of huIL-10 transcript and huIL-10 protein in EBV$^+$ human B cell tumors found in huPBL-SCID mice, as well as expression of the IL-10 [1]. Using concentrations of IL-10 found in vivo, these authors demonstrated that IL-10 could prevent programmed cell death of fresh EBV$^+$ human B cell tumors found in the SCID mice, in the absence of serum. Continued incubation with IL-10 alone induced tumor cell proliferation. IL-6, also produced by these EBV$^+$ tumors, had the same in vitro effects on EBV$^+$ B cell survival and proliferation as was found with IL-10. However, IL-10 has the additional property of deactivating host monocytes, as discussed above. Thus EBV has acquired the ability to induce cytokines that have seemingly redundant B cell survival and mitogenic effects, as well as some unique immunosuppressive effects. Consistent with this redundancy, the in vivo neutralization of either IL-10 or IL-6 does not reduce the incidence of fatal EBV-LPD in the huPBL-SCID mouse model (R. A. Baiocchi and M. A. Caligiuri, unpublished observations).

By analyzing cytokine gene expression at the single-cell level and using in situ hybridization in AIDS-related lymphoma, Emilie et al. showed that IL-10 was produced by malignant cells themselves [10]. Benjamin et al. evaluated B cell lines from patients with Burkitt's lymphoma and AIDS lymphoma and demonstrated high levels of huIL-10, the presence of high EBV titers, and a close association between EBV and IL-10 [3]. They postulated that IL-10 was a key factor leading to dysregulation of B cell growth and function in patients with AIDS lymphoma.

Masood et al. demonstrated the importance of IL-10 as a growth factor for AIDS-related B cell lymphoma and suggested an autocrine role for the cytokine [23]. Addition of huIL-10 antisense oligonucleotide in vitro inhibited IL-10 mRNA expression and protein production as well as the proliferation of all tumor-derived B-cell lines regardless of their EBV status. Addition of recombinant huIL-10 to the same B cell lymphoma lines that were pretreated with antisense oligonucleotide abrogated this inhibitory effect. Evaluation of fresh primary tumor tissue derived from patients with AIDS-related lymphoma showed similar responses particularly in the setting of mitogenic stimulation

with *S. aureus* Cowan I. Spontaneous lymphoblastoid cell lines, generated from patients with EBV-associated lymphoproliferative disorder without the addition of growth factors or virus, were shown to produce IL-6, IL-10, TNFα, and lymphotoxin α. Of all these cytokines produced by spontaneous lymphoblastoid cell lines, only IL-10 was shown to be a requisite autocrine growth factor in experiments using neutralizing antibodies [2].

Recent studies by Weber-Nordt et al. demonstrated the coincidence of EBV infection, IL-10 production and constitutive STAT1 and -3 activation in lymphoblastoid cell lines and Burkitt lymphoma cells [45]. Furthermore, Burkitt lymphoma cell lines lacking the EBV and IL-10 did not display constitutively active STAT binding. Thus, it is feasible that autocrine IL-10 production may lead to activation of STAT proteins in transformed B cells.

Clinical evidence in support of an association of IL-10 and B cell malignancies

Recent clinical evidence supports a role for IL-10 in the pathogenesis of B cell lymphoma. Several groups have documented the production of IL-10 by B cells derived from various lymphoproliferative disorders, such as acute lymphoblastic leukemia, chronic lymphocytic leukemia [12], Burkitt's lymphoma, and AIDS-associated lymphoma [3, 23]. The development of primary central nervous system lymphoma (PCNSL) in the eye was strongly associated with elevated vitreous levels of IL-10 relative to levels of IL-6 [47]. Moreover, in patients diagnosed with PCNSL, the risk for malignant involvement of the cerebrospinal fluid is about eight times higher when IL-10 levels exceed IL-6 levels [47].

Blay et al. reported elevated IL-10 levels in 46% of patients with active untreated non-Hodgkin's lymphoma (NHL), compared to none of the normal control subjects [4]. When the patients had achieved partial or complete remission, IL-10 was detected in only 8% and 4% respectively. Though IL-10 levels did not correlate well with the stage of the disease, those patients with detectable serum IL-10 levels had a significantly shorter overall ($P = 0.025$) and progression-free ($P = 0.03$) survival. This was particularly evident in patients with stage IV disease where the 5-year survival was 85% for those with undetectable IL-10 levels but 0% if IL-10 was detectable. Serum IL-10 was found to be an independent prognostic factor in multivariate analysis. Using the reverse transcription/polymerase chain reaction, Voorzanger et al. examined 54 NHL tumors and demonstrated expression IL-10 mRNA in all of them. The majority (61%) contained detectable amounts of IL-10 protein [41]. In 13 of the 54 patients, fresh tumor cell preparations were made and exogenous IL-10 was shown to increase their prolifertion significantly. What is more, IL-10, IL-6 and IL-2 had an additive effect on proliferation of tumor cell preparations, indicating a possible in vivo cooperative mitogenic effect of these cytokines in patients with NHL. Stasi et al. studied a group of previously untreated intermediate and high-grade NHL and identified a subgroup of non-responders who had elevated IL-10 and serum IL-2 receptor levels [36]. In addition, those patients who experienced relapse developed elevated IL-10 concentrations that were otherwise normal at presentation. Their data indicated that IL-10 was an important prognostic factor in patients with high tumor mass, and might identify those patients who would benefit from alternative therapeutic regimens. Again, IL-10 was undetectable in normal healthy controls.

Cortes et al. found no correlation between serum IL-10 and disease-free or overall survival in a cohort of 52 patients with diffuse large-cell lymphoma [8]. Serum levels of IL-10 were significantly higher ($P = 0.0000012$) in patients than in normal controls. Among the patients, those with B symptoms had the highest levels of IL-10. Interestingly, patients with serum IL-10 levels greater than 100 pg/ml appeared to have a favorable outcome. Further, the rate of complete remission tended to be higher in patients with elevated serum IL-10, although this difference was not statistically significant. The apparently conflicting results regarding the prognostic value of IL-10 in patients with non-Hodgkin's lymphoma may in part be due to differences in the assay sensitivity, therapeutic regimens used, and the histological subgroups of NHL studied.

In summary, the production of IL-10 appears to be relevant in some, but not all, human B cell tumors. This is consistent with the notion that a variety of molecular defects constitute the basis for malignant B cell transformation, and that only in some instances does such alteration in the genome lead to the overproduction of factors that promote tumor survival and growth relatively independently of host-derived factors. These properties, along with the potent immunosuppressive effects of IL-10, make its expression in virus-associated B cell lymphomas especially advantageous, where successful tumorigenesis is as much a result of a disarmed antigen-specific immune system as it is the result of autocrine production of tumor survival and growth factors.

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