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Review article

Interleukins as modulators of angiogenesis and anti-angiogenesis in tumors

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ABSTRACT

Interleukins (ILs) are secreted by leukocytes and macrophages and are involved in communication amongst leukocytes regulating numerous biological processes and immune responses. This review article analyzes the role played by ILs in the regulation of angiogenesis and anti-angiogenesis in both solid and hematological tumors.

1. Introduction

Interleukins (ILs) are secreted by leukocytes and macrophages and are involved in communication amongst leukocytes regulating numerous biological processes and immune responses. Interactions of ILs and their receptors with endothelial cells modulate angiogenesis and exert both pro-angiogenic and anti-angiogenic activity (Table 1).

2. Pro-angiogenic and anti-angiogenic activities of ILs

IL-1 isoforms (α and β) are secreted by activated macrophages and bind to three receptor antagonists [1]. IL-1 angiogenic activity is mediated by vascular endothelial growth factor (VEGF) and its inhibition reduces tumor growth, angiogenesis and metastatic potential [2]. IL-1β inhibits fibroblast growth factor (FGF)-induced angiogenesis [3], and in IL-1β deficient mice injected with B16 melanoma cells, no vascularization was observed [2].

IL-4 inhibits FGF-2 induced angiogenesis [4], and IL-5 triggers the release of VEGF from eosinophils [5]. IL-6 stimulates B-cell differentiation, acts as a pro- and anti-inflammatory factor, and is involved in anti-bacterial and anti-viral immunity [6]. IL-6 induces VEGF expression in different tumor cell lines [7]. IL-6 activation of STAT-3 drives angiogenesis inducing VEGF and FGF-2 release by tumor cells [8]. IL-6 induced angiogenesis in aortic ring assay [9] is associated to a defective pericyte coverage of new-formed blood vessels mediated by the Notch ligand Jagged1 [10] and angiopoietin-2 (Ang-2) [9]. Anti-IL-6 antibody restores pericyte coverage [9]. Moreover, IL-6 stimulates Notch3 and promotes breast cancer cells growth [11]. IL-6 induces resistance to anti-angiogenic molecules through induction of C-X-C motif chemokine 12 (CXCL-12) and secretion of angiogenic factors by immune cells [12]. Increased circulating levels of IL-6 are expression of a poor response to sunitinib and bevacizumab in hepatocellular carcinoma, renal cell carcinoma, glioblastoma and colorectal cancers [13–16].

IL-8 (CXCL8) binds to C-X-C motif receptor 1 and 2 (CXCR1 and CXCR2) [17]. Angiogenesis mediated by dendritic cells depends by IL-8 [18]. IL-8 binding to CXCR2 stimulates angiogenesis [19] and its expression correlates with tumor progression, angiogenesis, and metastatic potential [20–25]. Neutrophils angiogenic activity is in part mediated by IL-8 [26,27]. Angiogenesis is significantly increased in ischemic muscle of IL-10 deficient mice through an increase in VEGF levels [28].

IL-12 mainly secreted by dendritic cells [29], induces interferon gamma (IFN-γ) production, and exerts its anti-angiogenic activity in different experimental conditions [30–34]. IL-12 produced by monocytes-macrophages induces tumor regression due to a significant inhibition of angiogenesis [35]. IL-12 receptor (IL-12R) is expressed by natural killer (NK) and T cells [36], and suppress angiogenesis through NK cell cytotoxicity of endothelial cells [37]. In severe combined immunodeficient-non obese diabetic (SCID-NOD) mice, previously inoculated with non small cell lung cancer (NSCLC) cells expressing IL-12R in the lung and treated with IL-12, tumors are smaller and less vascularized as compared to controls [38]. IL-6 and VEGF are constitutively expressed by NSCLC cells and strongly reduced by IL-12 [38]. Moreover, IL-12 inhibits VEGF and matrix metalloproteinase-9 (MMP-9) and increased tissue inhibitor of MMP-1 (TMP-1) secreted by breast cancer cells [30].

Human pediatric acute myeloid leukemia (AML) cells express both chains of the IL-12R and IL-12 reduces the angiogenic activity of AML cells *in vivo* [39]. In IL-12-treated SCID-NOD mice previously inoculated with human U937 cells, tumor growth and angiogenesis are inhibited

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Table 1
Interleukins with pro-angiogenic and anti-angiogenic-activity.

Pro-angiogenic	*References*
IL-1	[2]
IL-5	[5]
IL-6	[7–16]
IL-8	[18–27]
IL-17	[42–56]
Anti-angiogenic	
IL-1β	[3]
IL-4	[4]
IL-10	[28]
IL-12	[29–41]
IL-18	[57–60]
IL-23	[66]
IL-25	[61]
IL-27	[62–68]

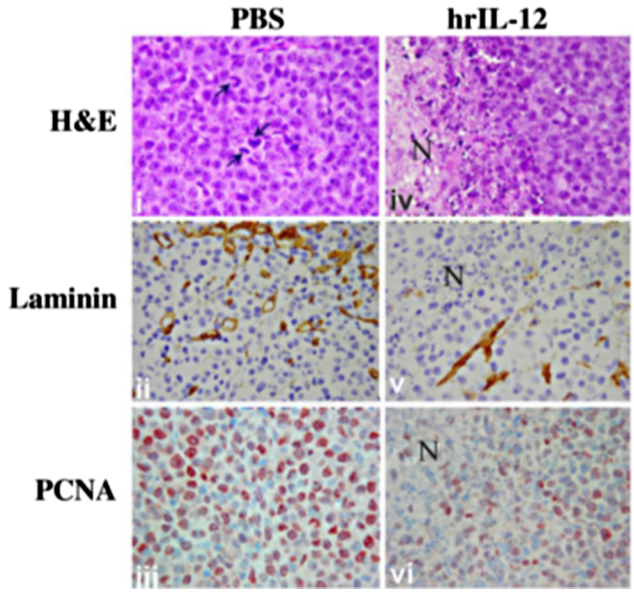

Fig. 1. Histologic and immunohistochemical features of tumors developed in PBS-treated (i-iii) and hrIL-12–treated (iv-vi) SCID/NOD mice 23 days after NCI-H929 tumor cell injection. NCI-H929 tumors are mostly formed by undifferentiated, proliferating (mitotic features indicated by arrows) blast cells that are large and pleomorphic and sometimes bi-nucleated or endowed with very prominent nucleoli (i). These tumors are supplied by a distinct network of mature microvessels, as assessed by laminin staining (ii), and show frequent PCNA expression (iii). In hrIL-12-treated mice, these morphologic features are frequently altered by the appearance of ischemic and hemorrhagic foci of necrosis (N; iv) associated with defective vascularization (v) and decreased tumor cell proliferation (vi). (Reproduced from 41).

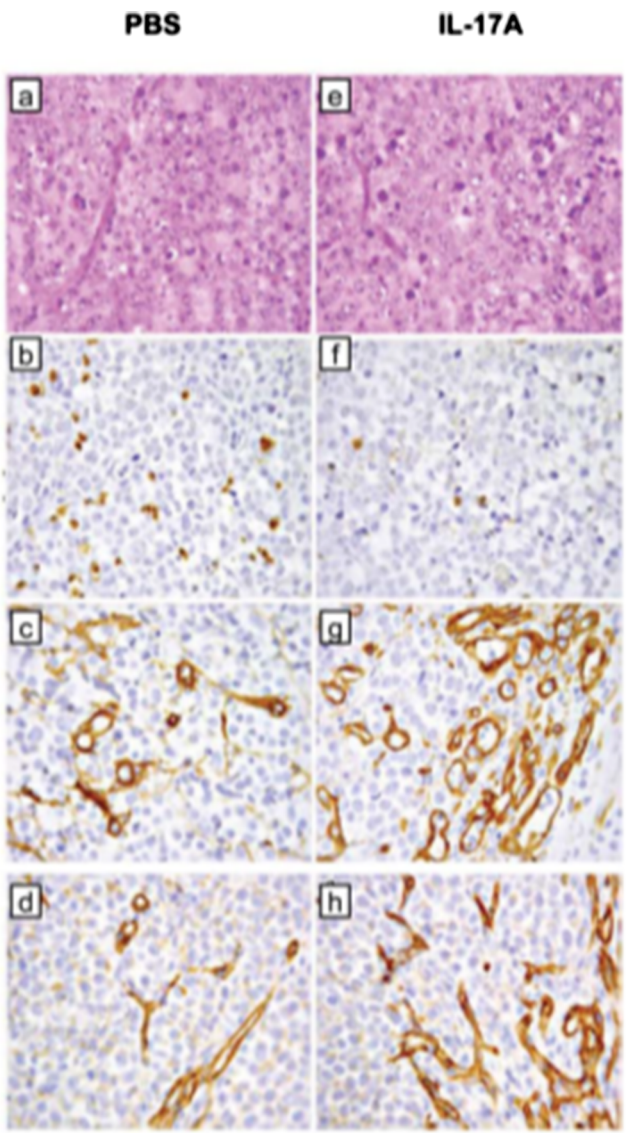

Fig. 2. Role of IL-17A on *in vivo* tumor growth and angiogenesis. (a) Volume of tumors grown s.c. in PBS or IL-17A treated mice 20 d after SUDHL-4 cell injection. Tumors developed after s.c. injection of SU-DHL-4 cells in PBS-treated SCID/NOD mice are formed by a mixture of small and large lymphoid cells with centrocytes and centroblasts morphology (a). These tumors display some apoptotic events (tunel assay (b)) and a distinct microvascular network (laminin immunostaining (c) and CD31 staining (d)). The histologic features of SU-DHL-4 tumors are not substantially altered by rhIL-17-A treatment (e), while apoptotic events appear less frequent (f) and the microvascular supply is clearly more developed (g-h), particularly at the tumor edge, in comparison with control tumors (Reproduced from 51).

[39]. The anti-angiogenic activity is a consequence of down-regulation of the expression of pro-angiogenic IL-8, CXCL-6, IL-6, and VEGF-C [39]. Also in SCID-NOD mice previously injected with IL-12Rβ2-transfected Raji Burkitt lymphoma cells are necrotic and less vascularized through an up-regulation of the angiostatic chemokine CXCL-9 [40]. Pre-treatment with IL-12 of supernatants from primary multiple myeloma (MM) cells reduces their angiogenic activity *in vivo* [41]. In mice injected with MM cells and treated with IL-12, the tumors are small and less vascularized (Fig. 1) [41]. This effect is associated to a down-regulation of angiogenic molecules (Ang-2, FGF-2, VEGF, IL-1β, IL-6) and up-regulation of angiostatic ones (CXCL-4, IFN-α, IFN-γ, and TIMP-2) [41].

IL-17 induces IL-8 release in tumors [42,43], and promotes tumor growth through IL-6 [44]. IL-17 production and poor prognosis are correlated to an increased expression of VEGF in colorectal cancer [45] and to a higher vascularization and inflammatory infiltration in hepatocellular carcinoma [46]. IL-17 modulates VEGF production in fibrosarcoma and osteoscarcoma [47,48], and inhibition of IL-17 suppresses CD31 and VEGF expression in tumors [49]. Pasche et al. [50]

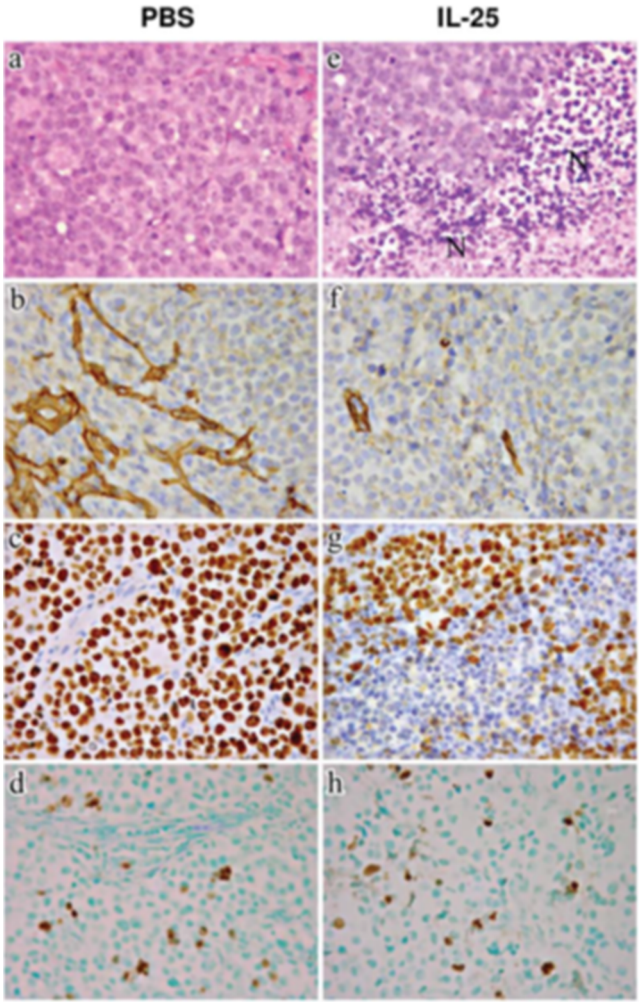

Fig. 3. Role of IL-25 on *in vivo* B-NHL growth. Tumors developed after s.c. injection of SU-DHL-4 cells in PBS treated SCID/NOD mice (a). These tumors displayed a distinct vascularization (b), a strong proliferative activity (c) and some apoptotic events (d). The histologic features of SU-DHL-4 tumors appeared heavily compromised by rhIL-25 treatment, since these tumors were characterized by wide areas of ischemic necrosis (N) (e), defective vascularization (f), and decreased proliferation (g), whereas apoptotic events (h) were comparable to those observed in control tumors (d) (Reproduced from 61).

realized a fusion protein, formed by the F8 antibody and murine IL-17. The resulted immune-cytokine selectively localized at the tumor vasculature, promoted angiogenesis.

IL-17A stimulates proliferation of B cell non Hodgkin lymphomas (NHL) enhancing tumor cell proliferation and angiogenesis through direct stimulation of endothelial cells and induction of pro-angiogenic gene expression in tumor cells (Fig. 2) [51]. Tumor infiltrating Th17 cells, and IL-17 signaling pathway are responsible of resistance to the anti-angiogenic and anti-tumor actions of VEGF blockade [52]. IL-17 enhances the expression of VEGF and Bv8 in bone marrow-derived myeloid cells and the expression of these two factors is reduced in IL-17 rc-/- bearing mice [52]. IL-17 recruits myeloid derived suppressor cells (MDSCs) and CD11b-positive Gr1-positive cells to promote tumor growth [53]. Th17 cell depletion or IL-17-blockage resulted in impaired angiogenesis as well as reduced VEGF production [54]. Finally, IL-17 inhibits expression of VEGF, IL-6 and IL-8 in hepatocellular carcinoma *in vitro* [55] and exerted a protective role in colon tumorigenesis via an inhibition of VEGF production [56].

IL-18 was discovered as an IFNγ-inducing factor and plays an immunomodulatory role on NK, T and Th1 cells. IL-18 inhibits angiogenesis *in vitro* and *in vivo* [57]. IL-18 is highly expressed in gastric cancer in association with a high microvascular density [58]. VEGF increases IL-18 production through regulation of reactive oxygen species (ROI) and the ERK pathway and blocking IL-18 in gastric cancer cells reduces VEGF-induced migration [58]. Adenovirus expressing IL-18 decreased VEGF and inhibited angiogenesis in renal cell carcinoma and melanoma [59], and endogenous IL-18 is an inhibitor of ischemia-induced neovascularization in the mouse hind limb [60].

Ferretti et al. [61] have demonstrated that IL-25 exert anti-tumor activity in two *in vivo* models of B-NHL lymphomas of germinal center origin, through anti-angiogenic activity and induction of ischemic necrosis (Fig. 3). IL-25 treatment down-regulates the expression of pro-angiogenic molecules, including VEGF-A, VEGF-C, angiopoietin like-3 (ANGPTL-3), CXCL-6, IL-6.

IL-27 induces the expression of anti-angiogenic cytokines CXCR9 and CXCR10 in melanoma [62], and inhibits angiogenesis in human NSCLC [63]. IL-27 exert anti-proliferative and anti-angiogenic effects in B-acute lymphocytic leukemia (B-ALL) [64], AML [65], B-cell lymphoma [66], and MM [67]. IL-27 inhibited MM cell growth, through reduction of the angiogenic activity of MM cells *in vitro* and *in vivo* [67]. IL-27 down-regulates the expression of angiogenic molecules, including Ang-1 and Ang-2, transforming growth factor beta1 and beta2 (TGF-β1 and TGF-β2), VEGF-A, -C, and -D, and up-regulates the expression of the angiostatic molecules CXCL-9 and CXCL-10 [67]. After injection of B-ALL and AML cells from pediatric patients into NOD/SCID mice, IL-27 treatment reduced *in vitro* B-ALL and AML cell proliferation, angiogenesis, and modulated the expression of different pro-angiogenic molecules [64,65]. IL-27 inhibited growth of human follicular and diffuse large B cell lymphoma through suppression of angiogenesis and induction of apoptosis [66]. Moreover, combined treatment of IL-23 and IL-27 amplified the anti-tumor and anti-angiogenic effects (Fig. 4) [66]. Di Carlo et al. [68] demonstrated that IL-27 significantly inhibited proliferation and reduced the angiogenic activity of prostate cancer cells down-regulating pro-angiogenesis molecules and up-regulating anti-angiogenesis molecules.

3. Concluding remarks

ILs may possess both tumor-promoting and anti-cancer effects. In fact, ILs are able to stimulate the immune system to attack cancer cells and eliminate tumors; in the meantime, ILs may also cause chronic inflammation, metastasis formation and immune escape of tumors.

The magnitude of the expression of angiogenic and angiostatic factors in a primary tumor correlates with both tumor growth and potential of spontaneous metastases. The above discussed studies have demonstrated that ILs exert either angiogenic or angiostatic effects on tumor growth (Table 1). These findings support the notion that therapy directed at either inhibition of angiogenic or increase of angiostatic activities of ILs may be a novel approach in the treatment of solid and hematological tumors.

A further understanding of ILs network and its abnormal regulation in cancer should lead to more successful therapeutic strategies to be added to the conventional therapeutic approaches to the cancer treatment.

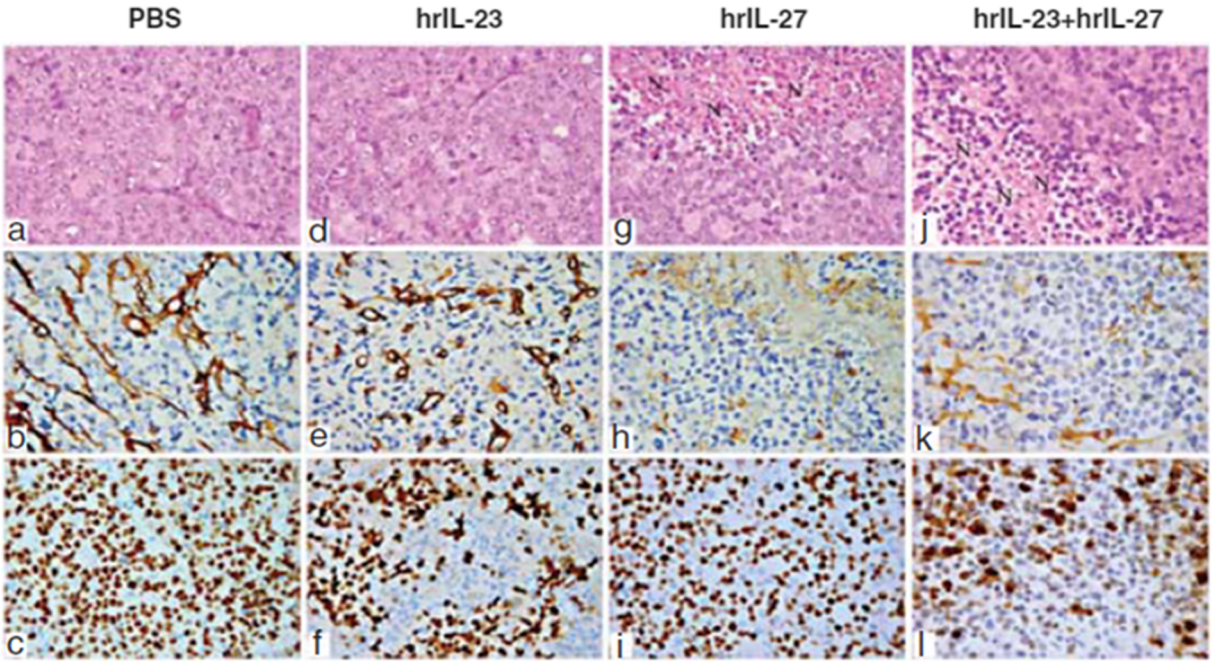

Fig. 4. *In vivo* anti-tumor activity of IL-23 and IL-27. Morphologic analysis of explanted tumors was assessed by hematoxylin and eosin (panel a, d, g and j); N in panel g and j indicate hemorrhagic necrosis areas. Tumors vascular network was evaluated by laminin immunostaining (panel b, e, h and k). Proliferative activity was assessed by Ki67 staining (panel c, f, i and l). (Reproduced from 66).

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