

## Vascular Endothelial Growth Factor and Its Relationship to Inflammatory Mediators

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**Abstract** Inflammation occurs in response to host injury or infection, as the result of an autoimmune disease, or in response to the development of a tumor. Although the immune system may be helpful in fighting the tumor, it may also fuel the tumorigenic process. In fact, recent data suggest a strong link between chronic inflammation, angiogenesis, and the development of cancer. For example, inflammation and scarring caused by recurring infections with *Mycobacterium tuberculosis* may be a cause for cancers of the lung. Inflammatory breast cancer exhibits increased angiogenesis and lymphangiogenesis and has a higher metastatic potential than noninflammatory breast cancer. Nonsteroidal anti-inflammatory drugs have been proposed as preventives for the development of colon carcinoma and ovarian cancer. Inhibition of nuclear factor- $\kappa$ B contributes to the proposed mechanism of action. Inflammatory cytokines, including interleukin-6, serve as autocrine and paracrine growth factors for several cancers, and high levels of these cytokines may correlate with a poor prognosis and increased production of angiogenic factors. The state of the art of our understanding of this critical interaction is reviewed.

### Background

Chronic inflammation has become a recognized risk factor for epithelial-derived malignancies (1, 2). Chronic inflammation can be caused by infection, autoimmune disease, malignant and benign tumors, or other pathologies and results in the infiltration of inflammatory cells at specific sites in the body. These so-called tumor-infiltrating lymphocytes include macrophages (3), T cells, B cells, natural killer cells, neutrophils, and granulocytes (4, 5). These cells excrete copious amounts of inflammatory cytokines into the microenvironment, including interleukin-6 (IL-6), IL-1 $\alpha$ , IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , and oncostatin M. For example, T lymphocytes and macrophages are the predominant inflammatory cells present in malignant prostate epithelium (4). These tumor-infiltrating lymphocytes play an important role in the induction of cyclooxygenase-2 (COX-2) expression by malignant prostate epithelial cells (4). It is thought that cytokines released by the T cells and macrophages are responsible for COX-2 up-regulation. COX-2 is another important inflammatory mediator that up-regulates vascular endothelial cell growth factor (VEGF) expression in tumor cells, thereby fueling angiogenesis. COX-2 is also up-regulated in stromal lesions of the gastrointestinal tract, particularly in

the stomach. Tumor-infiltrating macrophages have been identified in these lesions, and COX-2 was expressed in 80% of these tumor cells (3).

Inflammation is thought to contribute to the development and progression of various cancers, including lung (6), breast (7), gastrointestinal (1, 2, 8), ovarian (9), prostate (4), skin (10), and liver cancers (11). For example, lung cancer, which is caused in large part by tobacco carcinogens, may in part be caused by the inflammatory process that is a consequence of smoking (12). In addition, lung cancer may develop in scar areas from tuberculosis infection (6). Inflammatory breast cancer exhibits higher expression than noninflammatory breast cancer of proangiogenic molecules, such as angiopoietin-1, VEGF, and VEGF receptors. Inflammatory breast cancer also has a higher metastatic potential than noninflammatory breast cancer (7). As mentioned previously, stromal tumors of the gastrointestinal tract express a high level of the inflammatory mediator COX-2. Nitric oxide, another molecule produced by inflammatory cells, contributes to carcinogenesis during chronic inflammation in the gastrointestinal tract by functioning as an angiogenesis factor, by causing DNA lesions, and by blocking apoptosis (1). Infection with *Streptococcus infantarius* is associated with the presence of colorectal tumors in humans (8). Proteins isolated from this bacterium exhibit proinflammatory and procarcinogenic properties in rats, thus linking inflammation with colon carcinogenesis (8). Interestingly, nonsteroidal anti-inflammatory drugs have been proposed as preventives for the development of colon carcinoma and ovarian cancer because of epidemiologic studies suggesting a reduction in the risk of developing these cancers while taking these drugs (9).

Prostatitis and sexually transmitted infections are also associated with increased prostate cancer risk, whereas the intake of anti-inflammatory drugs and antioxidants decrease the risk of prostate cancer (13). Proliferative inflammatory atrophy lesions containing activated inflammatory cells may be

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precursors to prostatic intraepithelial neoplastic lesions and prostatic carcinomas (13). With regard to the skin, studies of the inflammatory cell infiltrate in nontumorigenic, pretumorigenic, and tumorigenic keratinocytic hyperproliferative lesions show an increase in macrophages, CD3<sup>+</sup> T cells, B cells, and cytotoxic T cells in all of the pathologic lesions when compared with normal skin (10). This increase in inflammatory cells may be due to altered antigenicity of the pathologic lesions (10). Chronic hepatitis B, an inflammatory process, predisposes infected patients to hepatoma. An assay has been developed to detect epsilon-DNA adducts, which may serve as a marker for assessing the progression of inflammatory "cancer-prone" diseases, such as hepatitis B virus infection (11). As molecular techniques are perfected, markers of inflammation may prove to be useful for predicting the potential for chronic inflammation to contribute to the development or progression of malignant disease.

### Clinical-Translational Implications

**Inflammation and its effect on VEGF expression and angiogenesis.** Inflammatory cytokines can enhance the tumorigenic process by up-regulating important mediators of angiogenesis, such as VEGF and IL-8. The vascular changes associated with angiogenesis occur not only in cancer but also in diseases in which chronic inflammation plays a major role, including cardiovascular disease (14), rheumatoid arthritis (15), diabetic retinopathy (16), delayed type hypersensitivity (17), and asthma (18). IL-1 $\beta$  (19), IL-1 $\alpha$  (20, 21), IL-6 (22), oncostatin M (23), tumor necrosis factor- $\alpha$  (24), and IL-8 (25) up-regulate VEGF expression using various molecular pathways and often function synergistically.

Although different signaling pathways are used, several key mediators seem to be necessary for the induction of VEGF expression by inflammatory cytokines in tumor cells, airway smooth muscle cells, cardiac smooth muscle cells, retinal vascular endothelium, and in the synovium of rheumatoid arthritis joints. For example, IL-1 $\beta$  induces VEGF production in gastric cancer cells through Erk- and p38-dependent pathways (ref. 19; Fig. 1). p38 kinase also acts to stabilize COX-2 transcripts in variant human mammary epithelial cells. These cells exhibit phenotypes important for the development of malignancy (26). The activation of p38 results in the up-regulation of COX-2, another inflammatory mediator that can increase VEGF production.

Oncostatin M treatment induces a threefold increase in VEGF production in astrogloma cells by binding to its receptor, which causes dimerization of gp130 molecules and subsequent phosphorylation and activation of signal transducer and activator of transcription 3. The addition of IL-1 $\beta$  to oncostatin M results in a 7-fold increase in VEGF production (23). Signal transducer and activator of transcription 3 can either bind the VEGF promoter alone or in a complex with Sp1 and Sp3 transcription factors (27). Similar pathways are activated by oncostatin M and IL-1 $\beta$  to increase VEGF production in asthma and may contribute to airway remodeling (28). Revascularization of the myocardium may also occur in part via oncostatin M induction of VEGF (14).

IL-6, which shares the gp130 signaling molecule with oncostatin M, also up-regulates VEGF expression in several tumors via the gp130 Janus-activated kinase/signal transducer

and activator of transcription 3 pathway (see Fig. 1). This type of up-regulation has been observed in non-small cell lung cancer (22), gastric carcinoma (29), prostate cancer (30), and glioblastoma (27) and may be vital to the angiogenic process that occurs in tumors to maintain and/or drive their growth. Interestingly, plasma levels of IL-6 and VEGF are significantly correlated in breast cancer patients (31). IL-6 also induces the dose-dependent release of VEGF from platelets, further linking the inflammatory process with angiogenesis (31).

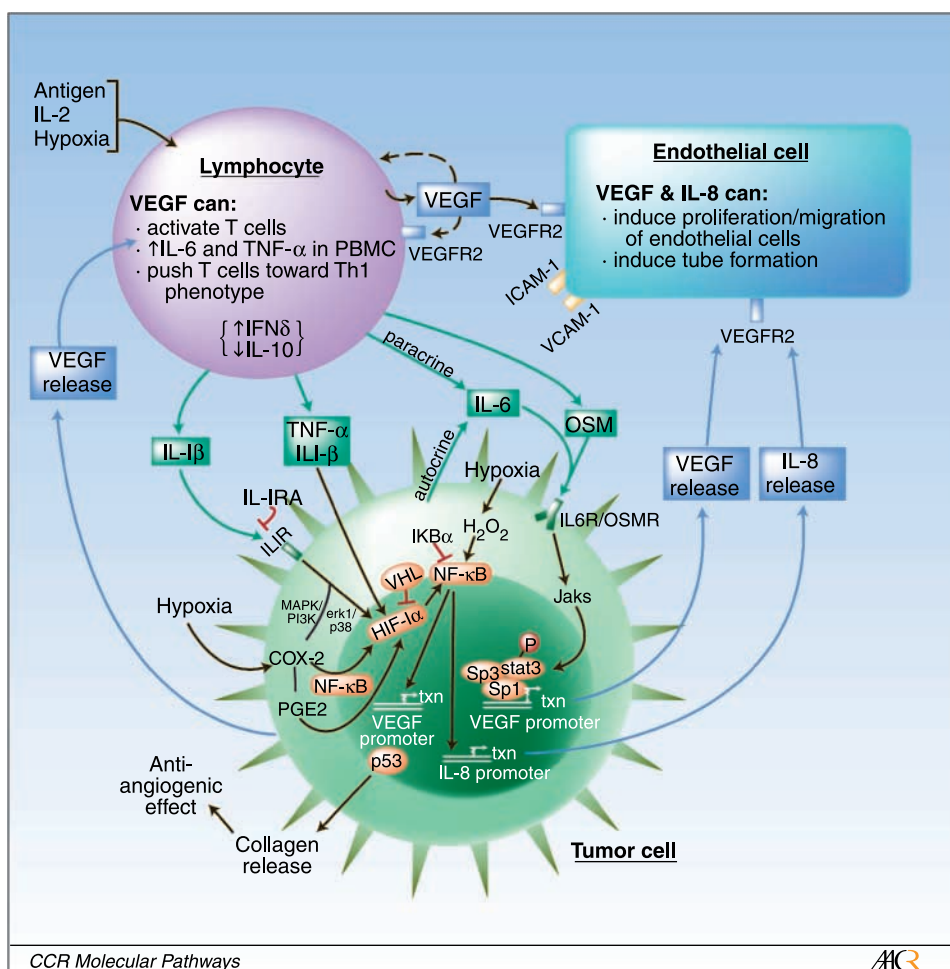
Another common pathway triggered by inflammatory cytokines involves the nuclear factor- $\kappa$ B (NF- $\kappa$ B) transcription factor. NF- $\kappa$ B activates VEGF and IL-8 gene expression by binding to NF- $\kappa$ B sites in the promoter regions of these genes (32). Inhibitors of NF- $\kappa$ B decrease the levels of VEGF produced in leukemia, glioma, and rheumatoid arthritis (33–35). Overexpression of inhibitor of NF- $\kappa$ B (I $\kappa$ B $\alpha$ ) in oral carcinoma also results in decreased VEGF levels (36). In addition to direct activation of NF- $\kappa$ B by various inflammatory cytokines, NF- $\kappa$ B-mediated VEGF expression can also be induced by other molecules or conditions.

For example, hypoxic conditions that occur in the tumor microenvironment can also induce NF- $\kappa$ B-mediated VEGF and IL-8 gene expression in tumor cells. Hypoxic conditions lead to the formation of hydrogen peroxide, which directly activates NF- $\kappa$ B (37, 38). Hypoxia also induces COX-2 expression, which then activates the hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) transcription factor through NF- $\kappa$ B (ref. 39; Fig. 1). Genes activated by HIF-1 $\alpha$  include proangiogenic molecules like VEGF, *heme oxygenase-1*, *inducible nitric oxide synthase*, and COX-2 (38). HIF-1 $\alpha$  can also be induced by IL-1 $\beta$  in endothelial cells (39). IL-1 and tumor necrosis factor- $\alpha$  stimulate HIF-1 $\alpha$ -mediated gene expression even during normoxic conditions. Further study is needed to determine how much of tumor cell VEGF production is induced by inflammatory cytokines and how much is due to other factors such as hypoxia.

COX-2 can also up-regulate HIF-1 $\alpha$  by causing the formation of prostaglandin E<sub>2</sub> (39). Prostaglandin E<sub>2</sub> is found in chronic inflammatory sites and in tumor sites (40). Prostaglandin E<sub>2</sub> strongly promotes angiogenesis in part by up-regulating HIF-1 $\alpha$  (38, 39). HIF-1 $\alpha$  induces VEGF and IL-8 gene expression by up-regulating NF- $\kappa$ B (39). As mentioned above, hydrogen peroxide can directly activate NF- $\kappa$ B so that HIF-1 $\alpha$ -negative colon cancer cells still make IL-8 by direct NF- $\kappa$ B activation (37). Hence, HIF-1 $\alpha$  activates many genes crucial to the angiogenic process and is an important transcription factor that links the inflammatory and angiogenic/oncogenic pathways (ref. 39; see Fig. 1).

HIF-1 $\alpha$  is normally targeted by the Von Hippel-Lindau gene product (VHL) for degradation. VHL is often mutated in renal cell carcinoma and has been identified as a tumor suppressor gene (41). When VHL is inactive because of mutation, HIF-1 $\alpha$  avoids degradation and dimerizes with HIF $\beta$ , leading to increased VEGF production (41).

Another tumor suppressor gene that may play a role in angiogenesis is p53. p53 is a positive transcription factor for the  *$\alpha$ (II) collagen prolyl-4-hydroxylase* gene [ *$\alpha$ (II)PH*]. Production of this enzyme results in the release of types 4 and 18 collagen. Types 4 and 18 collagen are antiangiogenic. Either p53 or collagen type 4/18 inhibits the growth of primary human endothelial cells (42). The  $\alpha$ (II)PH enzyme inhibits tumor growth in mice (42). When p53 is mutated, there is no collagen



**Fig. 1.** Complex relationship among tumor cells, cells of the immune system, and vascular endothelial cells. Lymphocytes respond to the tumor by secreting various inflammatory cytokines, including IL-1 $\beta$ , IL-6, tumor necrosis factor- $\alpha$  (*TNF- $\alpha$* ), and oncostatin M (*OSM*; green). These cytokines induce proliferation of the tumor cell and up-regulation of the *VEGF* gene through either the gp130/Janus-activated kinase (*Jak*)/signal transducer and activator of transcription (*Stat*) pathway (IL-6 and oncostatin M), or extracellular signal-regulated kinase (*Erk*)/p38, mitogen-activated protein kinase (*MAPK*), and phosphatidylinositol-3 kinase (*PI3K*) pathway (IL-6 and IL-1 $\beta$ ). These second messenger pathways activate various transcription factors, including signal transducer and activator of transcription 3 (IL-6 and oncostatin M) and NF- $\kappa$ B (IL-1 $\beta$  and TNF- $\alpha$ ). Signal transducer and activator of transcription either binds the *VEGF* promoter itself or as a complex with Sp1 and Sp3 transcription factors. NF- $\kappa$ B up-regulates transcription from both the *VEGF* and IL-8 promoters. VEGF can also be induced by IL-1 $\beta$  acting through COX-2 and prostaglandin *E*<sub>2</sub> (*PGE*<sub>2</sub>). These inflammatory mediators then up-regulate the HIF-1 $\alpha$  transcription factor, which activates NF- $\kappa$ B, resulting in increased VEGF expression. VEGF up-regulation can also be induced by hypoxic conditions. IL-1RA, VHL, p53, and I $\kappa$ B $\alpha$  indicate points of inhibition (red). VEGF and IL-8 released from the tumor cell (blue) can then act on endothelial cells and lymphocytes causing the inflammatory and angiogenic changes indicated. Activated T lymphocytes make VEGF and express VEGFR2, making them responsive to VEGF as described. IL-20 also up-regulates certain angiogenic proteins in endothelial cells as indicated. Intercellular adhesion molecule-1, ICAM-1; vascular cell adhesion molecule-1, VCAM-1.

type 4 or 18 release, which results in increased angiogenesis and tumor growth. p53 mutations may also result in IL-6 over-expression (43). This is especially relevant in tumors that express high constitutive levels of IL-6, use IL-6 as an autocrine growth factor, and contain a mutated p53 gene (43). Mutant p53 has also been identified in the synovial cells of arthritic joints, as they have high levels of IL-6 (44). p53 overexpression, which is indicative of the presence of mutant p53, has been identified in neoplastic skin lesions and also occurs in some inflammatory skin lesions. Normal skin can also exhibit p53 protein overexpression in the context of age and sun exposure (45). Interestingly, an aberrant p53 status is also related to IL-8 expression in non-small cell lung cancer (46). Thus, mutation of p53 results in the overexpression of autocrine growth factors, which may also be anti-apoptotic, and in the loss of anti-angiogenic mechanisms, resulting in increased tumor growth and vascularity.

Proinflammatory cytokines produced by tumor-infiltrating lymphocytes contribute to the up-regulation of IL-8 and VEGF in various tumors. This increase in angiogenic factor production results in increased vascularity of tumors and translates to greater metastatic potential and tumor progression in cancer. In chronic inflammatory conditions, including diabetic retinopathy and rheumatoid arthritis, increased angiogenic factor production may exacerbate chronic inflammation by increasing blood supply to the area.

**VEGF and its effect on inflammation.** It is quite clear from recently published literature that inflammatory mediators have a significant effect on the process of angiogenesis, mainly through up-regulation of VEGF and IL-8. The reverse is also true. VEGF, IL-8, and other pro-angiogenic factors can influence the inflammatory process in several ways.

VEGF is an important molecule in rheumatoid arthritis (15) and in T-cell-mediated immunity. Collagen-induced arthritis

in mice treated with an anti-VEGF peptide results in decreased IL-6 serum levels and decreased severity of the disease (47). Blocking VEGF, and thus angiogenesis, in rheumatoid arthritis can potentially decrease the nutrient supply to the synovium, inhibit leukocyte adhesion and migration, and decrease cytokine production by activated endothelial cells (47). PTK787/ZK222584, the VEGF receptor tyrosine kinase inhibitor, also causes significant anti-arthritis effects in animal models of rheumatoid arthritis (48). VEGF also induces peripheral blood mononuclear cells to produce increased levels of tumor necrosis factor- $\alpha$  and IL-6, with higher levels produced in the synovial fluid mononuclear cells from rheumatoid arthritis patients than from healthy controls (47). Levels of VEGF used for dose-dependent stimulation of cytokine production in mononuclear cells were 0.1 to 10 ng/mL, with the lower concentrations being more physiologically relevant (47). Primary T cells stimulated with antigen typically produce 0 to 225 pg/mL VEGF protein (49).

Antigen-, IL-2-, or hypoxia-activated T cells can produce VEGF and express VEGFR2 (ref. 49; Fig. 1). VEGF production can push T cells toward a Th1 phenotype by increasing the production of IFN- $\gamma$  and decreasing the production of IL-10 (49). A Th1 phenotype is associated with increased IL-2 and IFN- $\gamma$  expression and more cytotoxic T-cell activity. In addition, encephalitogenic T cells stimulated in the presence of VEGF cause more severe and prolonged encephalomyelitis. Thus, T cells can play a role in angiogenesis by delivering VEGF to inflammatory sites, and VEGF can augment T-cell differentiation, again showing the interdependence of these two processes (49).

In contact hypersensitivity, VEGF production is up-regulated in murine skin after challenge with dinitrofluorobenzene (50). Administration of an anti-VEGFR-2 monoclonal antibody (DC101) results in a decreased contact hypersensitivity response and a reduction in IFN- $\gamma$  expression in the skin. VEGFR-2 blockade also significantly reduces vascular enlargement and edema formation in the skin during challenge in contact hypersensitivity. In addition to contact hypersensitivity, delayed type hypersensitivity responses in mice are increased when VEGF is overexpressed (17).

VEGF increases vascularity at the site of inflammation, causing the reaction to be more severe. The VEGF produced by T cells, synovial cells, smooth muscle cells, or epithelial cells promotes the formation of new blood vessels by acting on nearby endothelial cells. Treatment of human vascular endothelial cells with VEGF or IL-20 results in the production of basic fibroblast growth factor, additional VEGF, IL-8, matrix metalloproteinase-2, and matrix metalloproteinase-9 (ref. 51; Fig. 1). These factors help to induce the proliferation and migration of pericytes and endothelial cells as well as aid in tube formation (25, 51), resulting in new blood vessel formation. VEGF production by tumor cells also results in the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on the surface of endothelial cells (52). These molecules aid in the adhesion of leukocytes to endothelial cells. The up-regulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 by VEGF can be inhibited in a model of skin inflammation by hepatocyte growth factor (52), presumably through inhibition of NF- $\kappa$ B. Thus, VEGF can enhance inflammatory processes, resulting in more severe inflammation. Blocking VEGF production in chronic inflammatory diseases may become an important means of ameliorating the severity of some of these pathologies.

## Therapeutic Implications

The idea that inflammation and angiogenesis are interdependent processes aiding the growth and spread of cancer should be considered when treating various tumors. Irradiation and chemotherapy may initially down-regulate inflammatory cytokines and tumor cell proliferation; however, there is a rebound of tumor cell proliferation and cytokine levels after treatment is discontinued (36, 53). As a result of these cytokines, VEGF production by tumor cells will increase, and tumors will become more vascularized. Clinicians may have to consider a multi-pronged approach that includes anti-cytokine, anti-VEGF, and cytotoxic therapy together, while monitoring patients for effectiveness and toxicity. Based on the literature linking inflammation with angiogenesis and tumor growth, there are several logical targets to consider when designing treatment protocols for various cancers.

Tumors that secrete copious amounts of IL-1 or IL-6 should be considered as candidates for anti-cytokine therapy, along with other treatments. This strategy may be effective due to direct interference with the autocrine or paracrine growth factor signal, or indirectly by suppressing angiogenesis. For example, in xenografts of SMEL, a human melanoma cell line constitutively producing IL-1, systemic treatment with IL-1 receptor antagonist results in significant inhibition of xenograft growth and neovessel density. Gene expression analysis of these treated cells showed a marked down-regulation of IL-8 and VEGF (54). Similarly, the anti-IL-6 receptor monoclonal antibody (MRA) inhibits IL-6 and VEGF production in human mesothelioma cell lines (55). This same anti-IL-6R antibody is successful in reducing serum VEGF levels in rheumatoid arthritis patients (56). Phosphodiesterase-4 inhibitors (so-called selective cytokine inhibitory drugs; CC-10004 and CC-1088) are also effective in reducing both IL-6 and VEGF production in myeloma and endothelial cell cocultures (57). Transcription factors, specifically NF- $\kappa$ B because of its pivotal role in inflammation and angiogenesis, also provide a logical target for therapy (refs. 32–36; Fig. 1).

Some drugs already show multiple effects. Drugs aimed specifically at angiogenesis or cytokine production frequently affect both arms of the process. For example, bortezomib, the anti-angiogenic proteasome inhibitor, down-regulates VEGF, angiopoietin-1, angiopoietin-2, insulin-like growth factor, and IL-6 in a dose-dependent manner in endothelial cells from multiple myeloma patients (58). Anti-angiogenic drugs that show promise in cancer treatment are also effective in the treatment of chronic inflammatory diseases. The angiogenesis inhibitor PTK787/ZK222584 is a tyrosine kinase inhibitor that has both anti-tumor and anti-arthritis effects in models of rheumatoid arthritis (48). Sorafenib and Sutent are two other protein tyrosine kinase inhibitors showing promise in renal cell carcinoma and other tumors (59). Bevacizumab, which is undergoing clinical trials for renal cell carcinoma (41), also shows promise as a treatment for age-related macular degeneration (60).

Atiprimod {2-(3-diethylaminopropyl)-8,8-dipropyl-2-azaspiro[4,5] decane dimaleate} has anti-inflammatory activities in animal models of rheumatoid arthritis and is well tolerated in phase I trials (61). Atiprimod also inhibits the proliferation of multiple myeloma cell lines *in vitro* by inhibiting signal transducer and activator of transcription 3 activation, thereby

blocking the signaling pathway of IL-6, an important growth factor for multiple myeloma (62). Atiprimod is being studied in phase I clinical trials for patients with advanced cancer, with activity shown in carcinoid tumors (63). Many other tumors, including metastatic renal cell carcinoma may prove to be suitable for treatment by these drugs that target not only angiogenic factors, but growth factors as well.

The processes of inflammation and angiogenesis are intimately linked. The immune system reacts to the presence of a tumor. Thus, inflammatory cells release many factors that

can aid in the release of VEGF and IL-8 by the tumor, resulting in increased tumor vascularity and growth. The immune response to the tumor is typically not enough to prevent tumor growth and may actually contribute to its growth and metastatic potential by aiding in the formation of blood vessels that feed and nourish the tumor and carry tumor cells to other parts of the body. This idea that inflammation and angiogenesis are strongly linked in the formation of cancer should be taken into consideration when considering therapeutic options.

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