

Tumor Inflammatory Angiogenesis and Its Chemoprevention

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Abstract

The importance of angiogenesis for the growth of tumors is widely recognized. Drugs that successfully target the endothelium, such as antivascular endothelial growth factor antibodies, are beginning to have an effect on the life expectancy of cancer patients. However, the endothelial cell is not the only possible target for antiangiogenic therapy or prevention of vascularization (angioprevention). It is evident from the literature that native immune cells recruited into tumors in turn stimulate the endothelium and are responsible for an indirect pathway of tumor vascularization. Inflammation-dependent angiogenesis seems to be a central force in tumor growth and expansion, a concept supported by the observation that the use of "classic" anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs, leads to angiogenesis inhibition. The mechanisms of inflammatory angiogenesis provide new approaches to target, cure, or even better, prevent tumor angiogenesis by treatment with synthetic or natural agents with anti-inflammatory properties. We propose chemoprevention of inflammatory angiogenesis as a way of checking the cancer before it progresses. (Cancer Res 2005; 65(23): 10637-41)

Background

The "normal" cell accomplishes tasks assigned by genetics, differentiative programs, and information from neighboring cells, the natural situation termed "homeostasis" from the Greek words *homeo* for "same" and *stasis* for "steady."

Physiologic stress or pathologic conditions require adaptation of both the cell and the microenvironment. When these stimuli exceed the capacity of the cell to react and then return to equilibrium, disrupting homeostasis, we speak of "injury," a broad definition of a wide range of situations. Inflammation is the primary and most important reaction to tissue and cell damage. Closely interlaced with the process of repair and reconstruction, the inflammatory response involves, after an initial leukocyte intervention, stromal and endothelial cell activation as well. Acute inflammation is a critical protective response to assaults by pathogens, toxins, and physical damage. However, should the host be unable to resolve the cause, the inflammatory response degenerates to become chronic, a condition causally associated with an increasing number of pathologies, including cancer.

The role of inflammation in the promotion of carcinogenesis was originally proposed by Virchow in 1863; recently, this concept has re-emerged and inflammation is now invoked as a key factor in

many cancers (1). The tumor cell, having lost its original growth control program, alters the microenvironment and recapitulates a range of effects typical of an injury. In addition to recruiting WBC, one of the actions of a growing tumor is to stimulate the formation of new blood vessels—the angiogenesis process.

Most of the studies on angiogenesis in tumor development, and on antiangiogenesis as a therapeutic approach, have focused on the endothelial cell. This is based on the observation that many tumor cell lines have been shown to directly stimulate the endothelium. However, recent data shows that the inflammatory cells infiltrating the tumor, which seem to be part of a normal response to tissue remodeling, besides being a defense mechanism, can in turn excite and recruit endothelial cells.

This indirect effect of the tumor infiltrate on angiogenesis has two major implications that we will discuss. First, that inflammation may be responsible for a substantial portion of tumor vascularization in what we call "inflammatory angiogenesis," with leukocytes acting as angiogenesis initiators. Second, that combating inflammation with appropriate drugs or substances could prevent inflammatory angiogenesis in carcinogenesis.

Evidence for the Role of Innate Immune Cells in Physiologic Angiogenesis

There is a tight interplay between innate immune and endothelial cells: they share a common embryonic origin, and endothelial cells mediate leukocyte recruitment into tissues. In turn, inflammatory leukocytes (neutrophils, macrophages, and others) release a number of factors that influence endothelial cell behavior [vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), matrix metalloproteinase-2 (MMP2), and interleukin-8 (IL-8)]. Two particularly suggestive examples of how the evolution has linked inflammation and angiogenesis in normal physiology are uterine vascularization in the estrous cycle and the development of vasculature in the intestine. In the endometrium, upon estrogen treatment, the vessels become enriched with adherent neutrophils that sustain vascular proliferation by producing VEGF (2). Another example of physiologic inflammation-driven angiogenesis is in the development of intestinal vessels. Elegant studies by J.I. Gordon and collaborators have shown that the lack of bacterial colonization of the intestine blocks the normal development of the villous capillary network. Germ-free mice have fewer (50% less) intestinal capillaries that are scarcely interconnected. This proangiogenic activity, provided by intestinal Paneth cells, is apparently mediated by the release of angiogenin 4; a soluble peptide originated as a microbicidal and evolved into a proangiogenic molecule (3). Extrapolating these observations to cancer, these data suggest that inflammatory leukocytes might provide the angiogenic stimulus in the initial phases of tumorigenesis, as well as growth stimulus permitting accumulation of further mutations that eventually render the tumor inflammation-independent and malignant. Recent studies that further support this concept will be addressed by inflammatory cell type.

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The Role of Neutrophils in Tumor Angiogenesis

Neutrophils, previously largely ignored in the context of tumors and angiogenesis, now seem to play a potentially important role. Initial studies in the *in vivo* Matrigel model suggested that these cells might play a lead role in vessel formation induced by laminin-derived SIKVAV peptide, which promotes angiogenesis weakly in neutropenic mice related to control mice (4). Furthermore, the HIV viral transactivator protein Tat activates neutrophils as part of its angiogenic activity (5). In skin carcinogenesis models, the requirement for MMP2 expression in tumor development was localized in a bone marrow compartment later identified as granulocytes (6). The neutrophil chemokine IL-8 and its relatives that are ligands for the chemokine receptor CXCR2 are well-known angiogenic factors. Although IL-8-driven angiogenesis in the cornea apparently uses direct IL-8-endothelial interactions, in other models it is neutrophil-dependent, as neutropenia abrogates IL-8- and GRO- α -induced angiogenesis in the *in vivo* Matrigel model (7). One required factor in this process is neutrophil release of VEGF upon stimulation with a CXCR2 ligand (8). Thus, the picture that emerges in angiogenesis induced by these chemokines is that of neutrophil recruitment followed by VEGF and MMP9 release that subsequently brings on endothelial cell invasion and vessel formation. Recently, this has been shown in a tumor model system: IL-8-induced, neutrophil-mediated angiogenesis was found to play a key role in tumor progression related to *ras* oncogene expression (9). These observations support a role for granulocytes in driving cancer development and progression. If the number of neutrophils in peripheral blood mirrors the situation in the tumor tissue, these data could support the investigation of leukocyte-targeted therapies as an anticancer strategy. Interestingly, recent studies have affirmed a correlation between neutropenia and efficacy in chemotherapy (10). Although neutropenia obviously reflects the intensity of the cytotoxic response, what if neutropenia also reflected the reduction of subsequent tumor inflammatory and stromal support?

Tumor Monocyte-Macrophage Phenotypes and Angiogenesis

Tumor-associated macrophages are known residents in most neoplastic tissues, where they seem to actually orchestrate and promote tumor growth. Importantly, they can be found closely with the very early stages of tumor development, underlying areas of hyperplasia and atypia, suggesting that macrophages themselves are a driving force, directly contributing to pre-neoplasia (11). Interestingly, it has become apparent that, like specific immunity, these cells can assume different phenotypes based on environmental stimuli, in which the M1 phenotype is associated with active microbial killing, whereas the M2 phenotype is associated with tissue remodeling and angiogenesis (1). In the growing tumor, macrophages seem to be skewed to the M2 phenotype that favors tissue growth, remodeling, and angiogenesis. However, a sufficiently strong activation of macrophages to the M1 phenotype can provide the tumor rejection observed in many experimental immunotherapy protocols. A novel aspect of inflammatory angiogenesis is the discovery of a new monocytic population (called Tie-2-expressing monocytes) recently found to have a primary role in angiogenesis in a glioblastoma model (12). The Tie-2-expressing monocytes accounted for a substantial degree of tumor vascularization, and genetic deletion of these cells blocked glioblastoma angiogenesis.

Role of Other Inflammatory Cells

Additional immune cell populations also seem to be effective promoters of angiogenesis. For example, myeloid suppressor cells have a phenotype expressing both macrophage and granulocyte markers that are associated with repression of the specific immune system, including high levels of arginase that alters the disposition of signaling molecules required by T cells (13). Recently, these same cells have been shown to participate in tumor angiogenesis, providing soluble factors such as MMP9 and VEGF, as well as by directly incorporating into the vessel walls (14).

Likewise, mast cells, which promote tumorigenesis in skin cancer models (6), are linked to angiogenesis induction in several tumor types (15). Finally, eosinophils may also influence angiogenesis. Numerous human cancers are associated with eosinophilia, including Hodgkin's disease, certain lymphomas, and diverse solid tumors such as colon, cervix, lung, breast, and ovary tumors, and this has been suggested to be a prognostic marker.

Eosinophils can be recruited by several chemokines (RANTES, eotaxin, eotaxin 2, MCP-3, and MCP-4), as well as by true angiogenic stimuli, as they express the Flt-1 and Tie-2 receptors. Like neutrophils, eosinophils also release VEGF prestored in granules and can actively produce new VEGF, mediating angiogenic responses. Interestingly, both neutrophils and eosinophils express functional Tie-2 (16), and deletion of cells expressing this receptor blocks tumor angiogenesis (12).

The Yin and Yang of Inflammation

Numerous studies have shown that a sufficiently potent activation of tumor infiltrating macrophages and/or granulocytes can lead to tumor destruction and tumor rejection. In fact, the molecular weapons used by inflammatory cells represent a double-edged sword. In principle, the ability to produce free radicals and a vast repertoire of proteases under specific stimulation, as it occurs in infection, could be driven to prime a destructive reaction against tumor cells. Nevertheless, most clinically successful tumors are those that generate a partially "activated" environment rich in growth factors, chemokines, and proteolytic enzymes such as MMP9, converting stromal cells into promoters of tumor growth and dissemination by improving angiogenesis, tissue breakdown and remodeling, and suppression of specific immunity.

In a simplified comparative view, inflammatory degenerative disease is theoretically a model where leukocyte infiltration and angiogenesis leads to opposite outcomes. For example, in rheumatoid arthritis, the apical damaging role of neutrophils has been recognized and attributed to their persistence in the joints due to Foxo3a-dependent extended lifetime (17). In other models of diseases, such as neurodegeneration, the inflammatory infiltrate, and neutrophils in particular, play an undeniable destructive role (18). In primary pulmonary hypertension, inflammation and endothelial cell proliferation do not lead to cancer (19). As we are focussing on the proangiogenic, and ultimately, tumor-promoting activity of phagocytes, a question arises: why neutrophils, that theoretically are acute response mediators, can survive (undisturbed for a sufficient length of time) and contribute to mount a destructive response in some tissues and organs, and why do they work in an opposite, proliferative direction in others?

These observations fit well with the apparent yin-yang effects of phagocytes: the innate immune system could display a certain

degree of tissue-specific plasticity, being differentially sensitive to particular environment signals. We are then tempted to speculate that a dual phenotypic potential exists for granulocytes, with a phenotype that favors angiogenesis and tissue remodeling, and another that favors degranulation, oxidative enzyme release and tissue destruction. In principle, if this hypothesis is confirmed experimentally, the ultimate proangiogenic or antiangiogenic effect of the innate immune system could be modulated under proper pharmacologic manipulation to exploit the positive sides and minimize the dark side, which pertains to the same process.

This dichotomic activity of neutrophils is naturally helped by the separation of the subcellular compartments where soluble mediators and enzymes are stored. Mild stimuli, like the triggering of CXCR2 by GRO- α (CXCL1) or GRO- β (CXCL2), are only able to activate the release of secondary granule content, mostly a mix of immune and angiogenic modulators. On the contrary, microbial components rapidly induce primary granule mobilization and an oxygen radical/lytic enzyme-based response.

Although the acute inflammatory response is transient and characterized by the ordered appearance of inflammatory cells, a heterogeneous array of inflammatory cells in cancer tissues, like a phoenix from the fire, seems to be subjected to cycles of expansion

at specific sites and often coexist instead of being replaced to allow the resolution of the process (Fig. 1). Factors such as necrosis, apoptosis, and hypoxia itself might clearly operate as environmental cues in advanced tumors.

Apoptotic cells and necrotic cells, generally recognized as a clinically negative prognostic factor for most tumors, are sensed and cleared by granulocytes and macrophages rapidly infiltrating the tissue. Among the immune signals probably released in this injured environment are the molecules that begin tissue remodeling and save the tissue remnants. In the case of cancer, these signals could eventually promote the pathology through constant leukocyte-endothelial reciprocal interactions.

The Setting: Preventing Inflammation and Angiogenesis as a Common Target

“Damaged” tissues have an extraordinary ability to repair, to sustain prohibitive metabolic conditions, to take under control, and even to reverse a precancerous phenotype before an irreparable point of no return in transformation is reached. The angiopreventive strategy to control cancer (20) takes root in our ability to discern these early phases of cancer development. The

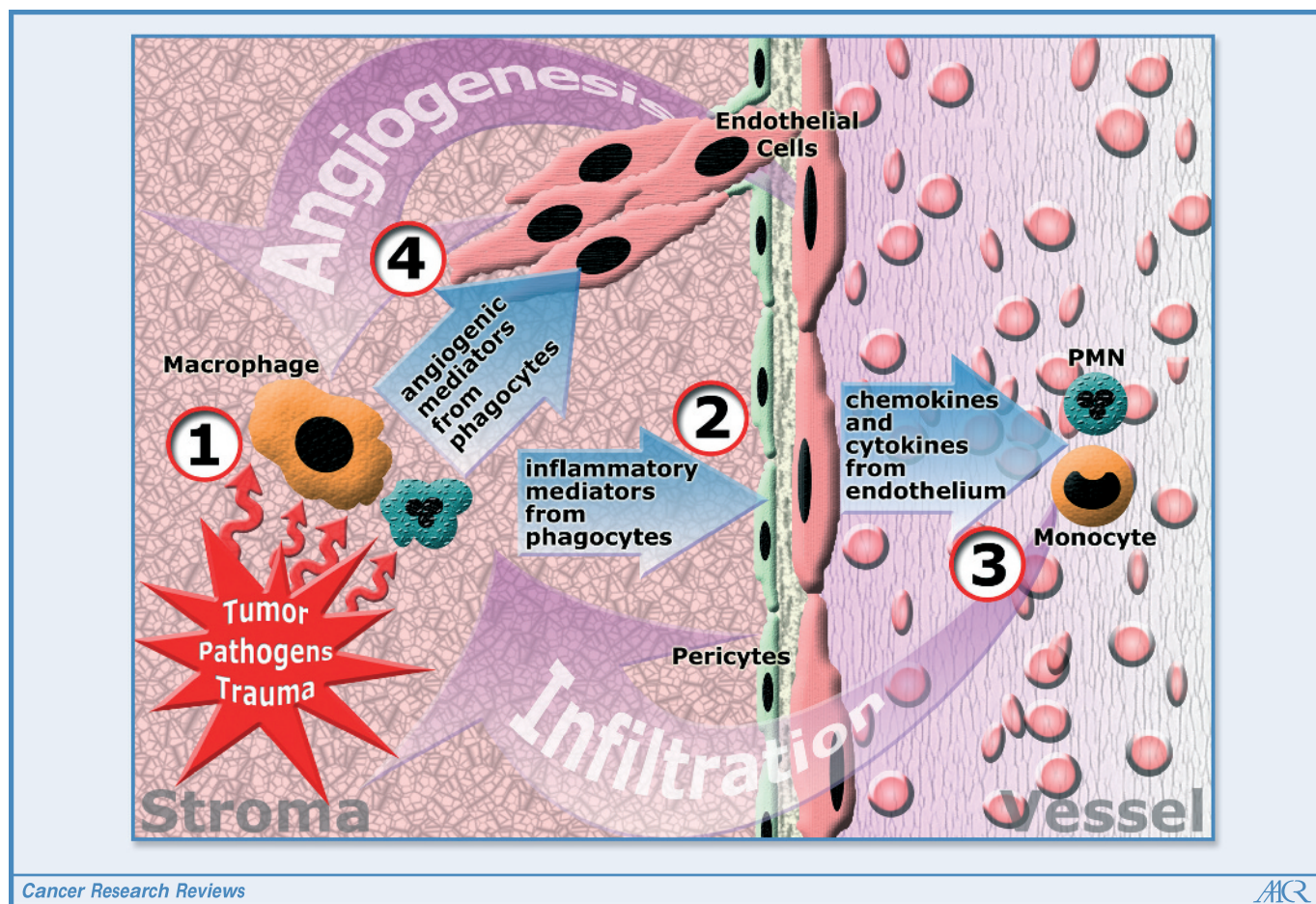


Figure 1. The “hot-start” and propagation of inflammatory angiogenesis. 1, different stimuli (tumor cell proliferation, necrosis, and apoptosis) cause activation of resident macrophages and other phagocytes causing release of proinflammatory mediators. 2, these phagocyte-derived factors activate the endothelial cells to produce adhesion molecules, chemokines, and cytokines. 3, the adhesion molecules and soluble factors from the activated endothelium recruit and stimulate circulating phagocytes thus increasing the mass of reactive cells. 4, the tissue remodeling-activated phagocytes, in turn, release soluble factors that promote the outgrowth and migration of endothelial cells to form new vessels. The effectiveness of the phagocyte-derived angiogenic stimuli must reach a “critical mass,” therefore, step (4) is possible only after additional phagocyte recruitment.

potential to interrupt the carcinogenic process by chemoprevention has recently focused on angiogenesis, as the role of direct mediators of angiogenesis secreted by tumor cells put forth by Folkman in 1971 has been well established. Furthermore, the clinical success of the VEGF inhibitor, Avastatin, has solidified the concept of tumor angiogenesis as a viable therapeutic target.

From the data presented here, it follows that inflammation is a target associated with cancer angioprevention. Several clinical studies have shown that regular use of nonsteroidal anti-inflammatory drugs (NSAID) is associated with reduced risk of some cancers (21). Given the intimate connection between angiogenesis and phagocyte activation, this family of drugs may also fall under the umbrella of angiopreventive molecules (Fig. 1; Table 1). The antiangiogenic activity of these drugs may even extend beyond that of innate immune cell suppression. NSAIDs all inhibit the cyclooxygenase (COX) enzymes, with varying specificity for COX1 or COX2. One reason why NSAIDs are antiangiogenic is that COX inhibition blocks the production of prostaglandins, which are powerful angiogenic mediators. Furthermore, COX itself seems to be upstream of VEGF production by stromal cells, as well as for the angiogenic factor HGF (22). Recently, we have proposed that the cardiovascular events associated with COX2-specific inhibitors, like those associated with Avastatin, may be due to the reduction of baseline VEGF (23).

Ideally, angioprevention should then not only directly suppress angiogenesis, but inflammation as well. Some angiopreventive compounds, in fact, seem to do both. A number of antioxidant anti-inflammatory drugs have antiangiogenic potential, probably by acting directly on inflammatory angiogenesis as well (Fig. 1; Table 1). The green tea flavonoids are a good example. Epidemiologic studies have shown that abundant green tea consumption significantly correlates with a substantial delay of the onset of a series of cancers, including some associated with inflammation, such as colon cancer. Green tea, and in particular, the main flavonoid of green tea, epigallocatechin gallate, has been shown to be a direct repressor of angiogenesis *in vivo* (24)

through mechanisms that include down-regulation of MMP9 and other metalloproteases, and interference with VEGF production and signaling (24, 25). Traditionally, green tea has been associated with an anti-inflammatory activity as well. Recently, green tea has been shown to inhibit inflammation *in vivo*, including inflammation-associated angiogenesis (26). Thus, epigallocatechin gallate, as well as other antiangiogenic flavonoids, seem to repress angiogenesis both directly and indirectly.

Given the common activity that many angiopreventive agents show, the search for central mechanisms that may represent critical targets has begun. We have analyzed the regulation of gene expression they exert in primary human umbilical vascular endothelial cells in culture with functional genomics (27). Expression profiles identified overlapping sets of genes regulated by antioxidant angiopreventive compounds, potentially representing a "fingerprint" of the antiangiogenic switch. Interestingly, key junctional pathways seem to converge on nuclear factor κ B (NF- κ B). The crucial role of NF- κ B in inflammation is well known. Recent data directly link NF- κ B activation in tumor and inflammatory cells to tumor progression (28), further supporting targeting NF- κ B as a strategy to concurrently obtain angioprevention through inhibition of inflammation and angiogenesis. This strategy could also be effective in metastatic cancer; for example, breast cancer metastasis suppressor 1 inhibits cancer metastasis gene expression by targeting NF- κ B activity (29).

Conclusion

The inflammation-dependent angiogenesis concept is reinforced by evidence that inflammation inhibition prevents angiogenesis. This mechanism of "indirect" angiogenesis places it as a target of therapy and, even better, as a target of prevention of tumor angiogenesis by anti-inflammatory agents. Ideally, a chemopreventive anti-inflammatory approach will be able to block neovascularization before the angiogenic switch point, resulting in a significant delay in clinically relevant cancer.

Table 1. Selected angioprevention molecules with anti-inflammatory activity

Molecule	Angiogenic targets	Inflammatory targets
NSAIDs	mitogen-activated protein kinase, COX, integrin signaling, RECK induction, HGF signaling (1–4)	COX, tumor necrosis factor signaling, lipoxin induction, down-regulation of L-selectin in neutrophils (5–7)
Epigallocatechin gallate (from green tea, <i>Camellia sinensis</i> L.)	metalloproteinases (MMP9), VEGF signaling, endothelial cell growth, chemotaxis, invasion (8, 9)	neutrophil chemotaxis, apoptosis, ROS production, NF- κ B signaling in T lymphocytes (10, 11)
Curcumin (from turmeric, <i>Curcuma longa</i> L. and synthetic analogues)	<i>in vivo</i> angiogenesis, endothelial cell migration, invasion, tube formation, MMP9 modulation, inhibition of VEGF and KDR expression (12–14)	Jak-STAT signaling, ICAM-1, MCP1 expression, inhibition of monocyte adhesion to endothelial cells, MMP9 activity (15–18)
Resveratrol (from red grape, fruit)	<i>in vivo</i> angiogenesis, VEGF-induced endothelial cell migration, tube formation, ROS-dependent Src kinase activation, VE-cadherin tyrosine phosphorylation (19, 20)	NF- κ B signaling (21), Toll-like receptor signaling (22)
<i>N</i> -acetylcysteine	angiostatin production, VEGF-induced KDR tyrosine phosphorylation, Kaposi sarcoma migration and invasion, VEGF production (23–25)	neutrophil migration, transforming growth factor- β signaling, NF- κ B signaling (26–29)

NOTE: Numbers in parenthesis refer to additional references available as supplemental material online.

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