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Chapter VIII

The Critical Role of Inflammatory Cell Infiltration in Tumor Angiogenesis: A Target for Anti-Tumor Drug Development?

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Abstract

Inflammatory responses are often associated with acquisition of malignant characteristics in various human tumors. In this article, we focus on the idea that inflammatory angiogenesis is a critical component of tumor progression. Inflammatory angiogenesis may confer a specific microenvironment on each tumor, resulting in characteristic formation of stroma in the tumor. In particular, we suggest a critical role of macrophage infiltration in the tumor stroma in the development of angiogenesis by presenting experimental angiogenesis models in response to IL-1β and other inflammatory cytokines. We also discuss the anticancer therapeutic potential of molecular targets or cells appearing during the inflammatory angiogenesis.

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Introduction

Since the first proposal that cancer is chronic inflammation by Dr. Virchow in 1863, the relationship between inflammation and cancer has often been disputed for almost one and half centuries. The appearance of a single precancerous cell with a mutated oncogene/ oncosuppressor gene, together with proliferation of cancer cells alone does not provide sufficient conditions to cause malignant tumor, because stroma components of cancer are essential for malignant tumor progression [1]. Inflammation in the tumor microenvironment enhances not only cell proliferation in the tissue injury during wound healing but also progression of cancer, injury without healing [2, 3]. Plausible mechanisms underlying the causal relationship between inflammation and cancer have recently been presented [1, 4]. Inflammation and tumor could be intercorrelated through hemangiogenesis [5] and lymphangiogenesis [6] (Figure 1). The mechanism for lymphangiogenesis as well as hemangiogenesis is now being investigated at the molecular basis [6]. Here we seek to give insight into the functional relationship between inflammation and cancer from the standpoint of angiogenesis.

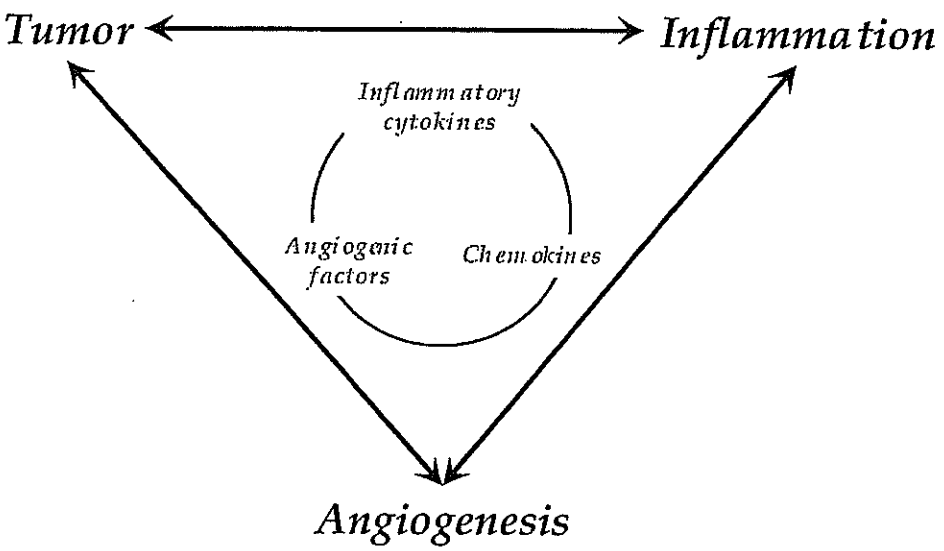

Figure 1. Inflammatory responders including inflammatory cells, cytokines and chemokines closely associated with angiogenesis greatly affect the stromal microenvironment in each malignant tumor. Cancer cells that produce abundant pro-inflammatory cytokines can induce activation of stromal cells including inflammatory cells to potentiate angiogenesis, resulting in the promotion of tumor growth and acquisition of various malignant characteristics.

Inflammatory Cells are the Main Components of Tumor Stroma

In the inflammatory response, wound healing is a self-limiting angiogenesis: neutrophils are the first recruited effector cells, and monocytes/ macrophages next migrate to the site of tissue injury in response to chemotactic cytokines. Once activated, monocytes produce

various proangiogenic cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), interleukin-1α/β (IL-1α/β), IL-6, as well as extracellular matrices-degrading enzymes such as matrix metalloproteinases (MMPs) and plasminogen activators (PAs), and switch on angiogenesis, resulting in healing the injury site. On the other hand, during the inflammatory responses in malignant tumors, tumor cells produce various cytokines and chemokines that attract leukocytes such as neutrophils, dendritic cells, monocytes/ macrophages, eosinophils, mast cells and lymphocytes, which also produce various cytokines, proteases, reactive oxygen species. Of these inflammatory components, infiltration of monocytes/ macrophages appears to play key roles in the development of tumor and its acquisition of malignant characteristics. Macrophage infiltration is often associated with poor prognosis of cancer patients with breast cancer, cervical cancer, lung cancer, bladder cancer, glioma and melanoma [7 - 10]. Monocytes recruited by monocyte chemotactic protein-1 (MCP-1) are educated by the tumor environment, and these tumor educated macrophages, called tumor-associated macrophages (TAMs), are thought to support tumor progression and metastasis [4]. TAMs produce VEGF-A, VEGF-C and VEGF-D, IL-8, TNF-α, IL-1α/β, transforming growth factor-β (TGF-β), arachidonate metabolites and proteases, resulting in promotion of angiogenesis as well as lymphangiogenesis [11 - 13].

Angiogenesis by Inflammatory Cytokines through Augmentation of Potent Angiogenic Factors and Cyclooxygenase-2

Of various inflammatory cytokines, IL-1α and β, members of the IL-1 family, induce their signals through interaction with type I and type II IL-1 receptor, and IL-1 receptor antagonist (IL-1Ra) antagonizes (Figure 2). Expression of this signaling by IL-1 is often up-regulated and associated with pathological conditions of rheumatoid arthritis, septic shock, graft-versus-host disease, arteriosclerosis, asthma, adult T cell leukemia, multiple myeloma and many other tumor types, and angiogenesis is also closely associated with pathological conditions in these diseases. Concerning the direct involvement of IL-1α/β in tumor development, Voronov et al recently reported that IL-1α and β are required for development of angiogenesis and tumor in an experimental animal model [14]. Angiogenesis is markedly diminished in both IL-1α - and IL-1β -knockout mice, and tumor angiogenesis is much less abolished in IL-1β knockout mice than that in IL-1α knockout mice (Table 1). IL-1β promotes growth and invasion of cancer as well as angiogenesis in animal models with concomitant enhanced production of VEGF, IL-8, MMPs and adhesion molecules [15, 16] (see also Figure 3). IL-1α promotes angiogenesis *in vitro* as well as *in vivo* through up-regulation of VEGF, IL-8 and other angiogenesis-related factors [7, 10]. Although IL-1α and IL-1β share their receptor, type I IL-1 receptor, Song et al have recently proposed differential effects of IL-1α and IL-1β on tumorigeniciy patterns, invasiveness and angiogenesis [18 - 20] (Table 1). Acquisition of malignant characteristics of invasion, metastsis, and angiogenesis thus appears to be mediated through these inflammatory cytokines, suggesting a close linkage between cancer and inflammation. Overexpression of IL-1α in highly invasive fibrosarcoma cells results in a marked loss of tumor development with activation of antitumor

immunological effector mechanism whereas IL-1β overproduction in fibrosarcoma cells results in enhancement of angiogenesis as well as enlargement, invasion and metastasis of tumor [18]. IL-1α thus reduces tumorigenicity by inducing antitumor immunity together with tumor suppression in the host, and IL-1β promotes invasiveness and angiogenesis of tumor.

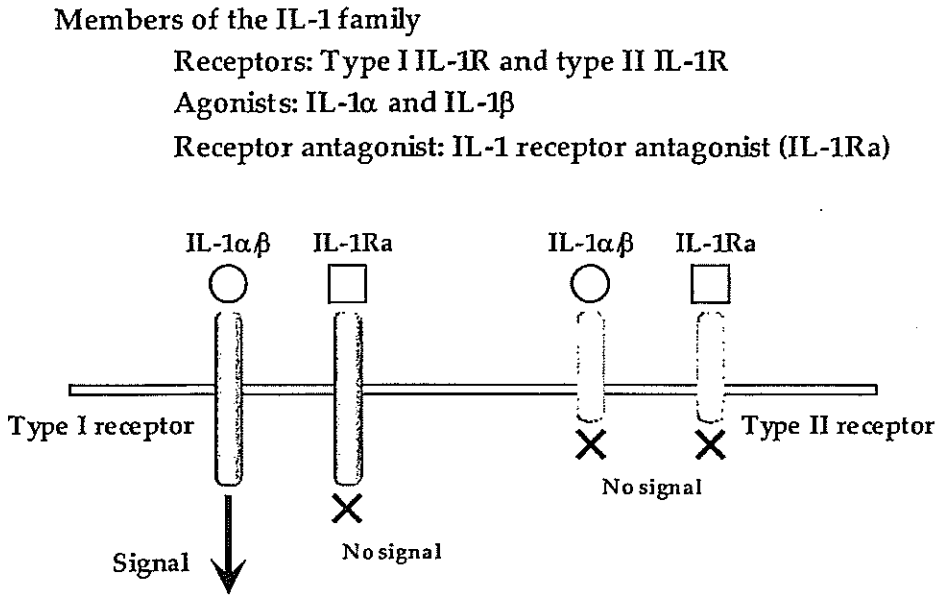

Figure 2. IL-1α and IL-1β induce their signaling through interaction with type I IL-1 receptor. The IL-1 family consists of IL-1 receptors type I (IL-1RI) and Type II (IL-1RII), receptor agonists IL-1α and IL-1β, and IL-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β are produced as inactive precursors, pro-IL-1α and pro-IL-1β, respectively. Pro-IL-1α is cleaved by calpains and pro-IL-1β is cleaved by caspase-1 to generate mature forms. The binding of IL-1α and IL-1β to IL-1RI transduces the signal whereas binding to IL-1RII does not. IL-1Ra binds to both IL-1RI and IL-1RII without signal transduction and abrogates the association of IL-1α and IL-1β to the receptor.

Inflammation induces up-regulation of various angiogenesis-related factors. Treatment with TNF-α of vascular endothelial cells and cancer cells results in a marked induction of VEGF, bFGF, IL-8 and PA through activation of Sp-1, AP-1, hypoxia response element, NF-κB and other regulatory elements [21 - 23]. TNF-α or IL-1α also enhances production of VEGF, IL-8, bFGF and MMPs from cancer cells and endothelial cells, resulting in a switch of angiogenesis through autocrine/ paracrine controls [9, 12, 13] (Figure 3). On the other hand, α4 integrins that are counter-receptors for VCAM-1 are expressed on the surface of vascular endothelial cells [24], expression of α4 integrin and VCAM-1/ soluble VCAM-1 by TNF-α induces angiogenesis in the corneas of mice through p38 and FAK signaling pathways [25]. Expression of soluble VCAM-1 is also dramatically enhanced in vascular endothelial cells by IL-4 or IL-13 derived from mast cells [26, 27]. In addition, Kaneko et al have recently demonstrated that the binding of VEGF receptor to its ligand transduces signals through integrin-linked kinase associated with the integrin β chain in human endothelial cells, suggesting that integrin-mediated signals also cooperate with VEGF receptor in vascular endothelial cells to induce angiogenesis [28]. Taken together, these facts suggest that inflammatory cytokines-induced angiogenesis is mediated through enhanced production of

angiogenesis regulatory factor and activation of various adhesion and integrin molecules by the cytokines.

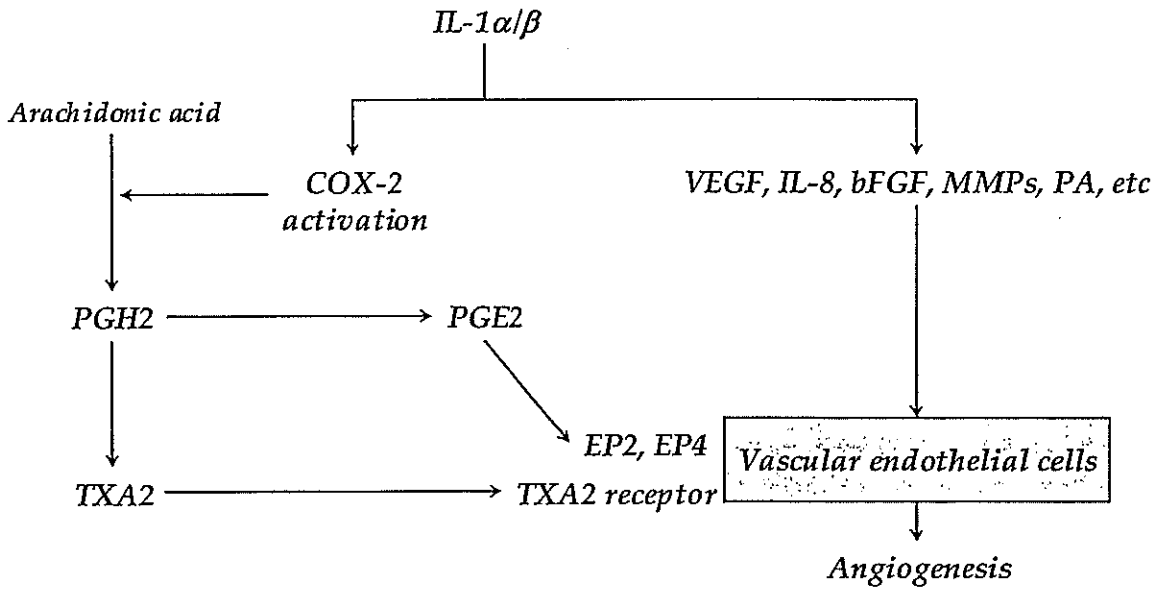

Figure 3. Angiogenesis by IL-1α/β is mediated through dual pathways: induction of angiogenesis-related factors and COX-2 activation. IL-1 stimulates induction of angiogenesis-related factors such as VEGF, IL-8, bFGF, MMPs and PA from vascular endothelial cells and other cell types. These factors co-operatively activate vascular endothelial cells resulting in angiogenesis. On the other hand, IL-1 induces angiogenesis through the activation of COX-2 in vascular endothelial cells and other cell types. PGE2 and TXA2 are expected to induce angiogenesis autocrine control. Recent study also demonstrates that PGF2 and TXA2 stimulate production of some angiogenesis-related factors, resulting in angiogenesis.

Table 1. The specific roles of IL-1α and IL-1β in various malignant characteristics of tumor including angiogenesis.

Experimental conditions	Findings	References
Tumor growth and angiogenesis by melanoma cells in IL-1α or IL-1β-knockout mice	• IL-1β is more closely associated with tumor growth and tumor angiogenesis than IL-1α	Voronov et al [14]
Lung cancer cell line expressing IL-1β	• Tumor growth and metastasis as well as angiogenesis are markedly enhanced by IL-1β	Yano et al [15] Saijo et al [16]
Mouse fibrosarcoma cells expressing IL-1α and IL-1β	• IL-1α reduces tumorigenicity by antitumor Immunity • IL-1β promotes invasiveness and tumor angiogenesis	Song et al [18]
Hepatic metastasis by IL-1α gene transfection in melanoma cell and effect of IL-1 receptor antagonist on tumor growth and metastasis	• IL-1α increases tumor cell adhesion to endothelial cell and VCAM-1 expression • IL-1α enhances melanoma hepatic metastasis	Anasagasti et al [19] Vidal-Vanaclocha et al [20]

On the other hand, cyclooxygenases (COXs) play a key role in tumor angiogenesis [29], probably in close association with inflammation. Of the two COXs, COX-1 and COX-2 that convert arachidonic acid to prostaglandins, the COX-2 can be induced by a variety of pro-

inflammatory cytokines and growth factors. In a model of human familiar adenomatous polyps using mice with a targeted mutation in the APC tumor suppressor gene (Apc-knockout mice), polyp formation is markedly reduced in Apc/COX-2-knockout mice [30], and Seno et al have further reported that stromal expression of COX-2 is required for induction of VEGF and tumor angiogenesis [31]. Tumor growth as well as angiogenesis can be suppressed by COX-2 inhibitors when cancer cells express COX-2 [32]. The primary prostanoids, prostaglandin E2 (PGE2), PGF2α, PGD2, PGI2 and thromboxane A2 (TXA2) mediate angiogenesis, partly through modulation of VEGF levels in response to these prostanoids. VEGF levels are markedly decreased in tumors in the COX-2-knock out mice, suggesting that a close link between COX-2 and VEGF in tumor angiogenesis [33]. Concerning the possible role of COX-2 in tumor angiogenesis, COX-2 expression is elevated not only in cancer cells but also in microvasculatures, various infiltrating blood cell types and fibroblasts in the tumor stroma [29]. COX-2-expressing cancer cells form larger tumors than cancer cells that lack COX-2 expression [34]. However, it remains unclear whether COX-2 activity is directly involved in the up-regulation of the VEGF gene. Chang et al have also reported up-regulation of both VEGF and EP1, 2, 4 receptors in COX-2-transgenic mammary tissue, and PGE2 mostly stimulates expression of this potent angiogenic factor, VEGF, in mammary tumor cells [35]. In the tumor angiogenesis, PGE2-EP3 signaling also regulates tumor-angiogenesis and tumor growth [36].

A recent study by Kuwano et al demonstrated a close association of COX-2 activity with inflammatory cytokine IL-1β-induced angiogenesis *in vitro* and *in vivo* [37]. In their study, EP2, 4 agonists and TXA2 receptor agonist themselves induce angiogenesis in mouse corneas, and IL-1β-induced angiogenesis is inhibited by an EP4 antagonists and a TXA2 receptor antagonist. Moreover, IL-1β-induced angiogenesis is markedly abrogated in COX-2-knockout mice, and this angiogenesis was only partly blocked by co-administration of a VEGF receptor tyrosine kinase inhibitor [37]. From these findings, one can expect that inflammatory cytokine-induced angiogenesis is mediated through dual pathways: up-regulation of angiogenesis-regulated factors and also prostanoids produced by COX-2 (Figure 3).

Inflammatory Angiogenesis and Macrophage Infiltration are Essential for Development of Malignant Tumors Including Multiple Myeloma

Tumor growth and metastasis of solid tumor are dependent on hemangiogenesis and lymphangiogenesis [6,38]. Angiogenesis also appears to play a critical role during development of multiple myeloma [39]. Concerning the development of multiple myeloma, the bone marrow microenvironment includes both cytokines and growth factor, and also physical interaction with stroma cells and extracellular matrices. In this microenvironment, the interaction of multiple myeloma cells with various stromal cells types plays a key role in the pathogenesis of multiple myeloma [40]. Bom marrow-related angiogenesis increases in multiple myeloma with malignancy progression [41, 42]. Bone marrow-related angiogenesis is thus expected to promote expansion of the multiple myeloma mass by inducing plasma cell proliferation. Moreover, high bone marrow angiogenesis is an adverse prognostic factor in

multiple myeloma [43, 44]. Multiple myeloma cells produce and secrete potent angiogenic factors, MMPs and PAs in their microenvironment with a concomitant appearance of cytokines recruiting inflammatory cells such as mast cells, monocytes/ macrophages and neutrophils [39]. Formation of a network system by multiple myeloma cells and various stroma cells might promote angiogenesis in the multiple myeloma environment. Moreover, IL-6, a key enzyme for tumor growth for multiple myeloma cells, affects production of the potent angiogenic factor VEGF [45]. Other cytokines, TNF-α and IL-1, also stimulate expression of VEGF and other angiogenesis-related factors such as IL-8, bFGF in various cell types [10, 22, 23], and VEGF production by multiple myeloma cells is also elevated by these inflammatory cytokines [46, 47]. Thus, angiogenesis is expected to play a key role in acquirement of pathological characteristics during tumor progression in multiple myeloma cells [37] as well as in other solid tumor types [38, 48]. Inflammatory cytokines are thus expected to be implicated in angiogenesis not only during solid tumor development but also during multiple myeloma development (Figure 4). This inflammatory network systems operating in multiple myeloma are also expected to function in other solid tumor types.

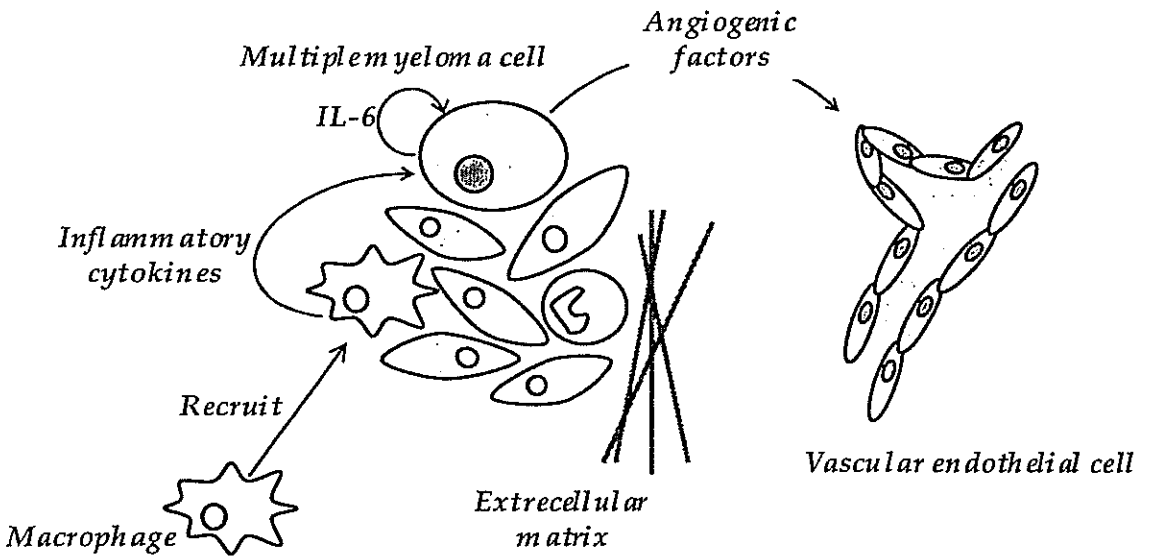

Figure 4. Multiple myeloma form a network near bone marrow through interaction with various inflammatory cell types. Angiogenesis plays a critical role in stroma formation for multiple myeloma through interaction of multiple myeloma cells with various stroma cell types and cytokines.

Monocytes and macrophages are expected to play critical roles in malignant tumor progression [1, 4]. In various inflammatory responses, macrophages play a key role in providing an environment that stimulates cell migration, survival and proliferation of cancer cells and various stromal cell types by producing angiogenic factors, growth factors, cytokines and proteases [1, 4]. In particular TAMs are a significant component of inflammatory infiltrates in tumors, and TAMs derived from monocytes are mainly recruited in response to MCP-1 and other chemokines resulting in tumor progression. Since the first clinical evidence indicating an association of macrophage infiltration with invasive breast cancer [7], many other studies also demonstrate that infiltration of TAMs is often closely associated with survival or prognosis in many tumor types, suggesting a role of TAMs in

tumor progression and metastasis. The close correlation of the abundance of TAMs in tumor stroma and poor prognosis appears to be due to at least in part to angiogenesis [1, 12]. In keeping with this notion, TAMs produce various proangiogenic factors (VEGF, bFGF, PDGF, HGF angiopoetin-1 and 2, IL-8, thymidine phosphorylase), inflammatory cytokines (TNF-α, IL-1), proteases (PA, MMP-7 and MMP-9), and NO [4, 11 - 13] (Figure 5). Infiltration of abundant COX-2-positive cells, including macrophages and neutrophils, is recognized near neovasculatures that are evident in cornea by IL-1β [13]. TAMs also express VEGF-C and D as well as VEGF receptor 3 (VEGFR-3), suggesting that TAMs could modulate not only hemangiogenesis but also lymphangiogenesis [11]. A recent study by Cursiefen et al demonstrated that VEGF-A recruitment of monocyte/ macrophages plays a crucial role in induction of inflammatory angiogenesis by supplying signals essential for both hemangiogenesis and lymphyangiogenesis [49]. TAMs are thus implicated in the formation of blood vessels and lymphatic vessels by alteration of the local balance of proangiogenic factors during tumor development.

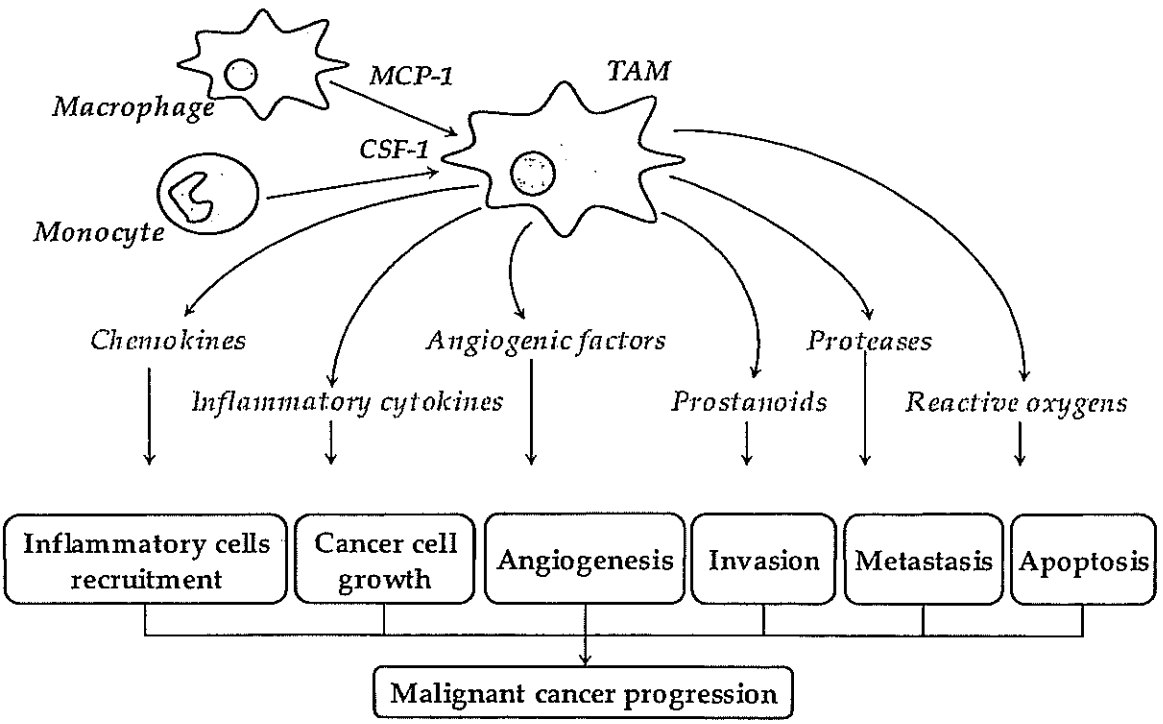

Figure 5. Tumor-associated macrophages (TAMs) have pro-tumorigenic and pro-angiogenic functions through formation of a complex network system of various cell types in the tumor stroma. Monocytes/ macrophages are recruited to the malignant tumor area by chemotactic cytokines, such as MCP-1, secreted by tumor. The soluble colony-stimulating factor (CSF-1), abundant molecule in the tumor microenvironment, transforms infiltrated macrophages to TAMs: CSF-1 has two forms both soluble CSF-1 (sCSF-1) and cell-surface CSF-1. TAMs are expected to promote recruitment of inflammatory cells, tumor growth, angiogenesis, invasion, metastasis and apoptosis by production of various factors.

Therapeutic Potential of Anticancer Drugs by Targeting Inflammatory Angiogenesis and TAMs

The significant contribution of COX-2 in cancer promotion has been demonstrated in a model of human familiar adenomatous polyps. Inhibitors of COXs may therefore reduce cancer risk. Representative drugs developed by targeting inflammation are both COX-1- and COX-2-targeting agents such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) that reduce colon cancers risk and also prevent breast, lung, esophagus and stomach cancer [50, 51]. There have been many clinical trials of NSAIDs not only for familial adenomatous polyposis and sporadic colorectal neoplasia but also for cancer of breast esophagus, stomach, pancreas, ovarian, urinary tract, prostate and other organs [50]. Aspirin and other NSAIDs may provide protection against cancer in gastrointestinal tract. However, the effects of NSAIDs on cancers outside the gastrointestinal tract remain to be investigated.

COX-2 contributes to angiogenesis in inflammatory diseases and malignant tumors [29], and the expression in both cancer cells and multiple cell types in the tumor environment may play an important role in tumor progression and angiogenesis through production of angiogenic eicosanoids, and angiogenic factors. COX-2 expression is apparently up-regulated in multiple cell types including macrophages that are infiltrated in neovasculatures developed by IL-1β in mouse corneas [37]. COX-2 inhibitors, as well as NSAIDs, may limit tumor growth, invasion and metastasis through inhibition of angiogenesis in some tumor types. Chang et al reported that COX-2 overexpression in the mammary glands of transgenic mice induces tissue specific tumorigenic transformation with angiogenesis in the stromal tissues of mammary glands [35]. Up-regulation of angiogenesis factor genes in COX-2-transgenic mice can be inhibited by treatment with indomethacin, an inhibitor of COX-2-induced prostanoid synthesis. Moreover, a COX-2-specific inhibitor, Celecoxib, can markedly reduce tumor growth and angiogenesis which are partly mediated through PGE2-EP1, 2, 4 receptor pathway in tumor in COX-2-transgenic mice [35].

TNF-α, a proinflammatory cytokine as well as IL-1α/β, mediates downstream signaling in inflammation. Antibody developed against TNF-α shows therapeutic efficacy in rheumatic disease [52]. Since these inflammatory cytokines play important roles in angiogenesis in inflammatory diseases and cancer [40, 53], drugs targeting TNF-α and IL-1α/β may be effective in anticancer treatment. For example, thalidomide which is now approved to treatment of Hansen's disease and multiple myeloma, affects production of various cytokines, in particular, TNF-α from monocytic cells in culture. Development of thalidomide derivatives that potently inhibit TNF-α production have marked antiangiogenesis activity [59], suggesting a close link between TNF-α and angiogenesis. D'Amato et al reported antiangiogenesis activity by thalidomide in a rabbit corneal angiogenesis model using bFGF [55]. However, further studies have reported disputed findings. Thalidomide-induced antitumor effects in mice appear not to be due to a decrease of VEGF level [56]. Thalidomide shows pleiotropic effects such as increase of T cells and activation of NK cell [57], inhibition of IFN-γ production [58], inhibition of αVβ3 integrin expression [59] and interaction with DNA [60], suggesting that its teratogenic activity and antitumor activity are mediated through complex mechanisms. Further investigations are required to understand at the molecular basis how thalidomide could induce antitumor effects in some malignant tumor types.

TAMs, the main components of tumor microenvironment, are expected to potentiate tumor progression together with other many immunity-related cells such as neutrophils and mast cells, and one of their pleiotropic responses is induction of angiogenesis in the tumor environment. TAMs, along with mast cells and neutrophils, promote tumor progression and metastasis by production of angiogenic factors, proteases, growth factors and cytokines, resulting in formation of tumor stroma characteristics for each malignant cancer [1, 4]. If continuous inflammation due to persistent infection and other irritants play a critical role in tumor progression, TAMs hold promise as target cells of intrinsic importance for the development of antiangiogenesis and antitumor drugs. One approach for the anti-inflammatory and antitumor strategy could be developed by targeting proteases such as PAs, MMPs, inflammation cytokines, COXs, growth factors, and inflammatory cytokines. Another approach is to target TAMs and other pronounced inflammatory cells by either blocking cell migration of inflammatoty cells such as TAMs, neutrophlis and mast cells, or killing the TAMs themselves. We need further study to understand which molecular targets or which tumor-associated inflammatory cells should be aimed at to develop antitumor drugs.

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Ⅳ-2. 抗がん剤感受性とDubin-Johnson症候群

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1. 抗がん剤感受性とABC蛋白質

1.1　多剤耐性

抗がん剤をがん患者に投与すると，投与するにつれて効果が減少してくることがよく知られている．つまり，生体内において抗がん剤に対して耐性の腫瘍細胞の出現が推察される．細胞が抗がん剤耐性を獲得する機構には，①抗がん剤の細胞内取り込みの低下，②解毒作用の増強，③標的分子の変化，④細胞外への薬剤排出などがある．このうち細胞内の抗がん剤が排出しやすくなるという機構は，がん細胞に同時に構造や作用機序の異なる複数の抗がん剤に対する耐性（多剤耐性，MDR：multiple drug resistance）を付与することからも重要である．その実体としてP糖蛋白質（*MDR1* 遺伝子）やMRP（*MRP1* 遺伝子）が同定され，いずれもがABCトランスポーターに属することがわかった．このP糖蛋白質（MDR1遺伝子）は，ATPのエネルギーに依存して作動する排出ポンプであることが明らかにされ，がん細胞は最初に用いた抗がん剤はもとより，他の抗がん剤に対しても耐性となり多剤耐性を示す[1-3]．

多剤耐性の出現は抗がん剤治療を困難なものにし，多剤耐性を獲得したがん細胞はさらに，ゲノム不安定性，チェックポイント機構の破綻などの変化を生じ，さらなるがん治療を困難かつ複雑なものにしている．また，薬の副作用や個人差などに影響を与える経口投与による腸からの吸収や，肝臓，腎臓における排出をはじめとする薬物動態にも，多大な関与が認められる[1,5]．

ABC蛋白質は生体における種々の異物に対する解毒，抱合，排出機構に大いに関与している．したがって，多くの疾病が各トランスポーターの機能異常によりもたらされると予測されている．このように，ABCトランスポーターは