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H. 知的財産権の出願・登録状況

1. 特許予定

該当なし

2. 実用新案登録

該当なし

3. その他

厚生労働科学研究費補助金（第3次対がん総合戦略研究事業）
分担研究報告書

分子標的薬物の臨床評価に関する研究

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研究要旨
BAY43-9006 (Sorafenib)はRafキナーゼおよびVEGFやPGDF受容体チロシンキナーゼの阻害作用を有する分子標的薬である。その作用機序から副作用は軽微であるが、一般の癌に対する効果は腫瘍増殖抑制であると考えられている。日本人におけるBAY43-9006の第I相試験を実施し、400 mgを1日2回連日投与する投与法の安全性を確認した。非小細胞癌および腎癌で奏効例がみられた。生物学的活性をPETで評価したところ、腫瘍縮小を認めた症例や長期間病巣が増大しなかった症例では代謝能の低下を認め、PETによる機能評価が本薬の臨床評価において有用である可能性が示唆された。

A. 研究目的

BAY43-9006 (Sorafenib)はRafキナーゼおよびVEGFやPGDF受容体チロシンキナーゼの阻害作用を有する経口投与可能な分子標的薬である。日本人における毒性プロファイルおよび薬物動態を明らかにし、推奨用量を決定する目的で第I相試験を実施した。合わせて、positron emission tomography (PET)で糖代謝能を評価することにより、本薬の生物学的活性を検討した。

B. 研究方法

各種固形がん患者を対象として"3+3"のデザインにより、1回100 mgより開始し200、400、600 mgと増量した。各患者で単回投与後の薬物動態を評価した後、1日2回の連日投与を行った。抗腫瘍効果の評価はCTを治療開始前、開始1, 2,ヶ月後、および以後2ヶ月毎に実施し、従来の方法によりpartial response (PR)、stable disease (SD)、progressive disease (PD)に分類した。同時期にFDG-PETを施行し、癌細胞の糖代謝能をstandardized uptake value (SUV)で評価した。SUVは食事や血糖値、FDG投与から撮像までの時間などに影響されるため、検査前6時間の糖分摂取を禁止し、FDG投与から撮影開始までの時間を厳密に60分とした。SUVの測定は8 mm以上の径の腫瘍病巣を3個選択して行った。SUVによる効果判定は、EORTCから提唱されている25%以上のSUVの低下を基準として採用し、SUVの変化とCTで評価した腫瘍の大きさの変化と比較した。

（倫理面への配慮）

BAY43-9006の第I相試験、および分子標的治療薬のPETによる評価の臨床研究の試験計画書をそれぞれ受託研究審査委員会、倫理審査委員会で審査の上承認を得た。さらに、第I相試験の性格、危険性などを患者に十分説明したのち、インフォームドコンセントの得られた患者のみを対象とした。

C. 研究結果

1回投与量として100 mg、200、400、600 mgの各用量でそれぞれ、3、15、6、7例、合計31例を治療した。高頻度に観察された副作用は、発疹/

落屑(61%)、手足皮膚反応(36%)、下痢(32%)、リパーゼ上昇(32%)であった。検査値異常としてグレード3以上のリパーゼ上昇が7例、アミラーゼ上昇が3例にみられたが、膵炎を起こした患者はいなかった。

600 mgでグレード2の手足皮膚反応を5例に、グレード3の疲労が1例に見られたこと、海外で400mgを第II相試験の用量として用いていることを考慮し、400mgの1日2回投与を推奨用量と結論した。

薬物動態の個体間差は大きかったが、AUCおよびCmaxは用量に依存して増大し民族間差もみられなかった。推奨用量の400 mgで前臨床試験でのIC_{50}を越える血漿中トラフ濃度が得られた。非小細胞肺癌10例中PRが1例、24週以上持続するSDが5例に見られ、腎癌3例中1例でPRが得られた。

FDG-PETを20例（非小細胞肺癌6例、大腸癌6例、腎癌2例、その他6例）で施行した。Clinical benefitが得られた7例（PR 1例、4ヶ月以上のSDが得られた6例）のうち6例でSUVが治療前値と比べて25%以上低下し、残りの1例でも23%のSUVの低下を認めた。

また、治療開始1ヵ月後のPETでSUVが25%以上の減少を示さなかった症例は9例あったが、このうち8例が2ヶ月目までに病状の悪化などでBAY43-9006による治療を中止していた。一方、1ヶ月の段階でSUVが25%以上減少した11例では5例のみが2ヶ月以内に治療を中止していただけであった。

D. 考察

BAY43-9006の副作用として重篤なものはみられず、推奨用量とした400mgの1日2回連日投与は認容性の高いものであった。病巣のPETによる代謝能の評価とCTによるサイズの測定を行ったが、4ヶ月以上のNCやPRといった、いわゆるclinical benefitが期待できる9例ではSUVが低下し、8例で25%以上の低下を示していた。分子標的薬物は長期間のNCが薬効として期待されているが、SUVはそれを早期に検出できる可能性が示唆される。これは以前に実施したGW572016の第I相試験でのSUV解析と同様の結果であった。分子標的薬の生物学的活性をPETで評価できる可能性を示しているものと考えられた

E. 結論

BAY43-9006を400mgの1日2回連日投与が第II相試験の用量として推奨された。PETで腫瘍の代謝能を解析することは抗腫瘍効果を早期に検出する可能性が示されたが、第II相試験あるいは第III相試験など均一な臨床条件のもとで薬物の臨床的有用性との対比を行うことにより、最終的に評価する必要がある。

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G. 知的所有権の取得状況

1. 特許取得

   なし

2. 実用新案登録

   なし

3. その他

   なし

研究成果の刊行に関する一覧表

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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.

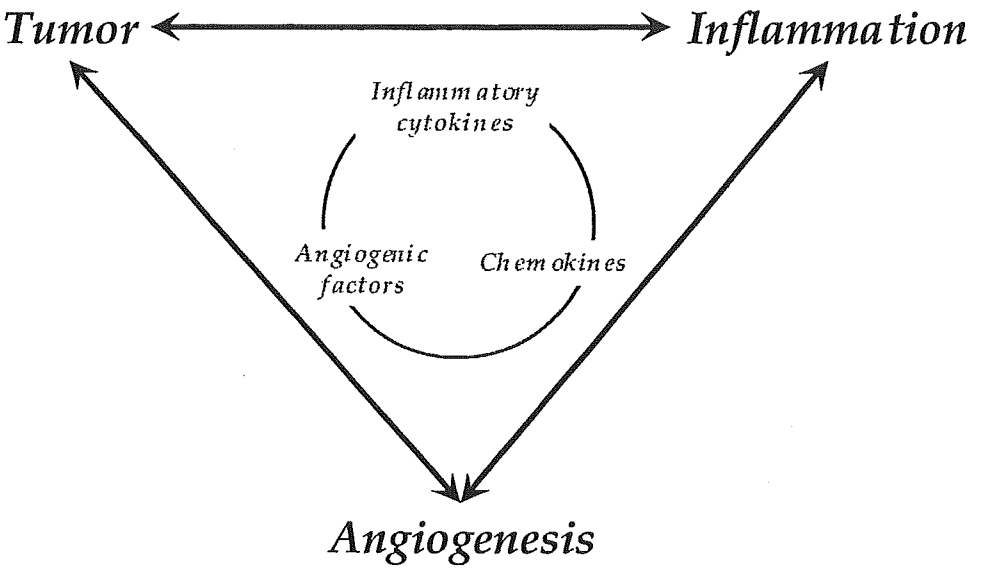

Figure 1. Inflammatory responders including inflammatory cells, cytokines and chemokines closely associated with angiogenesis greatly affect the stromal microenvironment in each malignant tumor. Cancer cells that produce abundant pro-inflammatory cytokines can induce activation of stromal cells including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

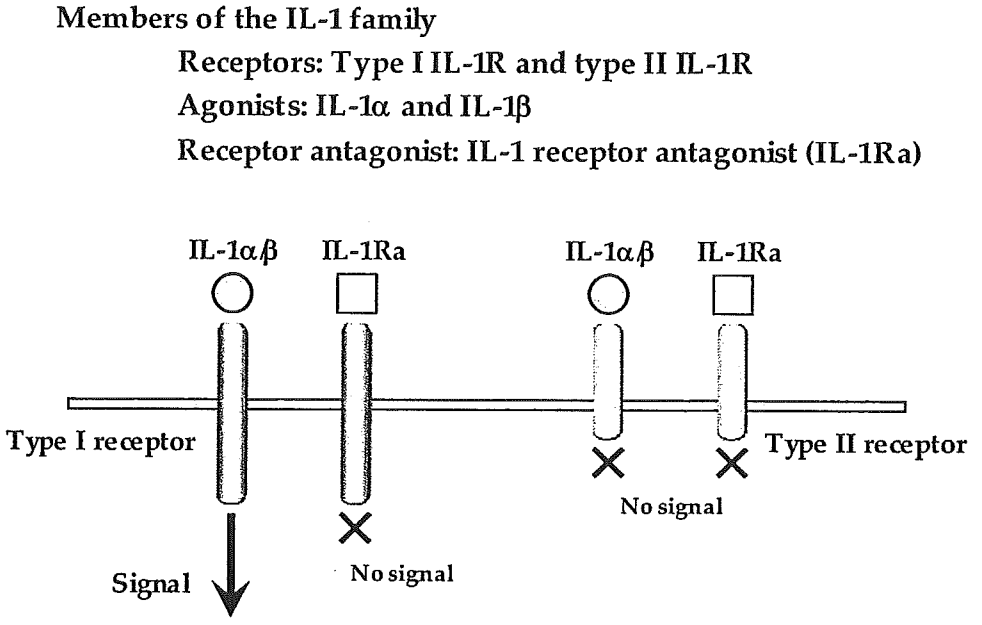

Figure 2. IL-1α and IL-1β induce their signaling through interaction with type I IL-1 receptor. The IL-1 family consists of IL-1 receptors type I (IL-1RI) and Type II (IL-1RII), receptor agonists IL-1α and IL-1β, and IL-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β are produced as inactive precursors, 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.

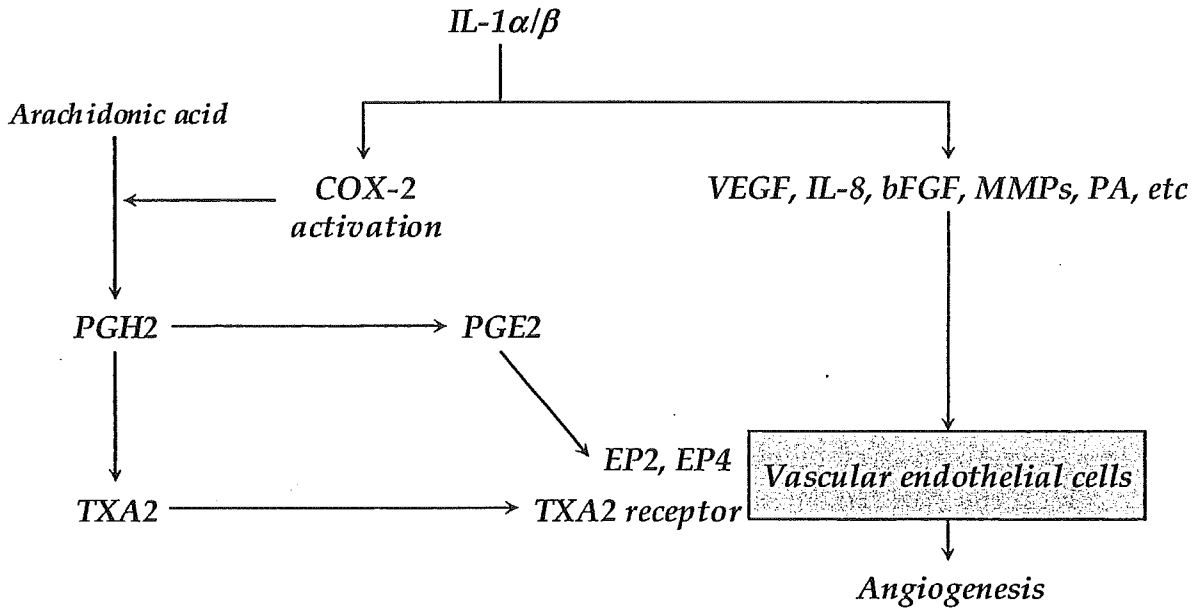

Figure 3. Angiogenesis by IL-1α/β is mediated through dual pathways: induction of angiogenesis-related factors and COX-2 activation. IL-1 stimulates induction of angiogenesis-related factors such as VEGF, IL-8, bFGF, MMPs and PA from vascular endothelial cells and other cell types. These factors co-operatively 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]. Born 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.

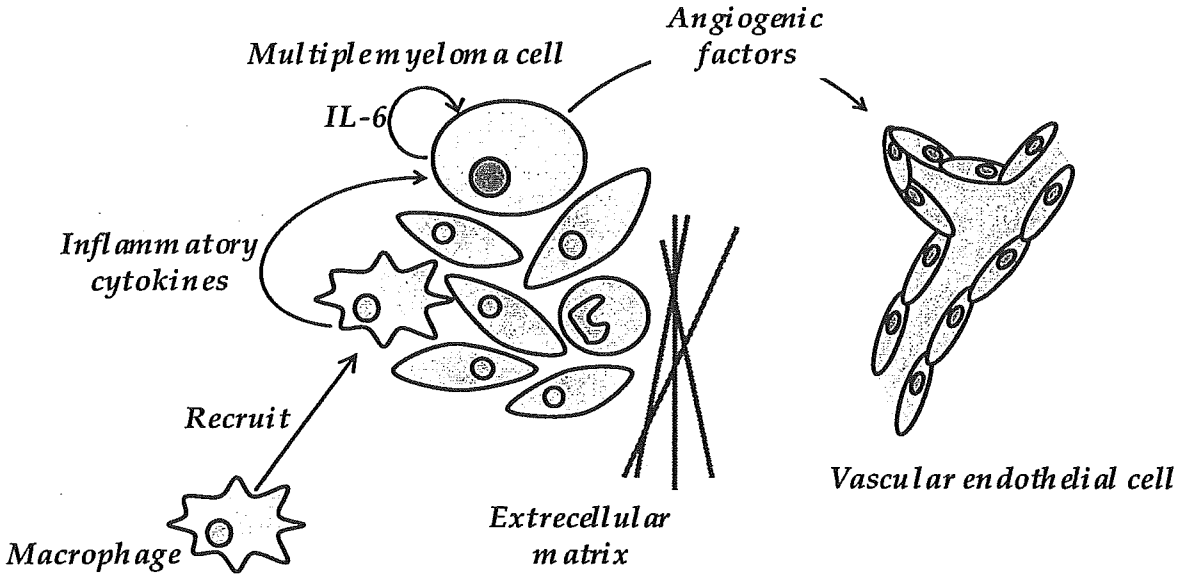

Figure 4. Multiple myeloma form a network near bone marrow through interaction with various inflammatory cell types. Angiogenesis plays a critical role in stroma formation for multiple myeloma through interaction of multiple myeloma cells with various stroma cell types and cytokines.

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