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Review Article

Unraveling the molecular mechanisms between inflammation and tumor angiogenesis

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Abstract: Inflammatory mediators in tumor microenvironment influence cancer occurrence, growth and metastasis through complex signaling networks. Excessive inflammation is closely associated with elevated cancer risk and mortality, in part through inflammation-induced angiogenesis. Mechanistically, multiple tumor-associated inflammatory cells increase the release and accumulation of various inflammatory products in cancerous sites. These products in turn activate tumor associated signaling cascades such as STAT3, NF-κB, PI3K/Akt and p38 MAPK, which mediate the recruitment of inflammatory cells and secretion of pro-inflammatory factors. More importantly, these events promote the secretion of various pro-angiogenesis factors from endothelial, tumor and inflammatory cells, which then drive malignancy in endothelial cells in a paracrine and/or autocrine manner. Its ultimate effect is to promote endothelial cell proliferation, migration, survival and tube formation, and to hence the formation of blood vessels in tumors. This review describes the signaling network that connects the interaction between inflammation and cancer, especially those involved in inflammation-induced angiogenesis. This will reveal potential targets for the design of anti-inflammatory treatments and drugs that inhibites tumor growth and angiogenesis.

Keywords: Inflammation, tumor angiogenesis, endothelial cells, signal pathway

Introduction

Multiple studies have correlated inflammation and tumors. Virchow observed the presence of inflammatory cells in tumor tissues as early as 1863, and was the first to propose that inflammation is associated with tumors [1]. Many studies have demonstrated the link between inflammation with tumor: an epidemiological study showed that inflammation accounted for a considerable proportion of tumors [2]; experimental and clinical studies have shown that chronic inflammatory diseases were closely related to tumors [3]. Angiogenesis is also involved in tumor progression. In 1971, Folkman proposed that tumor growth and metastasis depended on the formation of new blood vessels [4]. Tumor cells induce angiogenesis, and the new blood vessels provide essential nutrients for tumor development and promote tumor metastasis [5].

The respective roles of inflammation and angiogenesis in tumors have been clearly clarified. However, it remains unclear whether there is crosstalk between inflammation and angiogenesis, and whether tumors need inflammation to promote angiogenesis. Studies have shown that oncogenic signaling pathways, which are intersected with some pathways that drive tumor angiogenesis, were activated in the inflammatory response [6, 7]. The relationship between different pathways of angiogenesis is independent and complementary. One signaling pathway usually transmits alone, and also induces and changes the activity of another pathway, thereby ensuring the efficient and orderly transmission of signaling cascades. However, in pathological angiogenesis of tumors, the inflammatory response deviates or enhances the normal transductions of these processes, and this imbalance results in sustained activation of signaling pathways for tumor angiogenesis [8, 9]. This review summarizes the molecular mechanisms underlying the interaction between inflammation and tumor angiogenesis, and discuss their implications in anti-inflammatory therapeutic strategies for tumor angiogenesis.

Inflammation and tumor

Inflammation is defined as a self-protective response of the body against pathogen infection and tissue damage. An autoimmune system-mediated inflammatory response is activated under harsh conditions. The early stage is an acute inflammatory response with the primary aim of anti-infection and tissue repair. In this process, many inflammatory cells infiltrate local areas, engulf and remove foreign invaders and self-necrotic components. The inflammation develops into chronic stages when the inducing factors persist or the inflammatory response fails to terminate. Its outcome often results in parenchymal tissue damage unlike acute inflammation [10]. The body becomes susceptible to some chronic inflammatory diseases. For example, this causes malignant transformation of normal cells for the long term, and eventually develops into cancer [11].

Inflammation occurs at different stages of tumor development. Inflammatory lesions appear before the tumor in some cases. Inflammation may be induced by carcinogenic changes after other tumors initiation to promote the development of the tumor itself [3, 12]. Inflammation may destroy genome stability through inflammatory mediators such as reactive oxygen species (ROS) in the early stage of tumor development, which causes DNA damage leading to proto-oncogene activation and/or inactivation of tumor suppressor genes. This increases the risk of malignant carcinogenesis [13]. Tumors recruit inflammatory cells to infiltrate cancerous areas and drive them to release tumor-promoting products such as cytokines, chemokines, and growth factors. The products provide a microenvironment conducive for tumor cell survival and proliferation along with an extracellular matrix. Moreover, they also act as immunosuppressive agents, hindering the adaptive immune response to evade the host's antitumor defense [14, 15]. In the later stage, tumor cells mainly regulate inflammatory mediators, remodel extracellular matrix to promote epithelial-mesenchymal transition (EMT), increase tumor-dependent blood vessels and lymphatic vessels, thereby promoting tumor cell survival, mobility, and invasion [15-17]. The role of inflammation may be more comprehensive in various stages of tumor development. Regardless of the origin, inflammation provides a constant booster for the development of tumors and plays an important role in promoting tumors at all stages.

Tumor angiogenesis and tumor

Angiogenesis is a typical physiological or pathological process that is characterized by the growth of blood vessels from the existing vasculature. Angiogenesis is indispensable for some normal physiological processes such as fetal development and wound healing. Pathological angiogenesis is a significant symbol of solid tumors, and it is the rate-limiting step in tumor development [4]. The tumor diameter is limited to the distance that nutrients spread without vasculature, which forces solid tumors into dormancy or death [8, 18]. This is because tumor vasculature provides oxygen and nutrients, while also removing toxic metabolites. The biological functions of tumor blood vessels are largely similar to that of normal blood vessels. The process of formation is also similar, which is through angiogenic sprouting and is most closely related to endothelial cell proliferation and migration [19]. Pericytes in the normally quiescent blood vessels are activated due to stimulation by pro-angiogenic stimuli from inflammatory and cancer cells. They then detach from the basement membrane, partly aided by the proteolysis by matrix metalloproteinases (MMPs) [20, 21]. Meanwhile, vascular endothelial growth factor (VEGF) increases the permeability of the endothelial cell layer, synergized by the loosening of tight junctions between endothelial cells. These all cause massive extravasation of plasma proteins to form an extracellular matrix framework [22-24]. As a result, endothelial cells invade the surrounding matrix and form the primary sprouting vessel lumen by proliferation, migration, deformation, and tight junction with each other. This is accompanied by basement membrane and pericyte covering the endothelial layer. Finally, they fuse with the original blood vessels and tumor perfusion is obtained [19].

Tumor blood vessels, essentially pathological, are bound to have many defects. They have a significantly higher proportion of immature structures: incomplete basement membrane, reduced coverage of pericytes, lack of tight junctions between endothelial cells and insufficient blood perfusion. Therefore, the vascular

system in tumor tissues has a large proportion of twisted and deformed high-permeability neovascularization [25]. The high permeability of the vessel wall facilitates the tumor cells to enter the circulatory system, and then spread to other tissues throughout the body [26]. Also, structural abnormalities and inadequate perfusion result in the inability of tumor vessels to effectively transport nutrients and remove harmful metabolic waste, which exacerbates hypoxia and acidosis in the tumor microenvironment [25]. Solid tumors attempt to compensate for quality defects by increasing the number of blood vessels as they face the harsh conditions [27]. This reciprocal relationship promotes the development of tumors and stimulates more pathological tumor angiogenesis.

Inflammation and tumor angiogenesis

Pathologically, inflammation and angiogenesis are interrelated in tumors [28]. On the one hand, inflammation recruits various white blood cells to infiltrate the tumor microenvironment. These cells release various pro-inflammatory factors and growth factors. They also secrete proteolytic enzymes which selectively degrade the basement membrane and extracellular matrix to indirectly promote the release of cytokines. Ultimately, numerous pro-angiogenic mediators regulate the growth and migration of endothelial cells, thereby promoting the formation of tumor blood vessels [29]. The massive inflammatory cell levels coupled with the rapidly multiplying cancer cells cause a sharp increase in oxygen consumption, which is referred to as “respiratory burst”. This causes an oxidative stress response, which results in the release of reactive oxygen species (ROS) in the extracellular matrix [30]. Moreover, tumors also collude with inflammatory cells and prompt them to generate ROS [13]. This leads to the persistence of ROS in the tumor microenvironment, which also initiates tumor angiogenesis [31]. On the other hand, the activated tumor endothelial cells, in addition to serving as the bricks that make up blood vessels, also recruit malignant partners (multiple types of inflammatory cells) to gather in para-cancerous tissues. The endothelial cells activated by various inflammatory factors in the newly formed vasculature produce various adhesion molecules and chemokines. These mediate the rolling, adhesion and transendothelial migration of inflammatory cells in the vascular wall, thereby increasing the number of reactive cells [32]. The blood vessels also maintain inflammation by providing oxygen and nutrients to the inflammatory cells [3]. These series of positive feedback loops form a vicious circle, exacerbating the duration and scope of inflammation as well as causing more defective angiogenesis.

The concept of reciprocity of angiogenesis and tumor has been extended to the effector mechanism of inflammation signaling pathways, which is a link between inflammation-induced tumors and angiogenesis. The vasculature of adult mammals is mostly quiescent because the angiogenesis switch is in the off state due to the absence of angiogenesis growth factors and the high level of angiogenesis inhibitory factors. However, the normal regulation of angiogenesis signaling in tumor tissues is often deviated or enhanced, causing overexpression of growth factors and msnifesting as an increase in pathological tumor blood vessels [8]. Overexpression of pro-angiogenic growth factors in tumor tissues is largely dependent on the initiation of inflammation. Many signaling pathways, such as STAT3, NF-κB, PI3K/Akt, and p38 MAPK, have been associated with this process. A deeper understanding of these signaling pathways will provide potential targets for the prevention and treatment of cancer.

STAT3

Signal transducer and activator of transcription 3 (STAT3) exists in the cytoplasm and is coupled to the tyrosine phosphorylation signaling channel. Activated STAT3 translocates to the nucleus and regulates gene transcription [33]. The STAT3 signaling pathway is a vital endogenous and exogenous inflammatory signaling pathway in tumors. It mediates the expression of inflammatory products triggered by oncogenic stimuli [34]. Interstitial inflammatory cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), are the main force of these product formations, although some are produced by tumor cells [35]. This is due to the continuous activation of STAT3 inherent in tumor cells which is transmitted to the inflammatory cells. In tumor cells, STAT3 promotes gene expression of many pro-inflammatory products such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis

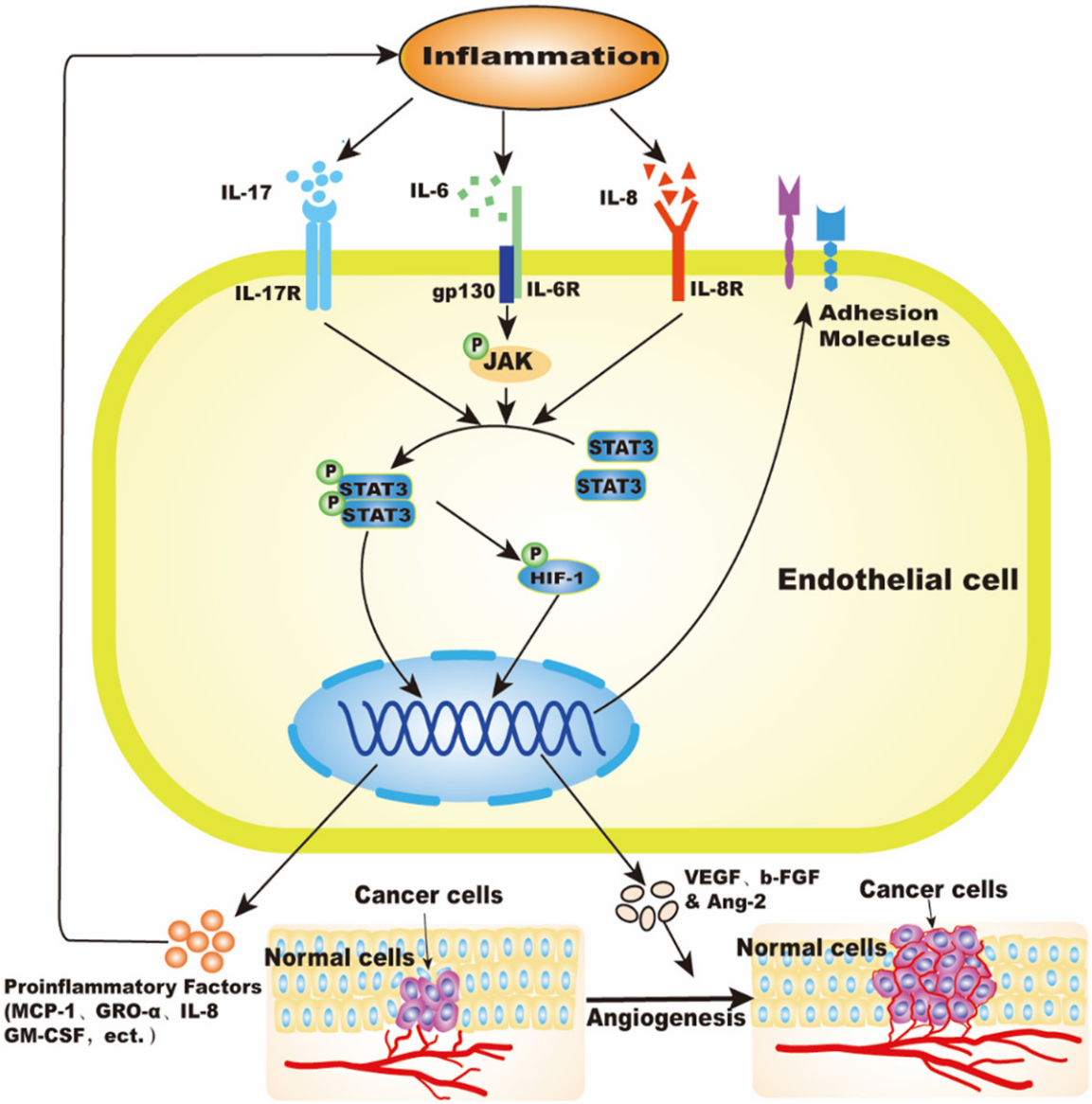

Figure 1. The role of STAT3 in inflammation-induced tumor angiogenesis. STAT3 is a downstream target of various cytokines. In response to the stimulation of cytokines secreted by inflammatory cells (e.g., IL-6, IL-8 and IL-17), STAT3 in turn regulates the expression of inflammatory factors and adhesion molecules to recruit inflammatory cells, thereby exacerbating inflammation. But more importantly, STAT3 promotes endothelial cell synthesis and secretion of various types of pro-angiogenic factors (e.g., VEGF, b-FGF, Ang-2), which promote tumor growth and angiogenesis.

factor-α (TNF-α), which bind to stromal cell receptors and activate the STAT3 signaling pathway. As a result, STAT3 further induces the expression of cytokines, chemokines, and growth factors in activated stromal cells [36, 37]. Therefore, the interaction between tumor cells and interstitial inflammatory cells establishes a STAT3 feedforward circuit between tumors and inflammation [12].

STAT3 plays a crucial role in angiogenesis in inflammation-promoted tumor initiation and development (**Figure 1**). The earliest evidence supporting the association of STAT3 and angiogenesis came from the study on granulocyte-macrophage colony-stimulating factor (GM-CSF), which was observed to stimulate chicken chorioallantoic membrane surface cells and induce angiogenesis on chicken aortic rings [38]. The supply of inflammatory stimuli that act on endothelial cells not only comes from other cells in the tumor tissue but also from endothelial cells. For example, interleukin-17 (IL-17)-induced STAT3 activation directly drives endo-

thelial cells to secret inflammatory factors such as growth-related oncogene-α (GRO-α), GM-CSF, and interleukin-8 (IL-8); these factors also mediate neutrophils recruitment [39]. Indirectly, STAT3 phosphorylation in endothelial cells upregulates intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and other potential adhesion molecules. They facilitate the aggregation of inflammatory cells in the perivascular stroma and promote the production of more inflammatory factors [40, 41]. Various initiators cause excessive activation of STAT3 in many cells including endothelial cells and tumor cells. Studies have shown that the overexpression of STAT3 in various solid tumors was associated with abnormal growth of tumor vasculature. STAT3 acts as a downstream target of IL-6 and IL-8 in astrocytoma. Phosphorylated STAT3 is not only found in the necrotic area around cancerous tissue, but also in perivascular inflammation and endothelial cells, which is positively correlated to tumor angiogenesis [42]. Moreover, IL-17 promotes tumor angiogenesis in a STAT3-dependent manner in gastric cancer, whereas the STAT3 inhibitor prevents this effect [43].

Notably, VEGF and hypoxia-inducible factor-1 (HIF-1) are the main transcriptional targets of STAT3. For example, STAT3 is activated by its upstream IL-6, which constitutes the classical activation pathway IL-6-IL-6R/gp130-JAK-STAT3. The activated STAT3 induces the expression of VEGF by binding to the promoter of the VEGF gene [44] (**Figure 1**). Also, STAT3 indirectly up-regulates VEGF levels by acting to HIF-1 [45] (**Figure 1**). Studies show that STAT3 also increases VEGF receptors in endothelial cells and mediates the transmission of the vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway [46].

STAT3 also upregulates the synthesis of MMP-2 and MMP-9 in endothelial cells [47]. Proteolytically active MMPs selectively degrade and remodel the basement membrane and extracellular matrix, which facilitates the release of VEGF stored in the extracellular matrix and allows endothelial cell migration [21]. The growth of some solid tumors is not inhibited when the signal transduction of VEGF is blocked. This is because the compensatory increase of b-FGF replaces the role of VEGF [48]. The expression of b-FGF in tumor tissues is upregulated by IL-6-induced STAT3 [47, 49]. Similarly, IL-6 drives STAT3 to promote the transcription of Angiopoietin-2 (Ang-2) in endothelial cells, which enhances mural cell detachment, vascular permeability and endothelial cell sprouting [50, 51] (**Figure 1**). Of note, studies have found that TNF-α-induced IL-10 also played an important role in endothelial progenitor cell migration, adhesion, and tubule formation in STAT3-dependent manner [52].

NF-κB

Nuclear factor κB (NF-κB) is a transcription factor assembled by the dimerization of two of five subunits of the Rel-family, and the classical heterodimer is a combination of p65 (RelA) and p50 (RelB). When stimulated, the inhibitory protein IκB is phosphorylated and separated from NF-κB. This allows NF-κB to transfer into the nucleus and regulate target genes [53]. Activation of NF-κB in tumors drives tumor cell proliferation, survival, and invasion. However, this activation does not seem to be associated with the oncogenic mutation of NF-κB. On the contrary, the activation of NF-κB is mainly driven by inflammatory cytokines (such as interleukin-1 (IL-1), TNF-α, etc.) in the tumor microenvironment. It is the result of precancerous persistent chronic inflammatory activation, and/or the activation of the inflammatory microenvironment induced and maintained after malignant transformation [54]. Most importantly, NF-κB has a similar role to STAT3 in the process of inflammation-induced tumors. In response to inflammatory stimuli, both NF-κB and STAT3 efficiently induce the expression of tumor-promoting cytokines including TNF-α, IL-1 and IL-6. The cytokines mediate the initiation signals to non-tumor cells, besides directly acting on tumor cells, and then interact with tumor cells in promoting tumors [34, 54].

The abnormal activation of NF-κB appears to positively correlate with the increase in the number of tumor vasculature. The pathological angiogenesis observed in the vasculature of colorectal cancer is related to the activation of NF-κB signaling, whereas blockade of NF-κB reduces the production of proangiogenic factors and microvessel density [55]. More importantly, the source of NF-κB positive effect on tumor blood vessels is mainly through inflammation. On the one hand, NF-κB activated by

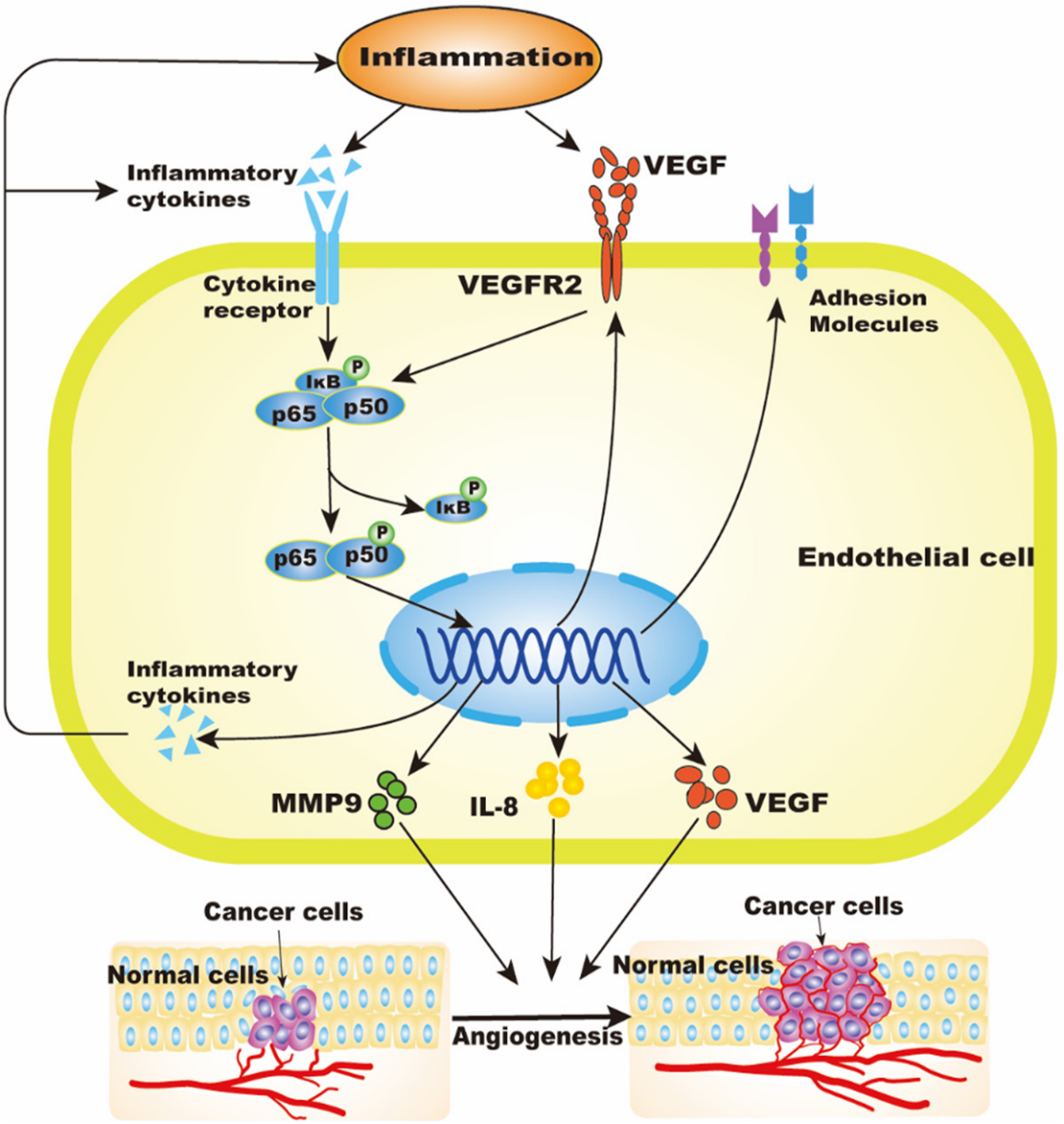

Figure 2. NF-κB-mediated angiogenesis in tumor-associated inflammation. The binding of inflammatory factors (e.g., IL-1, TNF-α, etc.) to their receptors activates NF-κB, which in turn increases the expression of inflammatory factors and adhesion molecules in endothelial cells. This promotes the recruitment of inflammatory cells and the secretion of inflammatory factors, thereby enhancing the activation of NF-κB. Meanwhile, NF-κB drives endothelial cells to up-regulate the expression of multiple proangiogenic factors, including MMP9, VEGF and IL-8, ect. NF-κB also increases expression of type 2 receptor for VEGF on the surface of endothelial cells, which mediates the phosphorylation of NF-κB as well as initiation of angiogenesis.

inflammatory factors is critical for the expression of pro-inflammatory genes in endothelial cells [56]. Meanwhile, NF-κB, like STAT3, activates the expression of various types of adhesion molecules in endothelial cells in response to the activation of proinflammatory cytokines, which facilitates the aggregation of inflammatory cells in the perivascular matrix [57] (**Figure 2**). On the other hand, activation of endothelial cells by inflammatory mediators induces NF-κB phosphorylation and nuclear translocation, which mediates the transcription of most angiogenic genes. VEGF is a recognized angiogenesis factor and a target of anti-vascular drugs.

The ways and target cell types in which NF-κB regulates VEGF expression are diverse. The VEGF is produced by endothelial cells, macrophages and tumor cells under the regulation of activated NF-κB [58-60]. The VEGFR2, as a classic receptor for VEGF, is also regulated by the NF-κB pathway. NF-κB directly binds to the promoter of VEGFR2 and regulates its transcription. The phosphorylation of VEGFR2 expressed on the surface of endothelial cells further promotes the activation of downstream angiogenesis signals [61] (**Figure 2**).

The activated NF-κB also binds to the promoter-related site of the MMP-9 gene to upregulate the expression level of its mRNA [62] (**Figure 2**). Other important angiogenic factors such as monocyte chemoattractant protein-1 (MCP-1), IL-8, and cyclooxygenase-2 (COX-2), are also upregulated by NF-κB to promote tumor angiogenesis [63, 64]. MCP-1 promotes angiogenesis by recruiting macrophages into the tumor microenvironment and stimulates these infiltrating cells to produce various growth factors, chemokines, proteases, and other factors [65]. IL-8, an inflammatory chemokine, also acts as a pro-angiogenic agent, through leukocyte-dependent effects as well as stimulating endothelial cell growth [66]. Coincidentally, IL-8 binds to its homologous receptor C-X-C motif chemokine receptor 2 (CXCR2) and upregulates the mRNA and protein levels of VEGF in endothelial cells, leading to the autocrine activation of VEGFR2; the process also requires activation of the transcription factor NF-κB [67]. COX-2 is overexpressed in malignant tumors including basal cell carcinoma, studies have shown that COX-2 expression promoted tumor growth by upregulating the production of various angiogenic proteins [68]. The NF-κB signaling pathway is also involved in the regulation of endothelial progenitor cells. However, this effect is mediated by a non-canonical NF-κB pathway by upregulating C-X-C motif chemokine 12 (CXCL12), but not the canonical NF-κB pathway induced by inflammatory stimuli (such as TNF-α). The CXCL12 directly regulates the physiological activities of endothelial progenitor cells and indirectly assists in promoting the production of pro-angiogenic factors, thereby leading to the formation of tumor blood vessels [56, 69].

PI3K/Akt

The activation of Akt is mainly mediated by phosphoinositide 3 kinase (PI3K), phosphorylated Akt regulates various physiological cell functions by acting on its downstream target sites [70]. However, dysregulation of PI3K/Akt signaling pathway has also been found in a wide spectrum of human tumors. The abnormal activity of PI3K/Akt not only leads to malignant transformation of cells, but is also closely related to tumor growth, invasion, and metastasis [71]. Meanwhile, studies show that Akt is involved in the regulation of inflammation in paracancerous tissues; either blockade of Akt or attenuation of para-cancerous inflammation inhibits tumors [72]. In tumors, Akt is activated by various inflammatory factors (such as IL-1, IL-6, TFN-α) and participates in the synthesis and secretion of inflammatory mediators [73, 74]. The integrated Akt signaling pathway affects the proliferation, differentiation, migration of various leukocytes, such as TAMs, neutrophils, lymphocytes, thereby driving inflammation [75, 76]. The positive effect of Akt on inflammatory cells is beneficial in promoting the aggregation of reactive cells, and the consequent oxidative stress reaction leads to the release and accumulation of ROS in the tumor site [30]. The non-specific destruction of peroxide (ROS) is related to the activation of some specific signaling cascades in cells exposed to higher oxidant loads, and this process includes the activation of PI3K/Akt signaling pathway [77].

The role of inflammation in tumors through the PI3K/Akt signaling pathway is multifaceted, mediating tumor angiogenesis is a key part. The PI3K/Akt regulates numerous downstream effectors. In ovarian cancer cells, ROS participates in the activation of Akt and its downstream effectors, mammalian target of rapamycin (mTOR) and p70 S6 Kinase 1 (p70S6K1), which mediate the production of VEGF [78]. IL-6 stimulation induces the PI3K/Akt pathway to upregulate b-FGF at the level of transcription and translation; the latter acts on basal cell carcinoma to promote angiogenesis in a paracrine manner [49]. Also, PI3K/Akt affects the physiological functions of various inflammatory cells, which are inextricably related to tumor angiogenesis [72, 79].

PI3K/Akt also regulates endothelial cell phenotype to promote tumor angiogenesis through various effectors, in addition to non-endothelial cells (**Figure 3**). mTOR and p70 S6K1, downstream effectors of Akt, directly play an effect

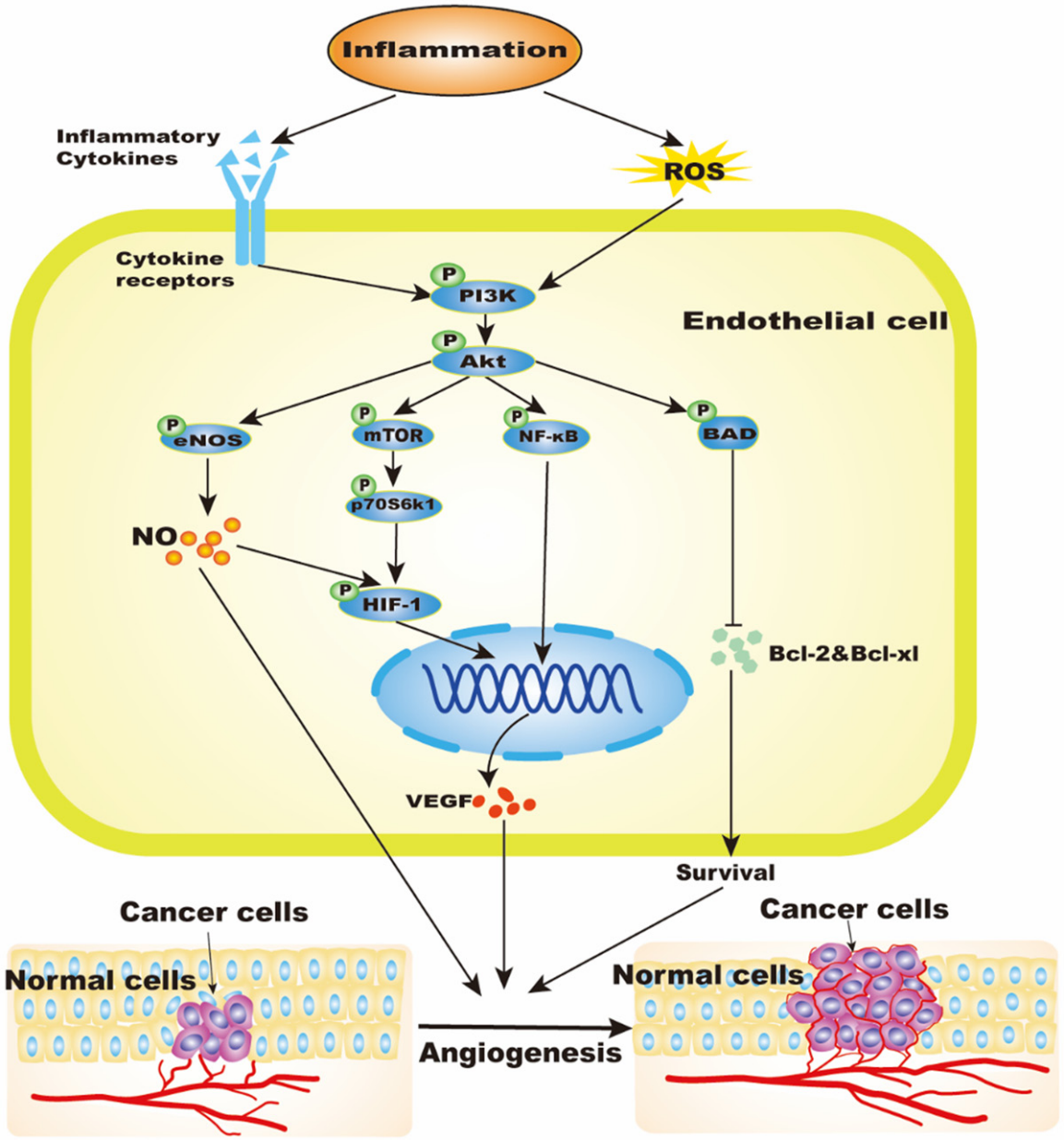

Figure 3. The role of PI3K/Akt in inflammation-induced tumor angiogenesis. Inflammation-induced cytokines and ROS activate PI3K/Akt signaling. Subsequently, PI3K/Akt increases the transcription of HIF-1 to promote VEGF expression by activating mTOR and p70S6K1. ENOS is a downstream effector element for PI3K/Akt, phosphorylated eNOS triggers the production of NO in endothelial cells. NO upregulates the expression of HIF-1 and VEGF, and promotes further angiogenesis by elevating endothelial cell motility. TNF promotes the phosphorylation of proapoptotic Bcl-2 family member BAD by activating PI3K/Akt pathway, which leads to the failure of BAD to inhibit the activity of survival protein Bcl-2 or Bcl-xl.

on endothelial cells [80, 81]. In human skin microvascular endothelial cells (HDMECs), p70 S6K1 upregulates the VEGF expression to enhance tumor growth and angiogenesis, and using p70 S6K1 kinase mutant or HIF-1 inhibitor blocks the processes [82] (**Figure 3**). Meanwhile, the phosphorylated p70 S6K1 reorganizes actin filament that enhances endothelial cell motility, inhibiting Akt with a dominant-negative mutant inhibits cell migration [83]. PI3K/Akt activated by inflammatory stimuli enhances endothelial nitric oxide synthase (eNOS) activity by phosphorylating the serine sites [84, 85]. This promotes nitric oxide (NO) production, a

key factor in angiogenesis, which regulates endothelial cell permeability and migration [86]. Nitric oxide donors increase HIF-1 expression and transcriptional activity to induce the expression of VEGF mRNA (**Figure 3**). PI3K/Akt plays an important role in the survival of endothelial cells under adverse conditions. Under the condition of co-culture with lung cancer cells, the microvascularization ability of endothelial cells is increased, while the proportion of apoptosis is decreased. This is because cancer cells activate the PI3K/Akt pathway to regulate these functions of endothelial cells [87]. TNF is considered a classical pro-apoptotic activator, Akt in endothelial cells ablates apoptosis caused by high doses of TNF. On the contrary, it utilizes low doses of TNF to self- activate and promote protein synthesis and survival of endothelial cells to induce angiogenesis, which requires the activation of Tie-2 by Ang-1 and integrin-mediated adhesion [88, 89]. TNF also promotes the phosphorylation of proapoptotic Bcl-2 family member BAD by activating PI3K/Akt pathway, which leads to the failure of BAD to inhibit the activity of survival protein Bcl-2 or Bcl-xl, while inhibitor LY294002 blocks the positive regulation of PI3K/Akt pathway on endothelial cell survival [90, 91]. Interestingly, the inhibition of apoptosis does not depend on the activation of NF-κB, but NF-κB also participates in endothelial cell survival as a downstream effector of Akt [91, 92]. Moreover, NF-κB activated by Akt is also involved in the expression of VEGF [93]. These studies indicate that inflammation induces angiogenesis through activation of PI3K/Akt pathway in tumor and other cells (in paracrine manner) and/or endothelial cells (in autocrine manner).

p38 MAPK

P38 mitogen-activated protein kinase (p38 MAPK) is one of the core components of three protein kinases in the MAPK cascade. It is activated by a wide range of extracellular stimuli and then regulates various cellular processes through diversification and extensive downstream effects [94]. P38 MAPK is involved in the crosstalk between inflammation and tumor, this interaction is partly connected through tumor blood vessels. It mediates tumor angiogenesis by affecting cellular processes and the production of relevant functional factors. The activity of p38 MAPK in both tumor cells and stromal inflammatory cells is significantly increased in tumor-related inflammation, which is induced by factors such as cytokines and oxidative stress [95, 96]. This increases the synthesis of inflammatory mediators at the transcriptional and translational levels, including IL-1, IL-6, IL-8, MCP-1, and TNF-α [97, 98]. Many inflammatory cells and cytokines accumulate in para-cancerous tissues, which induces the production of more inflammatory mediators. At this time, the endothelial cells in the tumor microenvironment inevitably suffer from various stimuli. The p38 MAPK cascade controls endothelial cell proliferation, migration, and survival, in response to exogenous and endogenous stimuli (stress, cytokines, and growth factors). This effect deviates from the normal physiological state of endothelial cells to promote cancer [99].

Different stimuli enable p38 MAPK to control endothelial cell functions by catalyzing diverse substrates (**Figure 4**). The levels of cytokines (such as TNF and IL-1β) rapidly and substantially increase in tumor tissues [100]. A pleiotropic cascade of p38 MAPK is initiated in multiple cells following the binding of these cytokines to receptors, which mediates the expression of proangiogenic factors including VEGFA, IL-8, IL-6, heparin-binding EGF-like growth factor (HBEGF) and fibronectin [100]. Similarly, TNF-α and IL-1α promote the transcription of IL-8 mRNA and protein translation in human pulmonary vascular endothelial cells in a p38 MAPK-dependent manner [101]. TNF-α induces MCP-1 expression in rat primary pulmonary artery endothelial cells via p38 MAPK signal transduction [102]. Another pro-inflammatory factor, IL-6, shows proangiogenic properties in the B16 xenograft mouse model. Interestingly, IL-6 simultaneously activates p38 MAPK, NF-κB and STAT3 to upregulate the production of angiogenesis agents VEGF and platelet-derived growth factor (PDGF), although the completion of this effect requires the assistance of death receptor 6 (DR6) [103].

Furthermore, endothelial cells are heavily exposed to ROS produced by inflammatory cells and endothelial cells themselves [30, 104], ROS activates p38 MAPK pathway to mediate the upregulation of HIF-1 stability and activity [105]. It is well known that HIF-1 acts as an important upstream regulator of VEGF and pro-

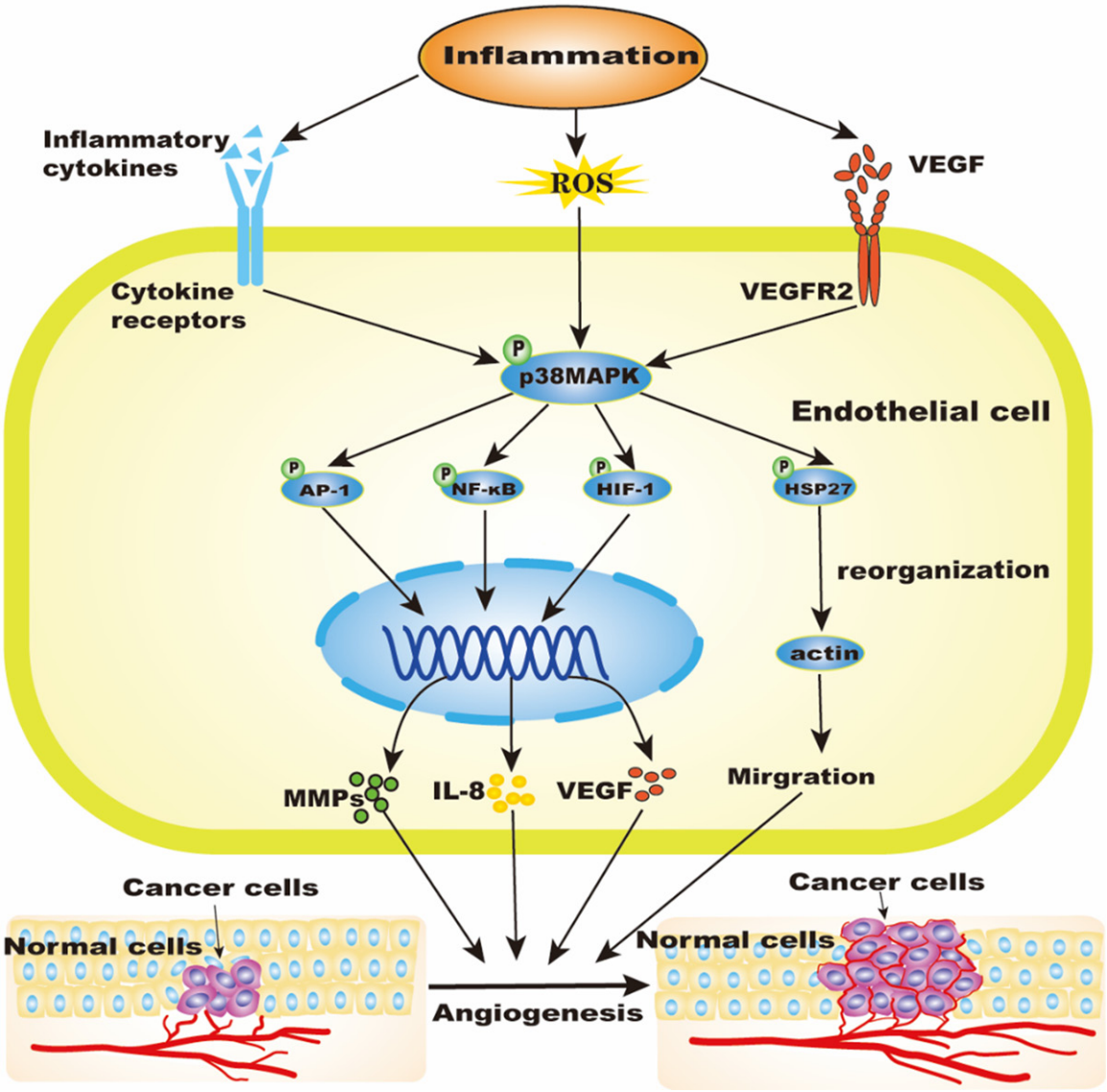

Figure 4. The role of p38 MAPK signaling pathway in inflammation-induced tumor angiogenesis. The p38 MAPK signaling is activated by several extracellular stimuli. Inflammatory cytokines (e.g., TNF, IL-1, IL-6, etc.) activate p38 MAPK, which then phosphorylates downstream targets AP-1 and NF-κB, thereby upregulating the expression of MMPs, IL-8 and VEGF. This is because the promoter regions of angiogenic genes contain binding sites for AP-1 and NF-κB. Under conditions where endothelial cells are heavily exposed to ROS, endothelial cells overexpress HIF-1 and VEGF in a p38 MAPK-dependent manner. VEGF and ROS produced by inflammatory cells increase the activity of p38 MAPK which phosphorylates HSP27. Activated HSP27 reorganizes actin and regulates the motility and migration of endothelial cells.

motes its expression to trigger angiogenesis [106]. Similarly, EGF promotes HIF-1/VEGF-mediated angiogenesis by inducing p38 MAPK activation [107]. VEGF binds to VEGFR2 on the surface of endothelial cells, which in turn triggers phosphorylation of p38 MAPK to regulate angiogenesis. For example, p38 MAPK participates in remodeling actin filament via the VEGFR2-Nck/p38 MAPK/HSP27 axis [108]. When endothelial cells are dysregulated by oxidative stress in the tumor microenvironment, ROS also mediates actin reorganization in vascular endothelial cells through the p38 MAPK/HSP27 pathway [109] (**Figure 4**). The endothelial cell motility is significantly elevated in both cases. Also, p38 MAPK participates in selectively degrading extracellular matrix and basement membrane to promote endothelial cell migration by increasing the expression of MMPs. For example, the overexpression of MMP-2 and MMP-9 has been observed in nasopharyngeal carcinoma, which was induced by

IL-17 in p38 MAPK-NF-κB dependent manner [110]. IL-1β-induced p38 MAPK activation has similar efficacy, but AP-1 is the downstream transcription factor of p38 MAPK rather than NF-κB [111]. Interestingly, the promoter of VEGF and IL-8 gene also contains different recognition sites for the transcription factor NF-κB and AP-1, which suggests that p38 may promote the expression of VEGF in a non-HIF-dependent manner [112] (**Figure 4**).

Perspectives

Inflammatory mediators are known to activate various tumor-promoting signaling pathways such as STAT3, NF-κB, PI3K/Akt and p38 MAPK, thereby promoting various physiological activities of tumor cells. Notably, the initiation and progression of these pro-tumor signaling pathways are not limited to tumor cells alone, but also involve in other stromal cells (including inflammatory cells and endothelial cells) in tumor microenvironment. Together, the aforementioned signaling pathways link tumor endothelial cells and inflammatory responses, forming a complex signaling network involved in inflammation-induced tumor angiogenesis. The ultimate effect of these signaling pathways is to promote endothelial cell proliferation, migration, survival and tube formation, which in turn promote angiogenesis and tumor growth (**Figure 5**). Therefore, targeting the molecular mechanism of inflammation-mediated angiogenesis with specific inhibitors may confer multiple beneficial therapeutic effects against cancer by regulating the synthesis and secretion of chemokines and cytokines.

Notably, NF-κB, STAT3, PI3K/Akt, and p38 MAPK pathways regulate tumor angiogenesis and endothelial cell resistance to available therapies. Both inhibitors in the experimental research stage and targeted drugs in clinical application show obvious inhibitory effects on tumor vasculature. Some of them work by blocking specific sites or disrupting normal physiological conformations of target molecules. For example, a xylene derivative TEL03 inhibits STAT3 activity by blocking its phosphorylation, while another low-molecular-weight compound STATIC directly prevents STAT3 dimerization to inhibit its activity by binding to the SH2 domain of STAT3, both of which suppress STAT3-mediated angiogenesis [113]. Similarly, thalidomide blocks the activation of NF-κB by decreasing the activity of IκB kinase, which mediates the anti-angiogenesis properties in tumor [114]. The development of small molecule inhibitors in clinic shows a flourishing situation, and they are at various stages of clinical trials or have been marketed in the treatment of many cancers. OPB-51602 as a novel inhibitor of STAT3 exhibits promising anticancer activity in the phase I study [115], and phase I studies of the pan-PI3K inhibitor buparlisib in advanced solid tumors demonstrates its safety and efficacy in tumor suppression [116]. Moreover, tucidinostat is an oral subtype-selective histone deacetylase inhibitor of NF-κB, which has been put into the market as a mature clinical anticancer drug [117, 118]. These small-molecule inhibitors can reduce the number and volume of tumor lesions, and prolong the progression-free period of tumors in patients. And the inhibitory effect of them on tumors may be mediated by blocking inflammation-induced tumor angiogenesis.

Apart from the compounds designed artificially based on “proof of principle”, extracts from some natural plants such as artemisinin, curcumin, and resveratrol also show anti-angiogenesis effects by regulating multiple signaling pathways [119]. Moreover, the extensive anti-inflammatory effects of these natural substances often simultaneously regulate multiple signaling pathways. For example, artemisinin inhibits tumor angiogenesis by blocking STAT3, NF-κB, PI3K/Akt and p38 MAPK signaling pathways [120, 121]. This means that natural anti-inflammatory drugs can minimize resistance because they are capable of blocking multiple signaling pathways simultaneously. More importantly, they have milder pharmacological processes and fewer severe adverse effects. These drugs hold great promise in cancer prevention and treatment [119].

In the review, we have shown the link between inflammation and carcinogenesis, and the molecular mechanisms through which inflammation regulates tumor angiogenesis. We reveal avenues for developing anti-cancer treatments.

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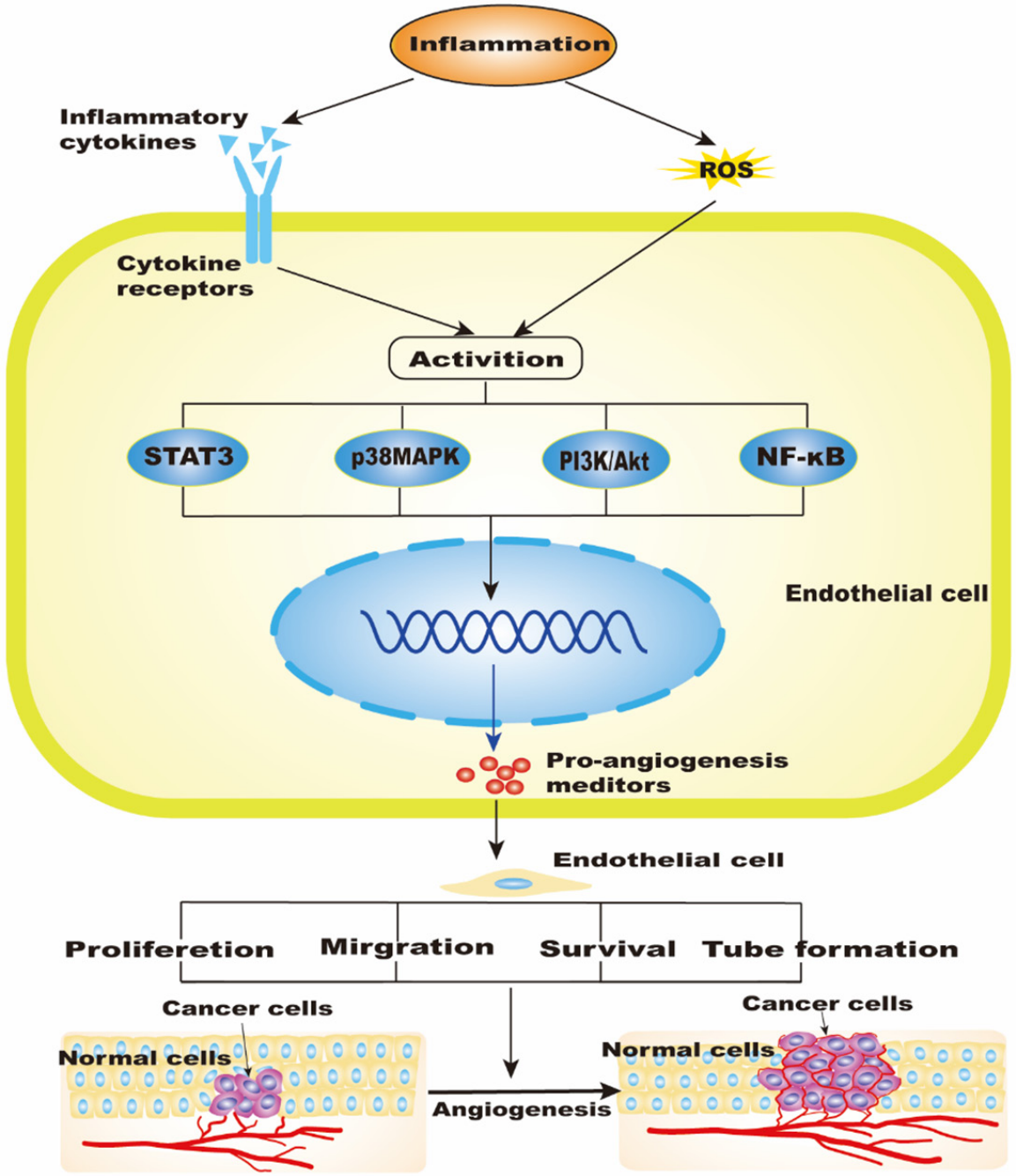

Figure 5. The integrated signal pathways in inflammation-induced tumor angiogenesis. Inflammatory mediators (e.g., inflammatory cytokines and ROS) activate several signaling pathways such as STAT3, NF-κB, PI3K/Akt and p38 MAPK. The latters control numerous downstream targets to upregulate the production of proangiogenic mediators. As a result, these mediators exert positive regulatory effects on proliferation, migration, survival and tube formation of endothelial cell, effectively promoting angiogenesis and growth of tumors.

Disclosure of conflict of interest

None.

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