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Roles of inflammation in cancer initiation, progression, and metastasis

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1. ABSTRACT

Inflammatory cells and signals contribute to the initiation and development of cancer. In fact, persistent inflammatory conditions resulting from infection or injury can exist before a normal cell is transformed into a cancer cell. Situations of chronic inflammation can promote genomic instability leading to DNA damage, oncogene activation, or impaired function of a tumor suppressor. Alternatively, cancer development unrelated to inflammation can stimulate the development of an inflammatory microenvironment that promotes tumor cell proliferation. Whether chronic or tumor-derived, inflammation and inflammation-related stimuli within the tumor microenvironment permits proliferation and survival of cancer cells, promotes blood and lymphatic vessel formation, and aids in invasion and metastasis. The inflammatory status of the tumor microenvironment can act to quell the body's natural immune response and effectively ameliorate a positive response to many commonly used anti-cancer antibodies and chemotherapeutic agents. New evidence suggests that the molecular pathways and consequences of inflammation specifically related to the tumor microenvironment are starting to be understood. This new information implicates novel cellular targets that could lead to improved diagnosis and treatment for a variety of solid malignancies.

2. INTRODUCTION

Cancer is a progressive disease typically initiated by acquired mutations in dividing cells that circumvent cellular senescence or programmed death leading to neoplastic progression (1). Secondary to these genetic alterations, the microenvironment of the developing tumor is an important mediator of tumor maintenance, progression, invasion, and metastasis. The stimuli responsible for this process include but are not limited to growth factors, cytokines, and vessel stimulating factors. These factors act in concert to aid in the recruitment of various cell lineages including immune cells, fibroblast, endothelial cells, and mural cells forming the blood and lymphatic vasculature.

Inflammation is a natural response of the body to superficial or internal injury. In either case, injury stimulates a cascade of chemical and inflammatory signals as the body attempts to quell the potential for infection and heal injured tissue. It is also this natural protective mechanism which is a contributing factor in shaping the tumor microenvironment and promoting tumor growth. The relationship between inflammation and cancer was first proposed by Rudolf Virchow in 1883 when he observed the presence of leukocytes in samples of malignant tumor tissue. His initial observations have since been corroborated by numerous clinical and epidemiological studies

Table 1. Signaling molecules in the tumor microenvironment that contribute to the initiation and progression of cancer

Signalling molecules	Role in inflammation-associated cancer
CYTOKINES	Stimulate cell proliferation and immune cell recruitment Activate transcription factors and maintain tumor microenvironment
iNOS	Elevated in precancerous and cancerous lesions Induces oxidative DNA damage
NF-kappa Beta	Promotes invasion and metastasis Protects transformed cells from apoptosis Stimulates production of proinflammatory mediators
Cox2	Overexpressed in various inflammation-associated cancers Catalyzes production of lipid-based inflammatory mediators Supports maintenance of a persistent inflammatory state
PGE2	Stimulates inflammatory angiogenesis Activates proinflammatory pathways within the tumor microenvironment

demonstrating that chronic inflammation contributes to cancer progression. Current studies estimate that underlying infection and inflammation is linked to 10-20% of cancer mortalities (2). Contributing mechanisms to this pathobiology include ectopic or inhibited gene expression, prevention of apoptosis, aggressive tumor neovascularization, invasion through tumor-associated basement membrane, and metastasis (3).

Inflammation-induced production of reactive oxygen and nitrogen species can damage cellular DNA, proteins, and lipids contributing to malignant cell transformation. While inflammation can promote the development of cancer, the compliment of cell types which make up the tumor microenvironment including tumor cells, stromal cells, and immune cells also act to promote the development of an intra-tumor inflammatory state by elevating production of pro-inflammatory cytokines. These cytokines act to stimulate expression of angiogenic switches, such as those regulated by vascular endothelial growth factor (VEGF), leading to neovascularization and cross-talk between the tumor and surrounding stroma.

Cancer-associated inflammation includes the presence of infiltrating leukocytes, increased expression of cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukins, as well signals controlling the formation of new vessels and tissue reconstruction. Inflammation is directly correlated to several cancers including inflammatory bowel disease, a condition of largely unknown origin that is often associated with colon cancer, and prostatitis or enlargement of the prostate gland incident with prostate cancer. Thus, treatment with non-steroidal anti-inflammatory agents dampens inflammation-related side effects and in some cases mortality that results from tumor number and type (4). This review intends to highlight the role of inflammatory cells Figure 1 and effector molecules Table 1 that constitute the tumor microenvironment and the consequences of inflammation as related to the initiation and progression of cancer.

3. INFLAMMATORY FACTORS INVOLVED IN FORMATION OF THE TUMOR MICROENVIRONMENT

3.1. Cytokines

Cytokines function in growth, differentiation, and activation of immune cells. Cytokines also promote tumo progression by inhibiting programmed cell death at the site of inflammation, a result of unchecked cell growth and differentiation (5-6). Specifically, elevated levels of IL-6 have been reported to promote the progression of colon cancer (7). In addition, TNF-alpha, interleukin-10 (IL-10), and tumor growth factor-beta (TGF-beta) have also been reported to contribute to cellular proliferation in cancers of the colon, breast, and prostate (8-9). TNF-alpha assists in maintenance of the tumor microenvironment in addition to stimulating cellular changes and promoting tissue remodeling (10). TNF-alpha also regulates a series of inflammatory signals resulting in the activation of additional inflammatory cytokines, chemokines, and growth factors at the site of tissue damage. TNF-alpha signaling can aid in the remodeling of tumor-associated tissues by mediating the interaction of tumor cells with surrounding stromal cells and the extracellular matrix. IL-10 has been shown to be involved in many types of malignant disease including carcinoma, lymphoma, and melanoma (11). Secretion of IL-10 by monocytes suggests that this cytokine can promote the establishment of an inflammation-associated and immune-suppressed microenvironment in proximity to the malignant cells.

3.2. Cyclooxygenases

Cyclooxygenases are enzymes that function during inflammation to mediate the release of prostaglandin, a metabolite of arachidonic acid. Prostaglandin metabolites E2 (PGE2) and F2alpha (PGF2alpha) have been shown to play a role in carcinogenesis (12). Expression of cyclooxygenase-2 (Cox2), the key enzyme in the biosynthesis of prostaglandins, is frequently found to be elevated in breast and colon tumors suggesting a role for Cox2 as a mediator between inflammation and cancer (13). Additionally, elevated levels of Cox2 can promote cellular proliferation, suppress apoptosis, and stimulate tumor vessel development. A recent study focusing on an esophageal model of inflammation in rats indirectly supports the hypothesis that induction of Cox2 can mediate tumor progression following inflammation (14). Importantly, selective inhibition of Cox2 with Refecoxib™ has been found to delay the onset and progression of colon tumors (12).

3.3. Hypoxia Inducible Factor

Hypoxia inducible factor-1-alpha (HIF-1alpha) is a heterodimeric transcription factor (15). Under reduced

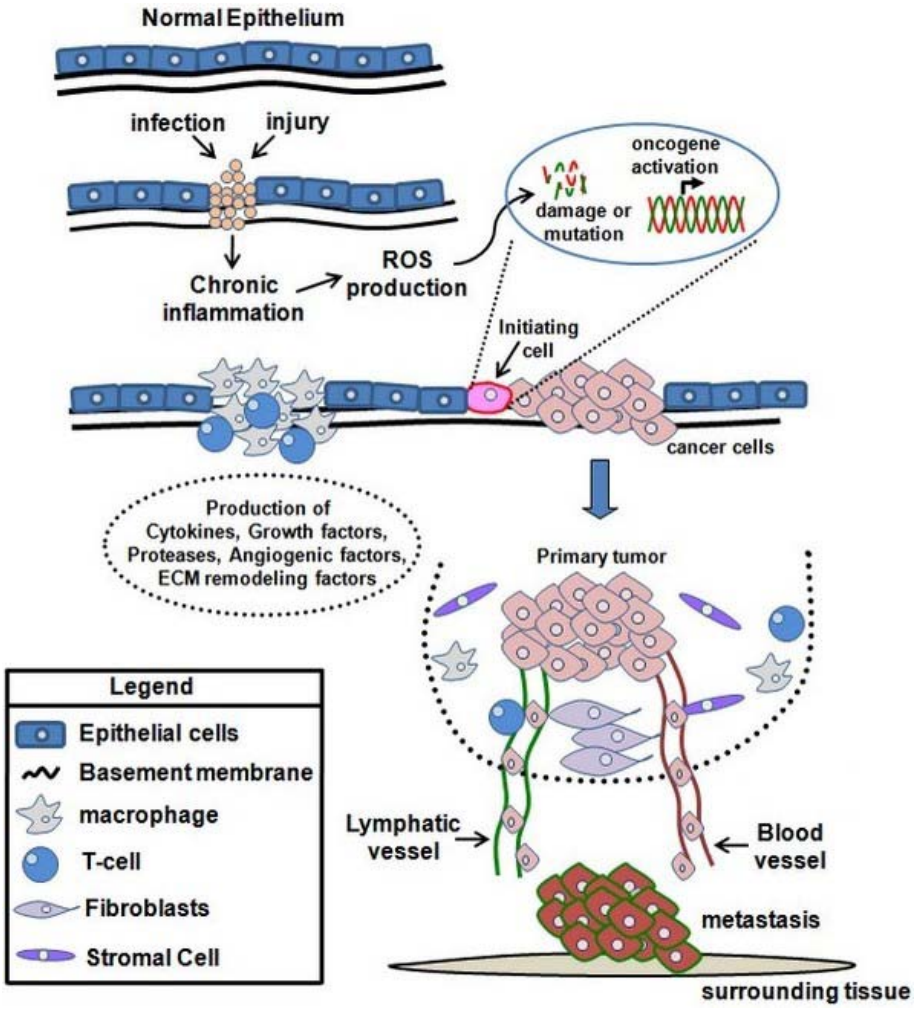

Figure 1. The potential roles of inflammatory cells and effector molecules during the development and progression of cancer are illustrated. Chronic inflammation resulting from infection or injury stimulates the production of reactive oxygen or nitrogen species (ROS) which mediates recruitment of immune cells. These molecules can simultaneously induce DNA damage, mutation, oncogene activation, or inactivation of a tumor suppressor that serves as the initiating event for carcinogenesis. Infiltrating macrophages, mast cells, and T-cells cooperate with resident stromal cells and the developing tumor to produce inflammatory mediators (cytokines and growth factors) that promote cellular proliferation and tumor progression. These signaling events induce the formation of new lymph and blood vessels angiogenesis and promote the epithelial mesenchymal transition which permits tumor cell migration, invasion, and metastasis.

oxygen conditions, HIF-1alpha can activate a range of molecules including inducible nitric oxide synthase (iNOS), VEGF, and erythropoietin (EPO). Hypoxia is a common characteristic of inflammatory lesions, a result of poor vascularization and subsequent blood flow. Thus, hypoxia is tied to inflammation and tumor growth within the microenvironment. HIF-1alpha plays a critical role in multiple models of inflammation such as colitis and esophagitis by inducing leukocyte adhesion and maintaining function of myeloid cells recruited to the site of inflammation (16). HIF-1alpha impacts tumor development as it facilitates growth of transformed cells, by increasing transcription of VEGF, a potent angiogenesis factor involved in tumor growth and metastasis (17). HIF-1alpha has been found to be activated by nuclear factor-kappa beta (NF-kappaB), TNF, and prostaglandins (18). Additionally, persistent expression of HIF-1alpha may result from NF-kappaB activation and Cox2-mediated induction by pro-inflammatory cytokines enriched within the tumor microenvironment.

3.4. Nuclear Factor-Kappa Beta

NF-kappaB is a critical mediator of inflammation, regulating the expression of inflammatory molecules such as cytokines and adhesion factors including interleukin-6 (IL-6), TNF-alpha, Cox2, iNOS and matrix metalloproteinases (MMPs) NF-kappaB is activated by inflammatory stimuli and its constitutive activation is known to be involved in cancer progression. Constitutive activation of NF-kappaB stimulates expression of vascular cell adhesion molecules which promote leukocyte adhesion and migration within the tumor, and prime the

inflammatory status of the tumor microenvironment. NF-kappaB also promotes cytokine expression by the tumor creating an autocrine signaling loop. This autocrine signaling of NF-kappaB and NF-kappaB target genes creates a situation of sustained inflammation (3). NF-kappaB also contributes to tumor development by stimulating cell proliferation through the activation of growth promoting factors, cMyc and CyclinD1 or production of reactive oxygen species that affect genomic integrity.

3.5. Inducible Nitric Oxide Synthase

Nitric oxide (NO) is a mediator of the inflammatory process and cancer development because it has been found to regulate angiogenesis, leukocyte adhesion and infiltration, as well as metastasis (19). Inducible nitric oxide synthase (iNOS) catalyzes the production of nitric oxide from arginine, and has been reported to be overexpressed in situations of chronic inflammation (20). Pro-inflammatory cytokines such as TNF-alpha and IL-1 induce expression of iNOS. Furthermore, iNOS may be a downstream effector of cytokines promoting both inflammation and tumor progression. During situations of chronic inflammation, continuous generation of NO causes DNA damage by impairing the activity of cellular machinery responsible for DNA repair (21). Increased NO production also leads to gene activation, e.g. p53 is rendered constitutively active through acquired somatic mutations. In the tumor microenvironment, iNOS expression may be induced through continuous stimulation by cytokines or directly as a target of NF-kappaB (22).

4. CHARACTERISTICS OF THE TUMOR MICROENVIRONMENT

The tumor microenvironment is not simply composed of cancer cells, but many resident cell types including fibroblast, adipocytes, and migrating hematopoietic cell types, such as macrophages, neutrophils, and mast cells. Inflammatory cells found in the microenvironment include members of both the adaptive and innate immune system. The interaction between the tumor, surrounding stromal tissue, and infiltrating immune cells promotes the production of inflammatory cytokines, chemokines, growth factors, and vessel-stimulating factors. These molecules effectively transform the tumor microenvironment to one which favors the survival, growth, and motility of cancer cells (23). Tumor associated macrophages (TAM), vascular endothelial cells, and fibroblasts all secrete growth factors and chemokines that promote tumorigenesis. The role of TAM in promoting tumor growth and invasion is highlighted by clinical evidence from breast cancer patients where increased numbers of TAM was found to correlate with poor prognosis (24-25). The growth promoting effect of TAM is mediated by their ability to produce or stimulate the production of angiogenic factors and cytokines, including EGF, fibroblast growth factor (FGF) family members, VEGF, and TGF-beta. In addition, TAM produce various members of the MMP family, for example MMP2 and MMP9, which actively degrade the extracellular matrix permitting tumor cell invasion into surrounding tissue (26).

5. INFLAMMATION AND THE TUMOR MICROENVIRONMENT

Chronic inflammation contributes to cancer progression and can exist prior to the neoplastic event. Tumors lacking an epidemiological cause can be characterized by enrichment for inflammatory signals within the microenvironment. Inflammation, as related to cancer, includes cytokines, chemokines, growth factors, and matrix/protein degrading enzymes. Consistent with this concept, are reports that approximately 15-20% of all malignancies are initiated or exacerbated by inflammation (2). The formation of new vasculature and the extracellular matrix transition are key events that shape the tumor microenvironment. Macrophages assist in this process by promoting the recruitment of additional inflammatory cells to the tumor site. The recruitment and infiltration of macrophages to the tumor site leads to their constitutive activation permitting these TAM to support the malignant progression of tumor cells. The surrounding stromal cells are subsequently activated and assist in modifying the milieu of the tumor environment through subsequent activation of the tumor cell secretome, which includes growth-promoting proteins involved in angiogenesis, inflammation, cell proliferation, and (27-28). Secretion of immune suppressing factors and cytokines by cells in the tumor stroma can induce cancer cells to undergo transdifferentiation or epithelial to mesenchymal transition (EMT) (29). In this process, the epithelial cells composing the primary tumor lose the requirement for cell-cell contact, and acquire the ability to migrate away into surrounding tissue. Important to this process is TGF-beta signaling and TGF-beta-related activation of bone morphogenic proteins (BMP).

The chronic inflammatory state of the tumor microenvironment is promoted by macrophages (30). Macrophages together with recruited neutrophils, mast cells, and esoniphils increase the concentration of reactive oxygen and nitrogen species in tumor microenvironment attempting to aid in the body's natural defense against infection (26). However, the increased concentration of reactive oxygen and nitrogen species can have mutagenic consequence through DNA lesions or altered gene expression in proliferating cells. In addition, the tumor inflammatory microenvironment can facilitate the cleavage of the basement membrane, a process required for the invasion and migration of tumor cells.

TAM contribute to tumor development by inducing the expression of growth factors, proteases, in addition to promoting angiogenesis and suppressing adaptive immunity. TAM release IL-10 and prostaglandin E2 which suppress antitumor immune response (26). TAM facilitate tumor growth by releasing angiogenesis factors, such as VEGF and endothelin-2 (31). TAM may also facilitate tumor cell invasion and metastasis by releasing MMP2 and MMP9, which degrade the extracellular matrix and basement membrane, or by inducing production of TNF-alpha and iNOS (32). TAM also mediate production of epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) to promote tumor cell proliferation

and migration. Activated mast cells generate angiogenesis growth factors, such as VEGF, vascular permeability factor (VPF), basic fibroblast growth factor (bFGF), heparin, and MMP.

6. ROLE OF INFLAMMATION IN CANCER DEVELOPMENT: EVIDENCE FROM EPIDEMIOLOGICAL AND CLINICAL STUDIES

Epidemiologic and clinical studies have clearly demonstrated an association between inflammation and cancer (33-34). For example, the risk of colorectal cancer was reported to be 10-fold higher in patients having inflammatory bowel disease as associated with ulcerative colitis and Crohn's disease (34-35). This relationship is underscored by the effective use of Cox2 inhibitors to reduce the occurrence of colon cancer (36). Furthermore, chronic inflammation induced by clonorchis sinesis infection results in cholangiocarcinoma of the bile tract and inflammation of the prostate gland is associated with increased risk of developing prostate cancer (37-38). Finally, chronic hepatitis is associated with increased incidence of hepatocellular carcinoma, the third leading cause of cancer death world-wide (39). The risk of esophageal cancer, pancreatic cancer, and gall bladder cancer may be increased by inflammatory diseases such as pancreatitis and esophagitis. Thus, increasing evidence supports the association between inflammation and cancer.

7. SIGNALING PATHWAYS INVOLVED IN TUMOR DEVELOPMENT

There are two pathways linking inflammation and cancer. The intrinsic pathway (oncogene-mediated) and an extrinsic pathway (microenvironment regulated) connect inflammatory reactions with neoplastic transformation and progression. A number of studies have indicated that pathways leading to inflammation include von Hippel Lindau (VHL), HIF-1alpha, the proto-oncogene RAS, as well as activation of the master transcription factor NF-kappaB (40). Introduction of an activated version of RAS oncogene into the cervical carcinoma cell line (HeLa) stimulates production of IL8/CXCL8 to levels which are sufficient to promote angiogenesis and tumor progression in immune compromised animals (40). The chemokine receptor CXCR, positioned downstream of VHL/HIF, is frequently expressed on malignant cells and implicated in cell survival and metastasis. In non-small cell lung cancer (NSCLC) mutation of tumor suppressor gene phosphatase/tensin homolog deleted on chromosome 10 (PTEN) results in upregulation of HIF-1alpha and expression of its target CXCR4 promoting metastasis.

It is well known that cytokines can activate signal transducer and activator of transcription (STAT) family transcription factors through a mechanism of janus-activated kinase (JAK) (41-42). Interleukin-6, a well established inducer of STAT-3, was found to be involved in the progression of colon cancer (41). Additionally, STAT3 has been found to be constitutively activated in various types of cancer (42). The JAK-Stat signaling pathway is frequently linked to inflammation and the development of the tumor microenvironment. Additional transcription factors including nuclear factor of activated T-cells (NFAT), which is expressed in both immune and non-immune cells, plays an essential role in inflammatory responses by regulating the expression of a wide range of proinflammatory cytokines. In colon carcinoma cells, NFAT has been shown to be involved in the expression of Cox2, which has extensive function in both inflammation and cancer development (43).

8. DRUG TARGETS

Synthetic and natural anti-inflammatory compounds are widely used agents in cancer therapy. The selective Cox2 inhibitor (Celexocib™) demonstrated significantly reduced chemopreventative effects in experimental colon and gastrointestinal tumor models (4,12). Antioxidants including epicatechin from tea, resveratrol from grapes and red wine, the plant extract curcumin, and sulforaphane from broccoli have also been found to be effective for tumor prevention (4). Studies conducted with cultured cells and antiviral models have demonstrated that inflammation is actively involved in tumor progression and that anti-inflammatory agents are effective in preventing and delaying tumor growth and progression. The natural compound curcumin acts by suppressing the signaling activity of NF-kappaB and activator protein1 (AP1).

Angiogenesis is a key event that occurs in the tumor microenvironment. Anti-angiogenesis agents like Thalidomide have been shown to significantly reduce tumor burden in prostate cancer (44). Likewise, chemokine and cytokine receptors are targets for the development therapeutic drugs intended to prevent inflammation-mediated cancer progression. Treatment strategies that target the tumor stroma have been implemented citing bevacisumab, an anti-VEGF neutralizing antibody as a combinatorial therapy to enhance chemotherapy in non small cell lung carcinoma patients (45). This treatment regimen has resulted in increased rates of patient survival and significant decrease in tumor size. Studies conducted by Pikarsly *et al* (46) and Greten *et al* (47) reported that NF-kappaB is a critical component in promoting tumorigenesis through effects on both tumor cells and tumor associated inflammation cells. Drugs targeting the NF-kappaB signaling pathway prove to be potential therapeutics for cancer prevention and treatment. Antibodies like Infliximab™, a chimeric monoclonal antibody specific for TNF-alpha, and Bortezomib™, which targets 26S proteasome, and several others proteasome inhibitors have already been approved by FDA for treatments of patients with advanced multiple myeloma.

9. SUMMARY AND PERSPECTIVE

The natural defense mechanism used to protect the human body, i.e. inflammation, is a considerable force in the formation of the tumor microenvironment and ultimately progression of cancer. It is surprising that transformed cells can exploit this natural defense mechanism to support their growth and survival. There is

substantial evidence supporting the connection between inflammation and cancer. In gastrointestinal stromal tumors (GIST), tumor growth is preceded by the inflammation of gastrointestinal tissues (48). While it is well accepted that chronic inflammation plays a central role in promoting the formation of the tumor microenvironment, studies are still required to determine the specific molecular events leading to this initiating and progression. Situations of chronic inflammation result in tissue damage, cell proliferation, and permit the generation of reactive oxygen and nitrogen species all of which contribute to a cancer prone environment (49). Inflammatory signals and cells such as cytokines and macrophages are consistently involved in protecting tumor cells from the host immune response. Cytokines also assist tumor cells by stimulating growth, facilitating angiogenesis, invasion and metastasis or by signaling for elevated production of other molecules such as MMP and VEGF (40). Therefore targeting molecules like cytokines, macrophages and other specific inflammatory signaling pathways that activate key events like angiogenesis, EMT, and tumor metastasis can be a promising approach in developing drugs that will be effective in reducing early neoplastic tumor progression.

Cancers of the gastrointestinal tract, liver, and prostate initiate from a site of chronic inflammation. Malignant tumor inflammatory cells constitute the considerable proporting of the tumor microenvironment. Restoration of the basal inflammatory state may be an effective method to reinstate the primary function of the host immune response. Thus, methods designed to reduce the levels of tumor promoting proinflammatory cytokines and chemokines in the tumor microenvironment as well as increase the levels of anti-inflammatory cytokines having tumor suppressor properties appears to be a promising approach to ameliorate inflammation associated formation of the tumor microenvironment and possibly even cancer progression.

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Abbreviations: AP1: activator protein1; bFGF: basic fibroblast growth factor; COX: cyclooxygenase; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; EMT: epithelial to mesenchymal transition; EPO: erythropoietin; GIST: gastrointestinal stromal tumors; HIF: hypoxia inducible factor; IL: interleukin; iNOS: inducible nitric oxide synthase; JAK: janus-activated kinase; MMP: matrix metalloproteinase; NFAT: nuclear factor of activated T-cells; NF-kB: nuclear factor kappa-beta; PGE: prostaglandin; PTEN: Phosphatase/Tensin homolog deleted on chromosome 10; STAT: signal transducer and activator of transcription; TAM: tumor associated macrophages; TGF: tumor growth factor; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VPF: vascular permeability factor; VHL: von hippel lindau; RAS: rat sarcoma

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