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Angiogenesis, Kaposi's Sarcoma and Kaposi's Sarcoma-Associated Herpesvirus*

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Abstract

Tumor angiogenesis is the uncontrolled growth of blood vessels in tumors, serving to supply nutrients and oxygen, and remove metabolic wastes. Kaposi's sarcoma (KS), a multifocal angioproliferative disorder characterized by spindle cell proliferation, neo-angiogenesis, inflammation, and edema, is associated with infection by Kaposi's sarcoma-associated herpesvirus (KSHV). Recent studies indicate that KSHV infection directly promotes angiogenesis and inflammation through an autocrine and paracrine mechanism by inducing pro-angiogenic and pro-inflammatory cytokines. Many of these cytokines are also expressed in KS lesions, implicating a direct role of KSHV in the pathogenesis of this malignancy. Several KSHV genes are involved in KSHV-induced angiogenesis. These studies have provided insights into the pathogenesis of KS, and identified potential therapeutic targets for this malignancy.

Keywords

Angiogenesis; Kaposi's sarcoma (KS); Kaposi's sarcoma-associated herpesvirus (KSHV)

Kaposi's sarcoma (KS) was first described in 1872 by the Hungarian dermatologist Moritz Kaposi. The etiologic factor of KS disease was not established until 1994 when the team of Chang and Moore discovered Kaposi's sarcoma-associated herpesvirus (KSHV) in a KS tumor from an AIDS patient (12). Since its initial discovery, extensive studies have been performed to confirm the causal link between KSHV and KS. It is now clear that infection by KSHV is necessary for the development of all clinical forms of KS. KSHV is also associated with two other lymphoproliferative diseases including primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) (59).

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Angiogenesis

The budding of new capillary branches from existing blood vessels is termed angiogenesis. Under pathological conditions, tumors stimulate angiogenesis to support extra consumption of oxygen and nutrition for their rapid growth (27). Tumor angiogenesis is a complex process involved with the tight interplay of tumor cells, endothelial cells, phagocytes and their secreted factors. Many different proteins such as Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), interleukin-8 (IL-8), matrix metalloproteinases (MMPs), as well as several smaller molecules such as adenosine and prostaglandin E_2 (PGE_2) have been identified as pro-angiogenic factors secreted by tumor cells to mediate angiogenesis. MMPs are expressed in a wide variety of cancers and involved in cancer invasion, metastasis, and angiogenesis (15). MMPs regulate cellular functions and microenvironments by cleaving extracellular matrix proteins, resulting in the escape of endothelial cells from the existing capillary, a key step in the angiogenic cascade.

VEGF and bFGF are important factors for the growth of blood vessels. VEGF is the main driving force behind tumor angiogenesis by inducing the secretion of proteases, and migration and proliferation of endothelial cells (18). By inhibiting apoptosis, VEGF is also a survival factor for endothelial cells.

Angiopoietin 1 (Ang-1) and Angiopoietin 2 (Ang-2) are key players in the angiogenic balance between the quiescence status and activation of the endothelium (35). They share the same receptor, Tie-2. Ang-1 is an agonist of the Tie-2 receptor and stabilizes blood vessels by promoting adhesive interactions between endothelial cells and mural cells. Conversely, Ang-2 is an antagonist of the Tie-2 receptor and induces the detachment of mural cells and destabilizes the existing blood vessels, a process that is essential for the formation of new blood vessels.

Most tumors are hypoxic because the tumor cell proliferation often exceeds development of new blood vessels. Hypoxia induces the expression of different factors such as hypoxia-inducible factor-1 (HIF-1) or platelet derived growth factor (PDGF) (48). These factors promote neoplastic angiogenesis by inducing specific angiogenic molecules. HIFs are master regulators of both developmental and pathological angiogenesis, composed of an oxygen-sensitive α subunit and a constitutively expressed β subunit (64). HIFs are post-transcriptionally activated by hypoxia as a result of increased protein stability of the α subunits (HIF-1α and/or HIF-2α) (64).

Kaposi's Sarcoma and Angiogenesis

KS is a multifocal vascular proliferative disease manifested in four clinic forms: classical KS, endemic (Africa) KS, immunosuppression (transplantation) iatrogenic KS and epidemic (AIDS) KS. Classical form of KS is a rare disease usually restricted to the skin and is predominantly found in elderly males of Mediterranean and Eastern European decent. This form of KS is generally not life-threatening. Endemic KS was described in several Central African countries. It can appear as classical KS, progressing slowly, or in a more deadly form that quickly spreads to tissues below the skin, the bones and lymph system, leading to death within a few years of diagnosis. Immunosuppression KS is observed in transplant patients treated with immunosuppressive agents. AIDS-KS, initially found among homosexual males, is associated with HIV-1 infection. This epidemic KS form usually progresses rapidly. In some HIV-1 endemic areas of Central Africa, this form of KS is the most frequent cancer, representing about 50% of all diagnosed malignancies (41).

The four clinical forms of KS share a common histology (61). All KS lesions contain the so-called spindle cells, which are the principal proliferating cell, the driving force behind KS histogenesis, named for its dramatically elongated morphology. All KS lesions contain

inflammatory cells and slit-like neovascular spaces, which are the features of KS. These new vessels are not intact, and lack of accompanied pericytes or smooth muscle cells, manifesting leakage, which is presumably the cause of edema and hemorrhage observed in KS lesions. KS lesions have aberrant expression of cytokines. Int-2, a pro-angiogenic factor, was found to be expressed in more than half of the KS tumors examined. Using reverse transcription PCR, the expression of int-2 was detected in 21 of 38 (55.2%) fresh KS biopsy specimens (28).

Early stage KS is not a true tumor but a hyperplasia. The progression of KS is linked to the inflammatory and angiogenic process as well as a disturbance of the immune system with a high level of interferon-γ. KS itself starts as a granulation-like tissue rich in inflammatory cells consisting of lymphocytes and monocyte/macrophages. These infiltrating cells produce inflammatory cytokines such as interferon-γ, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), and IL-8 and oncostatin M (21,57). These inflammatory cells induce the recruitment of circulating cells into tissues, promote the production of angiogenic factors that mediate angiogenesis and edema, and activate endothelial cells to acquire the phenotype KS spindle cells (3,4,19,20,52,72). Altogether these observations support the concept that early stage KS is a reactive inflammatory-angiogenic process.

KSHV-Induced Angiogenesis

KSHV infection directly induces several pro-angiogenic and pro-inflammatory cytokines, including VEGF, Ang-1, Ang-2, bFGF, IL-6, IL-8, GRO-α,TNF-β, and ephrin B2, most of which are expressed in KS lesions (38,39,46,65,69). The mRNAs of both Ang-1and Ang-2 have been detected at higher levels in KS tumors than in the adjacent normal tissues. Ang-2protein was highly expressed in KS tumors and that KSHV infection of primary human umbilical vein endothelial cells (HUVEC) induced Ang-2, which was required for KSHV-induced paracrine-dependent angiogenesis in vivo (71). The induction of Ang-2 by KSHV is medicated by ERK, JNK and p38 mitogen-activated protein kinase (MAPK) pathways (71). A number of MMPs, including MMP-1, -2, -3, -9, and -19, have been detected in KS tumor cells, implicating their roles in the pathogenesis of these tumors. KSHV infection of HUVEC enhances cell invasiveness by inducing the expression of MMP-1, -2, and -9 (49). KSHV infection also induces sustained levels of VEGF-A and VEGF-C early during in vitro infection of human microvascular dermal endothelial cells (DMVEC) (58). Angiogenesis induced by PEL cells is dependent on VEGF and VEGF receptors (26). Higher levels of serum VEGF were detected in HIV-1 infected persons with KS compared with HIV-1 infected persons without KS (68). KSHV infection of DMVEC induces mRNA of HIF1α and HIF2α (11). Consistent with the in vitro results, KS lesions express elevated levels of HIF1α and HIF2α proteins (11). KSHV infection of DMVEC also induces the expression of cyclooxygenase-2 (COX-2) and heme oxygenase-1, both of which play important roles in angiogenesis (40,46).

In a SCID mouse model with human skin grafts, VEGF was shown to be essential for the inoculated early stage KS cells to grow into KS-like tumors (54). Transfection of mouse bone marrow endothelial-lineage cells with the KSHV recombinant virus BAC36 led to cellular transformation and induced KS-like tumors in mice (45). The KSHV-transformed cells mECK36 expresses most KSHV genes and are angiogenic. In nude mice, mECK36 cells form vascularized spindle cell sarcomas that are LANA+/podoplanin+, overexpressed VEGF and angiopoietin ligands and receptors, and displayed KSHV and host transcriptomes reminiscent of KS (45). siRNA suppression of KSHV vGPCR, a pro-angiogenic gene upregulated in mECK36 tumors, led to the inhibition of angiogenesis and tumorigenicity.

Regulation of Angiogenesis by KSHV-Encoded Genes

ORF-K1

ORF-K1 encodes a small transmembrane immunoglobulin-like glycoprotein, which possesses a cytoplasmic immunoreceptor tyrosine activation motif (ITAM) similar to that of the B cell receptor (BCR) (25). This motif was shown to be sufficient for inducing cellular tyrosine phosphorylation (34). The phosphorylation of the ITAM domain allows subsequent binding of SH2 proteins Syk, Vav and phosphoinositide 3-kinase (PI3K) (31). K1 activates the transcription factor NFAT in KSHV negative B-cells. It also activates the PI3K/Akt pathway by enhancing the phosphorylation of the p85 subunit of PI3K and the kinase Akt in B cells (34,62). K1 also activates the transcription factor AP-1 and NF-κB in reporter assays (53). In KS cells, K1 is able to induce the secretion of inflammatory cytokines such as IL-6 and IL-12 (53). Full-length K1 downregulates the expression of the BCR complex at the cell surface of Bjab cells. This could potentially inhibit B-cell activation and allow a long-term survival advantage for KSHV-infected cells (33).

K1can induce the expression and secretion of VEGF in epithelial and endothelial cells (67). It induces the expression of MMP-9 in endothelial cells (67). The SH2-binding motifs in the cytoplasmic tail are necessary for VEGF secretion and MMP-9 induction. These results indicate that K1 signaling may contribute to KSHV-associated pathogenesis through a paracrine mechanism by promoting the secretion of VEGF and MMP-9 into the surrounding matrix.

ORF-K15

ORF-K15 gene is located at the most right side of the viral genome, and has two distinct isoforms. The M and P (for “minor” and “predominant”) forms of K15 are 67% divergent. The more common variant, K15-P, is considered to be the original K15 gene, whereas the other, K15-M, is thought to represent the result of a recombination event with a related rhadinovirus (29). K15 is able to interact with TRAFs (tumor necrosis factor receptor-associated factor) and Src kinases, and activates AP-1, NF-κB, and JNK and ERK MAPK pathways (6,66). The down-stream target genes of K15 signaling are investigated using DNA oligonucleotide microarrays (7). K15 is shown to be able to induce the expression of multiple cytokines and chemokines, including IL-8, IL-6, CCL20, CCL2, CXCL3, and IL-1α/β, as well as Dscr1 and Cox-2 (7).

vGPCR

vGPCR, encoded by ORF74, is a 7-transmembrane, IL-8 receptor homolog that constitutively engages pathways downstream of multiple G protein subunits in a phospholipase C and PI3K-dependent manner. The pathways engaged by vGPCR include protein kinase C, protein kinase B, Akt, NF-κB, and MAPKs, leading to increased transcriptional activity of their nuclear targets, stimulation of cellular proliferation, promotion of cell survival, transformation, tumorigenicity, and induction of VEGF-mediated switch to an angiogenic phenotype (16). Microarray experiments have shown that IL-6 and GROα are highly induced in endothelial cells which stably express vGPCR (47). Cells expressing vGPCR secrete increased levels of autocrine and paracrine cytokines and growth factors (IL-β, TNF-β, IL-6, IL-8, granulocytemacrophage colony-stimulating factor, VEGF, bFGF, and MCP-1), and produce conditioned medium that is chemotactic (16). In transgenic mice, vGPCR induces multifocal, angioproliferative, KS-like lesions (70). vGPCR expression in human pulmonary arterial endothelial cells (HPAEC) selectively activated MMP-2, a pivotal matrix modulating enzyme during angiogenesis. vGPCR induces MMP-2 activation in HPAECs through regulation of MT1-MMP and TMP-2 expression (55). vGPCR also induces Ang-2 expression in lymphatic endothelial cells in a paracrine manner through the ERK MAPK pathway (63). Thus, vGPCR

is a viral oncogene that exploits cellular signaling pathways to induce cellular transformation and angiogenesis.

vIL-6

vIL-6 encoded by ORF-K2 is structurally homologous to human and murine IL-6. vIL-6 triggers multiple cellular pathways to induce cell proliferation and extrahepatic acute-phase responses through engagement of the gp130 coreceptor independently of the IL-6 (gp80) receptor. vIL-6, but not human IL-6, protects PEL cells and heterologous cells from the antiviral, cytostatic effects of interferon-α, which down-regulates the surface expression of gp80 but not gp130 (13). vIL-6 induces endogenous human IL-6 secretion in various cell lines (MT-4, THP-1, U937, Raji, and CESS) and in patients with MCD (43). vIL-6 supports the growth of IL-6-dependent cell lines, and is an autocrine growth factor for PEL cells (22,43).

vIL-6-expressing NIH3T3 cells gives rise to tumors in nude mice more rapidly than control cells, and vIL-6-positive tumors are more vascularized than controls (1). VEGF was detected at higher levels in the culture supernatant of vIL-6-expressing cells compared to controls, and immunohistochemical staining detected VEGF in spleen, lymph nodes, and tumor tissues from mice bearing vIL-6-producing tumors but not in mice bearing the control tumors. vIL-6 also up-regulates Ang-2 expression in lymphatic endothelial cells in a paracrine manner through the MAPK pathway (63). Thus, vIL-6 is a multifunctional cytokine that promotes hematopoiesis, plasmacytosis, and angiogenesis, and might play an important role in the pathogenesis of KSHV-associated disorders.

LANA

LANA (latent nuclear antigen) encoded by ORF73 is expressed in all latently infected cells in KS tumors. It is considered as an oncogenic protein because it inhibits the p53 and pRb tumor suppressor pathways, and transforms primary rat embryo fibroblasts in cooperation with the cellular oncogene H-*ras* (23,50). LANA interacts with GSK-3β, an important modulator of the Wnt signaling pathway, leading to the accumulation of the β-catenin and subsequent upregulation of Tcf/Lef-regulated genes (24). LANA represses the reactivation and transcriptional activator (RTA), which is critical for the virus switch from latency to lytic reactivation, to control viral latency (32). LANA is essential for episome persistence by its critical role in episome replication and partitioning into daughter cells (2).

LANA directly associates with HIF-1α in transiently transfected 293T cells as well as in PEL cell lines during hypoxia. LANA regulates the hypoxia pathway by enhancing the transcriptional activities of HIF-1α and upregualting its mRNA level (8). Additional studies indicate that LANA targets the HIF-1α suppressors von Hippel-Lindau (VHL) protein and p53 for degradation via its suppressor of cytokine signaling-box motif by recruiting the EC5S ubiquitin complex (10). LANA is important for HIF-1α nuclear accumulation in normoxic conditions in KSHV latently infected PEL cells, as well as HEK293 cells infected by KSHV (9). Therefore, LANA can function not only as an inhibitor of HIF-1α suppressor proteins but can also induce nuclear accumulation of HIF-1α during KSHV latent infection.

vIRF3

vIRF3 (viral interferon regulatory factor 3), also called LANA2, is encoded by ORF-K10.5. vIRF3 is exclusively detected in KSHV-infected B cells (37,51). vIRF3 is most closely related to the cellular IRF4 and vIRF2, it functions as a dominant negative mutant of both IRF3 and IRF7, and inhibits virus mediated transcriptional activity of the interferon-α promoter, and thus blocks type I interferon signaling (37). vIRF3 is also able to inactivate the p53-mediated apoptosis and transcriptional activation (51) as well as apoptosis induced by activation of the serine/threonine kinase PKR (17). vIRF3 is able to bind to 14-3-3 proteins and the

transcriptional factor FOXO3a. When 14-3-3 proteins are overexpressed, vIRF3 inhibits the transcriptional activity of FOXO3a and blocks the G2/M arrest (44). Recently, vIRF3 has been shown to interact with HIF-1α leading to the HIF-1α stabilization and transcriptional activation of VEGF (56). The central domain of vIRF3, containing double α-helix motifs, is sufficient for the binding to HIF-1α and blocking its degradation in normoxic conditions. These findings suggest that vIRF3 may have a role in KSHV-mediated oncogenesis in hematopoietic tissues.

vCCL-1, vCCL-2, and vCCL-3

vCCL-1, vCCL-2 and vCLL-3 are encoded by KSHV ORF-K6, -K4 and -K4.1 respectively. vCCL-1 binds to a broad range of chemokine receptors including CCR1, CCR2, CCR5, CXCR4, and CX3CR1 (30). It may function as a competitive antagonist with the host chemokines. vCCL-1 blocked the chemoattractive properties of host CC and CXC chemokines (5,14,30,42). vCCL-1 suppressed the host inflammatory response and decreased the infiltration of inflammatory leukocytes in a rat model (14). vCCL-1 and vCCL-2 are able to bind to CCR-8, and vCCL-1 induces the secretion of VEGF-A in PEL cells (36). Both vCCL-1 and vCCL-2 are able to block dexamethasone-induced apoptosis in PEL cells (36). vCCL-3 binds to CCR-8 and CCR-4, and has been shown to be a selective chemoattractant for the Th2 cells (60).

All three vCCLs are able to induce angiogenesis in the chorioalantonic membranes of chicken eggs, suggesting that they may act synergistically with host factors such as VEGF, bFGF, and IL-6 to promote the abnormal angiogenesis in KS lesions (5).

Conclusion

KS tumor is a highly disseminated angiogenic tumor of proliferative endothelial cells, and the KS progression is linked to the inflammatory and angiogenic process. Recent studies have shown that KSHV infection induces several angiogenic and inflammatory cytokines, which directly contributes to the tumor neo-angiogenesis process, and the pathogenesis of the malignancy. A number of genes encoded by KSHV have been shown to promote angiogenesis. Nevertheless, the mechanism of KSHV-induced angiogenesis is very complex; additional research works are needed to further delineate the molecular basis of KSHV-mediated angiogenesis in the KS tumor.

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