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Systematic Review

Angiogenesis and Cancer progression: A systematic review

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Abstract
Angiogenesis, the growth of new blood vessels from preexisting ones, is one of the essential features of tumor formation and is also important in a number of physiologic processes including growth and development, wound healing and reproduction. Intra tumoral blood vessels are known to play an important role in cancer growth by supplying oxygen and nutrients as well as excreting metabolic products, and are also associated with metastasis. This systematic review is an attempt to discuss the various markers that can be utilized to diagnose the angiogenesis.
Keywords: Angiogenesis, cancer progression, tumors, carcinogenesis

1. Introduction

New growth in the vascular network is important since the proliferation, as well as metastatic spread, of cancer cells depends on an adequate supply of oxygen and nutrients and the removal of waste products [1]. New blood and lymphatic vessels form through processes called angiogenesis and lymphangiogenesis, respectively. Angiogenesis is regulated by both activator and inhibitor molecules [2]. More than a dozen different proteins have been identified as angiogenic activators and inhibitors [3]. Levels of expression of angiogenic factors reflect the aggressiveness of tumor cells. The discovery of angiogenic inhibitors should help to reduce both morbidity and mortality from carcinomas. Thousands of patients have received antiangiogenic therapy to date. Despite their theoretical efficacy, antiangiogeic treatments have not proved beneficial in terms of long-term survival. There is an urgent need for a new comprehensive treatment strategy combining antiangiogenic agents with conventional cytoreductive treatments in the control of cancer [4].

Algire *et al*. (1947) first reported the phenomenon of active neovascularization by the host to neoplastic tissues. Later Folkman *et al*. [1] conducted a series of studies on cancer growth and neovascularisation, and demonstrated that blood vessels in the host underwent angiogenesis and developed into intratumoral vessels, that were closely related to tumor growth. They stated that solid tumors cannot grow larger than 2-3 mm in diameter without being able to induce their own blood supply [5].

The expression of the angiogenic phenotype in the tumor microenvironment is an extremely complex process involving the interaction of many different cell types. Like all solid tumors, head and neck squamous cell carcinomas must develop direct and indirect ways to induce the production of new blood vessels in order to continue to expand and metastasize [6].

Assessment of tumor angiogenesis using micro vessel density is known to be an important tool in analyzing the tumor growth. MVD assessment was introduced by Weidner and the technique basically implies counting of routine immunohistochemically stained vessel wall profiles in tissue sections of tumors. This technique was designated as easy prognostic indicator for clinical behavior for a number of tumors [7].

Markers that play a role in angiogenenesis are

1. Vascular endothelial growth factor VEGF
2. CD 34
3. Nitrous oxide synthase (NOS-II)
4. Endoglin (CD105)
5. Fibrin and interleukin (IL-8)
6. FGF2

2. Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) is an important signaling protein involved in both vasculogenesis (the de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature). As its name implies, VEGF activity has been

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mostly studied on cells of the vascular endothelium, although it does have effects on a number of other cell types (e.g. stimulation monocyte/macrophage migration, neurons, cancer cells, kidney epithelial cells). *In vitro*, VEGF has been shown to stimulate endothelial cell mitogenesis and cell migration. VEGF is also a vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor [8, 9].

Structurally VEGF belongs to the platelet derived growth factor (PDGF) family of cystine-knot growth factors. Subsequently, several closely-related proteins were discovered (Placenta growth factor (PlGF), VEGF-B, VEGF-C, VEGF-D and VEGF-E) which together comprise the VEGF sub-family of growth factors [10].

VEGF is sometimes referred to as VEGF-A to differentiate it from these related growth factors.

Li C. *et al*. (2005) evaluated the microvessel density and expression of VEGF in oral cancers. Their results showed no difference between normal oral mucosa and epithelial dysplasia but a significantly increased difference in tumor tissue. Expression of angiogenic factors was not found in normal oral mucosa, but increased in association with increasing vascularity in OSCC tissue thus stating that VEGF expression positively correlates with the development of oral cancer [11].

Siriwardena B, *et al*., (2007) examined VEGF-C expression and its correlation with lymphatic status including the number of lymph vessels and lymphatic invasion, tumor invasion and metastasis in oral squamous cell carcinoma cases and found that high expression of VEGF-C was frequently observed in oral squamous cell carcinoma cases and was well associated with increased number of lymph vessels and lymphatic invasion, suggesting that VEGF-C may play an important role for lymphangiogenesis and invasion in the metastatic process and can be a strong predicting factor for metastasis of oral squamous cell carcinoma cases [12].

Johnstone S *et al*., (2007) investigated the presence of VEGF in normal, oral dysplasia and squamous cell carcinoma. The correlation between VEGF expression and the grade of dysplasia or differentiation of squamous cell carcinoma was also examined. An up-regulation of VEGF during the transition from normal oral mucosa, through dysplasia to squamous cell carcinoma was observed suggesting that VEGF may play an important role in the maintenance of a blood supply for developing pre-cancerous and invasive oral lesions [13].

3. CD 34

CD4 (cluster of differentiation 4) is a glycoprotein expressed on the surface of T helper cells, regulatory T cells, monocytes, macrophages, and dendritic cells. It was discovered in the late 1970s and was originally known as leu-3 and T4 (after the OKT4 monoclonal antibody that reacted with it) before being named CD4 in 1984 by Bernard *et al*. [14]

On T cells, CD4 is the co-receptor for the T cell receptor (TCR). It amplifies the signal generated by the TCR by recruiting the tyrosine kinase that is essential for activating many molecules involved in the signaling cascade of an activated T cell [15].

Sedivy R *et al*., (2003) identified immunohistochemically lymphatic and blood microvessels of oral squamous cell carcinoma by antibodies against podoplanin and CD34, respectively. Lymphatic microvessel density (LVD) and blood microvessel density (MVD), and the expression of VEGF-C were determined and concluded that VEGF-C expression in oral squamous cell carcinoma triggers lymphatic angiogenesis, which may result in a higher risk for cervical lymph node metastasis [15].

Nagatsuka H *et al*., (2005) used a panel of three antibodies (CD31, CD34, and endoglin) as blood vessel markers to investigate the distribution and properties of blood vessels in normal oral tissues and squamous cell carcinomas and found that many microvessels with strong remodeling activity as well as undifferentiated tumoral vascular endothelial cells and immature endothelial cells were present in the cancer cell nest and marginal area of cancer infiltration. They concluded that vascular distribution of endothelial cells appear to be closely associated with metastasis [16].

4. Nitric Oxide Synthase (NOS)

The nitric oxide synthase (NOS) is responsible for the synthesis of nitric oxide (NO) from the terminal nitrogen atom of L-arginine in the presence of NADPH and dioxygen (O_2). NOS is the only known enzyme that binds flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), heme, tetrahydrobiopterin (BH_4) and calmodulin [17].

NOS was first identified by Furchgott (1980) who experimented on the aortas of rabbits. Since then, the different forms of NO synthase have been classified as follows:

1. Neuronal NOS
2. Inducible NOS (iNOS or NOS2)

Can be found in the immune system but is also found in the cardiovascular system. It uses the oxidative stress of NO (a free radical) to be used by macrophages in immune defence against pathogens [17, 18].

NO appears to play a crucial, pivotal role in angiogenesis, since L-NAME, a competitive inhibitor of NOS, effectively blocks the angiogenic process.NO is an upstream signal for expression of VEGF, which

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together with its receptors, the Flt family are responsible for the mechanism of tumor angiogenesis. NOS-2 expression correlates with lymph node metatstasis in several cancers including oral squamous cell carcinoma thus confirming its role in this process [17].

Brennan *et al*. (2001) assessed the immunohistochemical expression of type II nitric oxide synthase (NOS2) in oral squamous cell carcinoma and correlated the findings with lymph node status. There was a significant relationship between NOS-2 expression and lymph node metastasis. Furthermore, lymph node metastasis correlated with the degree and intensity of staining seen. But no correlation was found between the size of the primary tumour, degree of tumour differentiation or smoking status and NOS-2 staining. Thus stating that its expression may be of value in assessing lymph node status prior to surgery, and may represent a target for possible therapeutic manipulation [18].

5. CD 105 (ENDOGLIN)

Endoglin is a type I membrane glycoprotein located on cell surfaces. It has been found on endothelial cells, activated macrophages, fibroblasts, and smooth muscle cells.

Endoglin has been found to be part of the TGF-beta1 receptor complex. It thus may be involved in the binding of TGF-beta1, TGF-beta3, activin-A, BMP-2, and BMP-7.

Endoglin is involved in the cytoskeletal organization affecting cell morphology and migration. Endoglin has a role in the development of the cardiovascular system and in vascular remodeling. Its expression is regulated during heart development.

Endoglin, also called CD105, is a homodimeric membrane glycoprotein primarily associated with human vascular endothelium [19].

Schimming R *et al*., (2002) concluded that Endoglin expression in tumor tissue was significantly higher than in normal healthy mucosa. Thus Endoglin expression is up-regulated in squamous cell carcinoma of oral cavity compared with normal healthy oral mucosa. Endoglin may have a significant role in the development of oral squamous cell carcinoma and might be relatively more specific than commonly used endothelial markers [9].

Kyzas PA *et al*., (2006) investigated endoglin expression and evaluated microvessel density in patients with squamous cell carcinoma suggesting that CD105 is a promising target for tumor imaging and prognosis [10].

Angiogenesis is essential for the development and progression of malignant tumours, and there is increasing evidence that microvessel density (MVD) can be considered an indirect marker of neo-angiogenesis.

Martone T *et al*., (2005) showed that a high CD105+ MVD was the only independent marker of tumour recurrence or death [11].

Marioni G *et al*., (2006) evaluated endoglin expression and its prognostic role in oral and oropharyngeal SCCs and showed a significant difference between CD105-assessed MVD in poor and good outcome groups suggesting that endoglin (CD105) assessed micro-vessel density (MVD) in primary oral and oropharyngeal squamous cell carcinomas (SCCs) may identify patients at risk of disease recurrence or poor oncological outcome after treatment [12].

Chuang C *et al*., (2006) investigated the expressions of vascular endothelial growth factor (VEGF) and endoglin (CD105) in the biopsy tissues of squamous cell carcinoma of the tongue in early tumor stages and their relationship with the clinicopathologic features. High expressions of VEGF and CD105 significantly correlated with a relatively advanced tumor stage, positive nodal status, presence of tumor necrosis and greater tumor thickness suggesting the expression of CD105 as a useful predictive prognostic factor in early tongue cancer [13].

6. Fibrin and Interleukin-8 (IL-8)

Fibrin deposition is a histologic feature of a variety of pathologic processes, including inflammation and wound healing. Because tumors can be considered “Wounds that do not heal” fibrin deposition may be expected in tumor tissues.

In both wounds and tumors, fibrin deposition results from the local extravasation of plasma fibrinogen from blood vessels that have increased permeability. This fibrinogen coagulates, forming a fibrin gel in the extravascular tissue space [10, 11, 12].

IL-8 is a small protein consisting of 79 residues in its mature secreted form. It is produced by a variety of cell types, including epithelial cells, endothelial cells, and fibroblasts.

IL-8 has long been known to be an important proinflammatory cytokine. It serves as a chemical signal that attracts neutrophils at the site of inflammation, and therefore is also known as Neutrophil Chemotactic Factor [10].

Cohen RF *et al*., (1995) in their study concluded that patients exhibiting higher IL-8 levels in tumor tissue, have clinically more aggressive diseases manifested by higher TNM stage, more recurrences and shorter disease-free intervals [14].

Lingen MW *et al*., (1996) demonstrated that IL-8 is the major inducer of neovascularization caused by oral squamous cell carcinoma cell lines [15].

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Lalla RV, (2001) examined the ability of fibrin to stimulate IL-8 expression from oral squamous cell carcinoma cells *in vitro* and concluded that fibrin may promote angiogenesis in oral tumors by directly upregulating the expression of IL-8 from tumor cells [16].
Lalla RV *et al*., (2003) demonstrated that fibrin induces a specific, dose-and time-dependent upregulation of the angiogenic factor interleukin 8 (IL-8) from human oral squamous cell carcinoma cells and observed that fibrin staining was found in 100% of the tumor sections tested. IL-8 staining was found in the cytoplasm of tumor cells in 100% of the studied tumors, including areas adjacent to fibrin and hence concluded that there is association between fibrin and IL-8 in oral squamous cell carcinomas [17].
Tanzer ML, Kreutzer DL *et al*., (2003) Demonstrated that in addition to fibrin formed in situ, both fibrin-derived liquid expressates (soluble fibrin) and preformed fibrin clots induced an over eight-fold stimulation of IL-8 expression from human oral squamous cell carcinoma cells as compared to media controls. IL-8 upregulation by soluble fibrin was dose-dependent [18].

7. Fibroblast growth factor 2 (FGF2)
Fibroblast growth factors, or FGFs, are a family of growth factors involved in wound healing and embryonic development. The FGFs are heparin-binding proteins and interactions with cell-surface associated heparan sulfate proteoglycans have been shown to be essential for FGF signal transduction.
Functions of bFGF (FGF2) is the promotion of endothelial cell proliferation and the physical organization of endothelial cells into tube-like structures. It thus promotes angiogenesis, the growth of new blood vessels from the pre-existing vasculature It stimulates the proliferation of fibroblasts that give rise to granulation tissue, which fills up a wound space/cavity early in the wound healing process.
Wakulich C, (2002) determined whether FGF-1, FGF-2, and high affinity receptors FGFR2 and FGFR3 are present in the pathogenesis of oral epithelial dysplasias and oral squamous cell carcinoma and concluded that the loss of FGF-1 is consistent with loss of differentiation in dysplasias and some squamous cell carcinomas. Changes in the localization of FGF-2 and FGFR2 into upper epithelial layers with increasing dysplasia suggest increased mitotic potential of high-level cells. The co-localization of FGF-2 and its high affinity receptors in neoplastic tissues suggests an autocrine mechanism of influence on carcinogenesis [19].
Vairaktaris E *et al*., (2006) Determined the gradual FGFR-2 and FGFR-3 expression in sequential stages of oral carcinogenesis and found that there was a significant elevation in both FGFR-2 and FGFR-3 expression during the stages of dysplasia and early invasion, while in the later stages of oral carcinogenesis the expression of both FGFR-2 and FGFR-3 decreased although not significantly hence concluded that FGFR-2 and FGFR-3 seem to play an important role in the initial stages of oral cancer progression [20].
Hase T *et al*., (2006) evaluated the relationship between the expression of basic fibroblast growth factor (bFGF) and fibroblast growth factor receptor-1 (FGFR-1) in cancer cells and fibroblasts at the invasive front of oral squamous cell carcinoma and the pathologic and clinical characteristics and concluded that bFGF and FGFR-1 expressions in fibroblasts at the invasive front are linked to the mode of invasion and the prognosis in oral squamous cell carcinoma [21].
Freier K *et al*., (2007) indicated that an increase in FGFR1 expression contributes to oral carcinogenesis at an early stage of development [22].

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