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Review Article

Role of Angiogenesis in Oral Squamous Cell Carcinoma – A Review

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***ABSTRACT*:**
Angiogenesis, the process that leads to the formation of new blood vessels, it is main hall mark of carcinogenesis in tumour progression. It plays major has been studied in many type of human cancer including head and neck cancer. Squamous cell carcinoma of head and neck is the sixth most common cancer in worldwide. In the last year many efforts have been made to understand mechanisms necessary to the formation of new blood vessels in tumour tissue. Main goal of this review to understand the tumour angiogenesis and it is angiogenic markers will facilitate accurate identification of tumour transformation, progression and metastasis. Targeting tumour angiogenesis with specific inhibitors that will help in treatment of oral squamous cell carcinoma.
Key words: Angiogenesis , angiogenic marker, tumour progression , metastasis , angiogenic inhibitors , angiogenic promoters

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INTRODUCTION:

Angiogenesis is a process by which development of new blood vessels from existing vasculature, physiologically it occurs in normal embryonic development, wound healing and also certain angiogenesis occurs pathological such as chronic inflammation, immune reaction, pre malignancy and malignancy.[1, 2] Tumor angiogenesis plays avital role in tumour growth, progression as well as metastatic spread of tumour cells, that depends on supply of oxygen and nutrients and lymphatic drainage. Angiogenesis is very important because it regulate by activator and inhibitor molecules, there are more different types of proteins are discovered as angiogenic activators and inhibitors.[3,4] Severity of expression of angiogenic factors directly proportional to the aggressiveness of tumour cells. It helps to reduce morbidity and mortality. Main goal of this review is to understand the tumour angiogenesis and the angiogenic markers will facilitate the accurate identification of tumour transformation, progression and metastasis. Targeting tumour angiogenesis with specific inhibitors will help in treatment of oral squamous cell carcinoma.

Research in the field of tumour angiogenesis follows three main directions:

1. Identify the expression of angiogeneic markers in pre malignancy and malignancy.
2. Quantification of positive angiogeneic marker shows tumour transformation, progression and metastases.
3. Prevent pre malignancy to malignancy with use of anti-angiogenesis therapy.

Normal angiogenesis:

Angiogenesis is the new growth of blood vessels from the existing capillary. It occurs throughout life in utero and continuing on through old age. It occurs in normal and diseased conditions. Capillaries plays very important role in all tissue for diffusion exchange of nutrients,

metabolites and oxygen plays a vital role in regulation of angiogenesis.[2,3]

Orgin of normal angiogenesis:
Angiogenesis are derived from mesodermal stem cells that differentiate from hemagioblasts. Hemangioblasts cells precursor give rise to hematopoietic stem cells and angioblasts.
Hematopoietic cell can differentiate to form all cell types found in circulating blood.
Angioblasts differentiate into endothelial cells. Angioblasts are important cell type potentially differentiate into endothelial cells. It has two distinct mechanism A, vasculagensis and B, angiogenesis.

A, Vasculognesis give rise to the heart and first primitive vascular plexus in the extraembroyonic and intraembroyonic tissues of embryos.

B, Angiogenesis is responsible for the remodeling and expansion of this network, occurs in utero and in adults
Angiogenesis comprises of two different mechanisms.
I, endothelial sprouting
II, Intersusceptive angiogenesis

I, Endothelial sprouting
Sprouting angiogenesis process is based on endothelial cell migration, proliferation and tube formation. Sprout angiogenesis is composed of endothelial cells, which usually grow with angiogenic stimulus as VEGF- A.

II, Intersusceptive angiogenesis:
The intersuspective angiogenesis is a process of splitting the existing vessel lumens by forming and insection the tissue folds and colums of interstitial tissue into vessel lumen.

History of angiogenesis:
Before 1960's, cancer researchers believe that , since preexisting blood vessels get dilated, the blood supply will reach tumour but later, they showed that, for the growth of cancerous tumours and for spreading of tumours , the angiogenesis is necessary. In 1971, Folkman first advanced the hypothesis that tumor growth and metastasis depends on angiogenesis and lymphangiogenesis triggered by chemical signals. According to this hypothesis, endothelial cells may be switched from a resting state to rapid growth phase by diffusible chemical signal emanating from the tumor cells.[3,4,5]

Role of angiogenesis in Head and Neck cancer:
Squamous cell carcinoma is a most common cancer worldwide. Despite the recent treatment like surgery, radiotherapy, chemotherapy and advanced treatment like molecular targeted therapies, angiogenesis is a process that leads to the formation of new vessel and is a hallmark of tumour progression. It plays a major role in human cancer including the head and neck cancer. [5, 6] VEGF –A (Vascular Endothelial Growth Factor) is the important agent that induce angiogenesis. There are several other factors involved in angiogenesis such as epidermal growth factor (EGF), hypoxia inducible factor (HIF-1), platelet derived growth factor (PDGF), Prostaglandins, Cox-2 and IL-6. Chemical signals released from tumour cells that helps in human growth and metastasis that depends on angiogenesis and lymphogenesis.[7,8,9]

Role of angiogenesis in premalignant condition:
The Premalignant conditions are usually leads to development of malignant neoplasia. Pre malignant lesions are defined by the epidemiology observation that patients with such lesions have an increased risk of cancer, and conversely, patients with cancer of a specific organ also display a high incidence of premalignant conditions. To achieve this switch, epithelial cells usually increase the amount of inhibitors they secrete.[10,11,12] There is considerable interest in determining how cells progressing from normal to tumourigenic, switch from being anti angiogenic to angiogenic. During premalignant stages, oral epithelial dysplastic cells manifest altered responses to factors present in the stroma, resulting uncontrolled cell proliferation.[13,14] However, Continued growth of transformed cells requires the induction of angiogenesis, which is thought to occur as a discrete step termed the "angiogenic switch". Angiogenic switch occurs when the balance between the levels of activators and inhibitors of angiogenesis at the premalignant lesion.[12,13,15]

Role of angiogenesis in oral squamous cell carcinoma:
Oral squamous cell carcinoma is the most common malignant neoplasm of oral cavity, which is usually preceded by premalignant disorders. Understanding of the molecular mechanisms underlying the pathogenesis and progression of OSCC is crucial for development of more rational and successful techniques for effective treatment.[16,17] Recent advancements in cancer therapeutics is targeted drug therapy. Angiogenesis is the hallmark of carcinogenesis. It plays very important role in cell survival and metastasis. Many angiogenic markers have been found to be elevated in cancer and displayed direct prognostic relevance. Angiogenesis related markers have been considered as very encouraging potential therapeutic targets for cancer treatment.
In 1971, Folkman first advanced the hypothesis that tumour growth and metastasis depends on angiogenesis and lymphangiogenesis triggered by chemical signals. According to this hypothesis, endothelial cells may be switched from a resting state to rapid growth phase by diffusible chemical signals emanating from the tumour cells.[18'19,20]

Angiogenesis markers:

Angiogenesis is regulated by both activators and inhibitors molecules. Normally, the inhibitors predominate, blocking the growth new blood vessels that arise and hence the angiogenesis activators increases in number and inhibitors decrease.[21,22,23] This results in growth and division of vascular endothelial cells and leads to the the formation of new blood vessels.(Table- I)

Table I: Angiogenic promoters and inhibitors

ANGIOGENIC PROMOTERS (Increased vascularity)	ANGIOGENIC INHIBITORS (Reduced vascularity)
Chemokines CXC -1, -2,-3,-5,-6,-7,-8	Angiopoietin Ang-1,-2
Fibroblast growth factor FGF -1,-2	Angiostatin
Hepatocyte growth factor HGF	Chemokines CXC-4,-9,-10,-11,-12,-14
Hypoxia – inducible factor HIF -1,-2,-3	Endostatin
Platelet–derived growth factor PDGF-A.-B,-C,-D	Interferon IFN-α , -β
Transforming growth factor TGF β1,-2,-3	Pigment epithelium – derived factor PEDF
Vascular endothelial growth factor VEGF-A,-B,-C,-D and PIGF	Thrombospondin TSP-1,-2,-3,-4,-5

Targeting therapy for angiogenesis:

The anti-angiogenesis concept uses first proposed by Judah Folkman where he stated that "the inhibition of neo vascularization at an early stage of cancer development will prevent tumours from growth and metastasis. The angiogenesis inhibitors are fighting agents since it inhibits the growth of blood vessels rather than tumour cells.[24, 25]the angiogenesis inhibitors are most effective when combined with chemotherapy and other additional therapies.[26](Table –II)

Table II: ANTIANGIOGENIC DURGS USED IN ORAL CANCER THERAPY

S No.	ANTIANGIOGENIC DRUG
1	Bevacizumab
2	Sunitinb
3	Vandetanib
4	Sorafenib
5	Motesanib
6	Linifanib

CONCLUSION

Relationship of angiogenesis and tumour progression is a well-established factors. However many studies related to the role of angiogenesis and oral squamous cell carcinoma is still limited. It is important to understand the molecular pathology and role of angiogenesis in oral cancer it is potential of anti-angiogenic therapy.

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