

## Review Article

# Tumor Micro Environment- A Neighbourhood in Oral Squamous Cell Carcinoma

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### ABSTRACT:

Tumour microenvironment (TME) is a complex tissue environment in and around the tumour cells which includes extra cellular matrix, cancer associated fibroblast, blood vessels, immune cells, etc. tumour microenvironment plays a vital role in progression, metastasis and resistance to immune cells and anti-cancer therapy. Tumour microenvironment contains altered stromal and immune cells, also signals the tumour to progress very efficiently. Recent studies suggest targeting the altered molecules giving better prognosis. The purpose of this review is highlighting the molecular events taking place in tumour microenvironment which is being initiated and progressed by altered cell signals. The better understanding of tumour microenvironment in oral squamous cell carcinoma will give improved and combined anticancer therapy, to which may increase the survival rate of OSCC patients.

**Key words:** Oral Squamous Cell Carcinoma, Tumor Micro Environment, Cancer Associated Fibroblast, Angiogenesis, Hypoxia.

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### INTRODUCTION:

Oral squamous cell carcinoma (OSCC) accounts for 90% of oral malignancies and the 6th most common cancer in the world.<sup>[1]</sup> The 5 years survival rate is 50% mainly because of its invasion to surrounding vital tissues and metastasis.<sup>[2]</sup> Carcinogenesis is a multistep process by genetic mutations and alterations due to various carcinogens.<sup>[3]</sup> Carcinogenesis is not only due to alterations in the cancer cells, other factors also plays important role like altered homeostasis, failure of immune response to cancer cells etc.<sup>[4]</sup>

Tumor microenvironment (TME) is recently recognised as important factor for tumor progression, distant spread and drug resistance.<sup>[5]</sup> Malignant tumors not only composed of cancer cells also composed and surrounded by non-cancersstromalcells, connective tissue, immune cells etc. this whole thing is called TME.<sup>[6]</sup>

TME includes <sup>[7]</sup>

1. Cancer associated fibroblast
2. Immune cells
3. New blood vessels and lymphatics

4. Adipose tissue
5. Extra cellular matrix

TME is a key factor in OSCC it causes dysregulation of immune cells and interaction between tumor cells and stromal cells also leads to progression and metastasis of tumor.<sup>[5]</sup>

### Epithelial mesenchymal transition (EMT):

EMT refers the epithelial cells will obtain mesenchymal properties during invasion of tumor cells in to surrounding tissues, which is very important in distant and lymphatic spread.<sup>[8]</sup> EMT is physiologically seen in embryonic development and pathologically in wound healing. Epithelial cell adhesion and polarity is maintained by E-cadherin, loss or decreased expression of E-cadherin is the hall mark of EMT in head and neck carcinomas. EMT will promote invasion, migration of tumor cells, prevent apoptosis and resistance to chemotherapy and radiotherapy. In EMT the tumor cells show loss of adhesion and positive for mesenchymal markers.<sup>[9]</sup>

### **Cancer Associated Fibroblast (CAF):**

Connective tissue around the tumor cell contain fibroblast, endothelial cells, adipocyte and immune cells in extra cellular matrix. According to Droak et al "Tumor is a wound that never heals". Fibroblast in the stroma of malignancy is called Cancer associated fibroblast and appeared as large spindle shaped cells looks similar to myoepithelial cells in wound healing.<sup>[10]</sup>

CAF is derived from resident fibroblast, adipocytes, mesenchymal stem cells and endothelial cells. CAF usually express the following biomarkers  $\alpha$  smooth muscle actin, fibroblast activation protein  $\alpha$  (FAP $\alpha$ ), Podoplanin  $\alpha$ , S100 A, Vimentin, Fibroblast specific protein-1(FSP-1) and Platelet derived growth factor (PDGF) receptor  $\alpha$  and  $\beta$ .<sup>[6]</sup> The key functions of CAF are promote tumor progression, induce angiogenesis, helps in metastasis and more importantly resistance to cancer therapy.

### **Extra cellular matrix (ECM);**

ECM is composed of structural proteins, glycoproteins and proteoglycans which maintains the tissue structure.it also permits various cellular signals. Fibroblast produces maximum bulk of collagen fibers in normal connective tissues but cancer cell also produces minimum amount of collagen fibers in TME.<sup>[11]</sup>

ECM is actually act as barrier for tumor cell migration in stoma, so the destruction of dense ECM by tumor cells is the mandatory process. The tumor cells capable of secreting Matrix metalloprotease(MMPs) like MMP-2 and MMP-9 are usually over expressed in HNSCC.<sup>[12]</sup>The Ph. of ECM is acidic due to secretion of lactic acid by glucose by tumor cells. AcidicpH in TME will enhance metastasis and give resistance to anti-cancer drugs.<sup>[13]</sup>

### **Hypoxia:**

OSCC with more necrotic areas will show high level of hypoxia due to reduced supply of oxygen. In normal cell metabolism sufficient oxygen will be available but in malignancy less oxygen will be available for cancer cells its leads to hypoxia in TME.Recent studies show hypoxia in HNSCC is giving poor prognosis. Hypoxia inducible factor -1 (HIF-1) is a key regulator of hypoxia in TME it has two subunits HIF  $\alpha$ , HIF  $\beta$ . Recent studies show strong relationship between HIF  $\alpha$  and VEGF in tongue SCC patients with low expression of HIF  $\alpha$  giving good prognosis.<sup>[14]</sup>

### **Tumor associated Macrophage (TAM):**

Macrophages are the immune cells distributed all over the body tissues the main functions are defence mechanism, homeostasis and tissue repair.<sup>[15]</sup> Macrophages are divided into two types: classically activated M1 polarized macrophage, which take part in defence mechanism against infection activated by cytokines and alternatively activated macrophages activated by Th2 cytokines.<sup>[16]</sup> The TAM closely resemble M2 polarized macrophages. Circulating monocyte are differentiating into TAM,

chemokines and growth factors produced by stromal cells tumour cells in TME.

Stroma of OSCC usually contains fibroblast, ECM, blood vessels, inflammatory cells includes monocytes and resting macrophages. These macrophages will differentiate into TAM and expressing LyC16, CD 163<sup>+</sup>, CD204<sup>+</sup> and CD 68<sup>+</sup>.TMA promotes angiogenesis, cervical lymph node metastasis, suppression of anti-tumour immunity and tumour relapses. Relation between tumour cells, inflammation and TAM in TME of OSCC should be taken into serious consideration for future molecular target therapy.<sup>[17]</sup>

### **NK CELLS:**

The role of NK cells in innate and adaptive immunity is by releasing cytokines or by direct interaction with dendritic cells. It gives resistance to microorganism by two mechanisms; (i) cytokine release interferon gamma (IFN- $\gamma$ ) (ii) Perforin dependant target cells elimination.<sup>[18]</sup> Tumour cells escaping from immune system is an important aspect of tumour progression and metastasis. The recent studies show NK cells plays critical role in immune mechanism against OSCC. Functional inactivation of NK cells by over expression of Fas ligand, loss of mRNA for granzyme B and decreased CD 16. Then leads to further progression of tumour and escape from immune resistance in OSCC.<sup>[19]</sup> NK cells divided into two types based from surface molecule expression CD16 and CD 56. CD 16 constitutes90-95% of total NK cells and are characterised by low cytokine production and high toxicity.<sup>[20]</sup>

### **Formation of new blood vessels and lymphatics (Angiogenesis)**

Tumor angiogenesis is a formation of new blood vessels in tumor for the purpose of nutrition supply.it is due to activation of activation of proangiogenic signals by tumor and stromal cells.<sup>[21]</sup>Angiogenesis plays a vital role in tumor growth and progression as well as metastatic spread of tumor cells that depends on supply of O<sub>2</sub>,nutrition and lymphatic drainage. There are more different types of protein discovered as angiogenic activators and inhibitors like VEGF, Angiostatin.<sup>[22]</sup>

### **CONCLUSION:**

Primary and metastatic tumour will comprises more than 50% of non-malignant cells. TME contribute many aspects of tumour progression development and new drug against altered molecules is mandatory process like immune modulations for immune suppression in TME. Small molecules targeted therapy along with immunotherapy chemotherapy and radiation therapy based on individual patient and tumour parameters may give better prognosis.Further research and better understanding of cells and signalling pathways in TME is mandatory for future treatment regimen in OSCC is needed.

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