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An Insight Into The Changes In The Tumor Microenvironment: A Malicious Network

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Abstract:
Oral Cancer is one of the most prevalent types of Cancer among the Asian countries. Oral Carcinogenesis is a complex sequential process, in which the cells undergo numerous morphologic and genetic changes of the phenotypically altered tumor cells, governed by various factors. The tumor microenvironment (TME) is a dynamic structure that is collectively made up of several cells, micro and macromolecules, fibroblasts, immune cells, blood vessels, etc. that surround and feed a tumor. The components of TME are extremely interactive with each other and they play a major role in regulating the biological characteristics of the tumor. Understanding the Tumor-associated inflammatory responses and changes in TME is necessary for predicting the disease progression and prognosis. This narrative review aims to provide a brief insight into the changes in the tumor microenvironment of OSCC and its implication in the disease characteristics.

Key Word*: Oral Cancer, Tumor, Prognosis, Metastasis, Microenvironment.*

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I. Introduction

Cancer is a worldwide prevalent disease, The term 'Cancer' has its origin from the Latin word meaning "crab". Cancer is also referred to as neoplasm or tumor. According to the British oncologist Willis, Neoplasm is an abnormal, excessive growth of a mass of tissue that is formed as a result of autonomous, uncoordinated proliferation of cells and it even continues after cessation of the stimuli that have caused the growth.[1,2] More than ninety percent of cancers in the head and neck region arise from the Squamous cells and hence Squamous Cell carcinomas are the most prevalent type of cancer. Head and neck squamous cell carcinoma (HNSCC), which includes oral squamous cell carcinoma (OSCC), is the sixth most prevalent form of cancer across the world. Despite the advancements in the diagnosis and therapeutics in the field of oncology, the five-year survival rate of OSCC is about 50%–60%.[3,4]

Oral carcinogenesis is a complex multifocal process in which the cells undergo numerous morphologic and genetic changes resulting in uncontrolled proliferation of the altered cells, governed by various factors in the tumor microenvironment. The action of various carcinogens such as tobacco can cause alteration in the genetic makeup of the cells resulting in altered cellular lifespan, stimulation of adjacent stromal cells, etc. [5,6] The tumor microenvironment (TME) is a dynamic structure composed of several types of cells, molecules, and blood vessels that surround and feed a tumor. The components of TME are extremely interactive with each other and are responsible for shaping the tumor.[2] The tumor microenvironment exerts a major influential role in the tumor characteristics and offers unexpected therapeutic benefits.[7] This narrative reviews the changes in the tumor microenvironment of OSCC and its implication in the disease characteristics.

II. Role of inflammation in OSCC

A direct relationship exists between the inflammation associated with Cancer and the tumor microenvironment.[8] Inflammation is defined as a biological response that occurs due to various causes and stimuli. During the inflammatory process, several changes are encountered in vascular permeability, leukocyte recruitment, leukocyte accumulation, and release of inflammatory mediators.[9]

The immune-mediated changes in the tumor microenvironment play an important role in determining the behavior of malignant lesions. It is well known that some tumors are densely infiltrated by cells of both the innate and innate and adaptive immune systems. With the advancement in histochemical markers and techniques for the accurate identification of immune system cell types, It is now evident that nearly all neoplastic lesions contain immune cells in densities ranging from subtle infiltrations detectable only with cell-type-specific antibodies to extensive inflammations visible even with standard histochemical staining techniques.[10]

Tumor-associated inflammatory responses have been studied extensively in recent decades for their effect of enhancing tumorigenesis leading to disease progression. Several shreds of evidence are remarking the function of immune cells in the tumor-promoting activity by releasing bioactive mediator substances to the tumor microenvironment. Besides, inflammation can also contribute by providing the tumor with multiple hallmark capabilities, by providing inductive signals that cause epithelial–mesenchymal transition, growth factors that sustain proliferative signaling, survival factors that limit cell death, proangiogenic factors, extracellular matrix-modifying enzymes that assist angiogenesis, invasion, and metastasis of the tumor.(11)

Inflammation is visible at the earliest stages of neoplastic progression in some cases, and it has been shown to promote the progression of incipient neoplasia into full-blown cancers.(12) In addition, inflammatory cells can release chemicals, such as reactive oxygen species, that are actively mutagenic for adjacent cancer cells, thereby accelerating their genetic evolution towards states of increased malignancy.(13) As a result of its contributions to the acquisition of core hallmark capabilities, inflammation can be considered an important feature of tumors. (11) Literature evidence has established the relationship of various inflammatory mediators such as nuclear factor kappa B, vascular endothelial growth factor (VEGF), cytokines, prostaglandins, p53, nitric oxide, reactive nitrogen species (RNS), reactive oxygen species (ROS), and microRNAs in the pathogenic mechanism of OSCC.(14)

III. Components of tumor microenvironment

The tumor microenvironment is primarily composed of tumor cells with proliferating capability, fibroblasts, the tumor stroma, blood vessels, endothelial cells inflammatory cells, and the extracellular matrix. All these components interplay in a sophisticated mechanism, as a direct consequence of the interactions in the TME and between the tumor–host interactions, resulting in the progression and evolution of the tumor.(7)

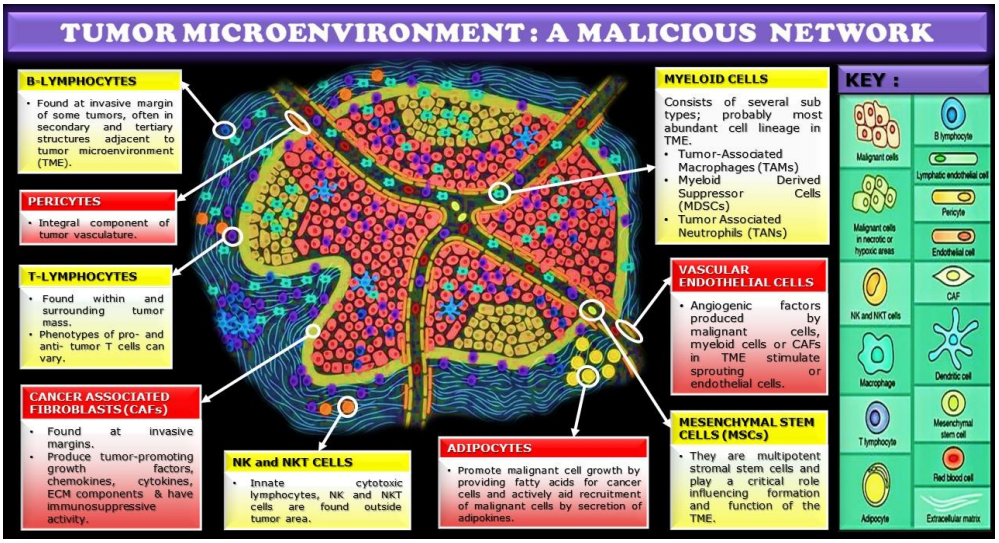

Figure no.1: The tumor microenvironment. This diagram shows the various cells and structures that comprise the tumor microenvironment.

Immune cells in TME

Immune cells are present in the microenvironment of a tumor. Several cells such as PMNs, T lymphocytes and occasionally B cells, macrophages especially M1 and M2 subtypes, Natural Killer (NK) cells, Myeloid dendritic cells, mast cells, and other effectors of innate immunity are the significant tumor-associated inflammatory cells present in the TME. These cells secrete chemokines, prostaglandins, proteinases, and complement components which promote an exacerbated inflammatory state, as well as the growth of cancer, tissue invasion, and metastasis. (16)

Interleukins especially 1, 6, and 8 are the major type of Interleukins that were known to represent the inflammatory status of the host.(17) Inflammatory processes that a tumor undergoes, result in the subsequent recruitment of various cellular components such as macrophages, dendritic cells, and B - B-cells at the tumor site, that secrete cytokines and in turn aid in the release of IL-6.(18) Further, IL-6 contributes to the tumor progression through various vital activities such as epithelial-to-mesenchymal transition (EMT) and also induces the lymphatic spread of the tumor by complex cytokines and protease mechanisms. We observed high IL-6 in the advanced stages of lymph node involvement. The activity of IL-6 in lymph node metastasis and invasion of OSCC is related to the activation of NLRP3 and inflammasomes, the NLRP3 pathway could participate in the IL-6-mediated downstream pathway of Sox4.(19) Metastasis is also favored by the IL-6-mediated signaling

pathway of the JAK and STAT family of transcription factors. Activation of JAK2, and STAT 3 occurs by the dimerization of IL-6.[20] It is well known that an increase in IL-6 has an impact that induces the production of the vascular endothelial growth factor (VEGF-C), resulting in the lymphatic spread of the tumor.[20]

Neutrophils act as key mediators of the inflammatory response; the neutrophils present in the tumor microenvironment aid in programming the antigen-presenting cells to activate the T cells and release localized factors to attract monocytes and dendritic cells.[9] Neutrophils also play an important role in the metastatic cascade as effectors of angiogenesis. The net activity of the platelets and neutrophils at the tumor site promotes the leakage of tumor cells into the circulation by endothelial leakage, thus contributing to the rerouting of the inflammatory response in a tumor-promoting direction.[21]

Neutrophils present at the tumor microenvironment are attracted by the CXCR2 ligands and they carry out multiple tasks contributing to various stages of oncogenesis.[22] The major functions of neutrophils present at the tumor site include the initiation of tumors by the release of proteases and ROS. They are also active in providing Matrix Metallo protineases (especially MMP-9). The proliferation of tumors is brought about by arginase and nitric oxide synthase, which are released from the neutrophils. Neutrophil-induced angiogenesis helps both in the proliferation and metastatic spread of the tumor cells. Neutrophils are active in the inhibition of NK cells and lend support for the escape of tumor cells.

Tumor-infiltrating lymphocytes are one of the prevalent immune cells present in the TME. Rodrigo et al.[23] in their systematic review and meta-analysis have emphasized the prognostic value of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment of laryngeal squamous cell carcinomas. It was reported that High stromal lymphocyte content along with intra-tumoral and stromal CD3+, CD4+, and/or CD8+ lymphocytes could reflect a better prognostic state of the tumor. The anticancer immune response of the host is heavily reliant on lymphocytes distributed in specific areas. Some immuno-inflammatory responses in the tumor-associated stroma, particularly T-helper cells (Th1 and Th17) are responsible for producing anti-tumor protective reactions which aid in the eradication of the tumor cells by cytotoxic T lymphocytes (CTL) and natural killer cells.[24] Lymphopenia associated with the tumor can reflect the disease severity and immune escape of tumor cells from tumor-infiltrating lymphocytes, reduced cellular immunity, a lower number of CD4 lymphocytes, and a higher activation of CD8 lymphocytes.[25,26] Chaves et al**,** have reported a reduced number of T lymphocytes (CD8+ cells) to increase the chance of malignant transformation.[27] Reduced lymphocyte count in OSCC may be attributed to the lymphocytic destruction caused by tumor cells. The tumor cells are known to express pro-apoptotic ligands that can induce apoptosis of the lymphocytes. Tumor cells can cause changes in the configuration of the zeta chain of T-cell receptors resulting in a reduced T cell response. Other possible causes of lymphopenia include increased expression of Regulatory T cells (Tregs) contributing to immunosuppression and in vivo synthesis of proapoptotic ligands such as Fas-Ligand within the tumor enabling activation-induced death of lymphocytes.[28,29,30]

Platelets in TME

Platelets are anucleate components of blood that are present abundantly in the tumor microenvironment.[31] Initially, the active functions of platelets in promoting cancer growth and invasion led to the hypothesis that an abnormally high platelet count could serve as a biomarker of cancer risk. According to the reports of various studies, cancer incidence increases with increasing platelet count, individuals with a greater platelet count demonstrated more than a 3% risk of cancer in one year of observation.[32,33]

Platelets play an essential part in carrying out the coagulation process and in maintaining hemostasis after a mechanical injury to the vasculature. Platelets also contain several bioactive molecules within their granular structure. There exists a variety of receptors on the cell surface of the platelets, both the mediators and receptors contribute to the inflammatory process, directing the progression of cancer, and metastasis. In addition, platelets play a role in the spread of cancer. When tumor cells initially detach from the original tumor and enter the bloodstream, Platelets are the first cells that encounter the tumor cells.[34] Literature evidence has reported a direct relationship between circulating platelet counts with the serum vascular endothelial growth factor which is responsible for angiogenesis. Induction of angiogenesis is considered as a major cause promoting the progression and dissemination of the tumor cells resulting in lymphatic spread by the release of VEGF from platelets that have a direct role in promoting the spread and invasion. Thus, Platelets have a multifaceted role in the progression of cancer.[35] Ren et al. (2016) reported elevated levels of platelet-related microparticles in OSCC, which may be due to the release of inflammatory mediators contributing to increased procoagulant activity.[36] When a tumor cell and platelet interact, two types of aggregation and adhesion are known to occur. Homotypic adhesions occur within the tumor cells while heterotypic adhesions occur between the platelets and tumor cells, both of these adhesions promote the survival of the tumor cells. Apart from these mechanisms, a dose-dependent increase in the invasion of the tumor cells to the adjacent sites by the action of activated platelets present in the tumor environment has also been reported.[37,38]

Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAF) are the major non-immune cells present abundantly in the tumor stroma. CAF can account for up to 80% of the total tumor mass in an advanced stage of HNSCC, Literature evidence reports CAF to be tumor-promoting in nature. However, the phenotype of CAF cells is widely diverse in composition and may differ based on the phenotype of HNSCC.[39] A study by Hassona et al.[40] compared CAF from genetically stable versus genetically unstable OSCC and it was found that genetically unstable tumors had senescent CAFs which demonstrated high levels of reactive oxygen species (ROS), associated with increased tumor-promoting activity.

CAFs modulate the microenvironment primarily by the exertion of various factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), C-X-C motif chemokine ligands (CXCCLs) CXCL12 and CXCL14, C-C motif chemokine ligands (CCLs) CCL5 and CCL7, and interleukins (ILs) IL-6 and IL-17A. (41-44) CAFs are also essential producers of matrix-metalloproteinases (MMPs) and modulate the microenvironment through remodeling and degradation of extracellular matrix (ECM), which ultimately promotes the invasive phenotype of cancer cells. [45] Various markers of CAF have been documented in the literature, such as fibroblast activation and Fibroblast specific proteins, α-smooth muscle actin, platelet-derived growth factor receptor α/β, and vimentin.[46,47,48]

Extra Cellular Matrix

The extracellular matrix (ECM) is a significant constituent of the TME, which is composed primarily of a non-cellular network of macromolecules such as fibrous structural proteins, glycoproteins, proteoglycans, etc. The Components of ECM exert physical and biochemical support to the surrounding cells. Each of these macromolecules constituent of the ECM possesses its own unique set of physical and biological characteristics. There is a high concentration of fibrillar collagens and proteoglycans in the interstitial matrix, which is largely produced by stromal cells. Analyses of the CAF secretome reveal an increase in the production of bone morphogenetic protein (BMP)1, thrombospondin-1, and elastin interface 2.[49,50]

Matrix Metalloproteins is produced in large quantities by the ECM. MMPs are primarily composed of zinc-dependent proteins and peptide hydrolases that are released and activated by the tumor cells. They possess the ability to degrade the ECM proteins of the basement membrane and facilitate the migration of tumor cells to local and distant regions. Increased expression of MMPs has been reported in various types of Cancers including OSCCs. Malignant cells secrete and activate various types of MMPs such as 1,7,8,9,10,12,13, etc. In addition, they also play a major role in tumor angiogenesis by activating basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta.[49,51]

Collagens make up as much as thirty percent of the total protein mass in the ECM. Collagen provides tensile strength and support for the migration of the cells, and as a result, it plays a vital part in the control of the behavior and development of the tumor cell. In addition to their contributions to the mechanical and structural aspects of the body, collagens are essential for the performance of a vast array of biological processes.[52] Some of these roles include tissue scaffolding, cell adhesion, cell differentiation, cell migration, and wound healing. ECM proteins such as collagen, elastin, fibronectin, laminin, and tenascin exert a direct impact on cell adhesion and proliferation, they also offer a structural support along which cells migrate out of and into the TME. In addition, these ECM proteins provide structural support along which cells migrate out of and into the ECM. The higher synthesis of collagen, laminin, and elastin also contributes to the increased stiffness of the tumor in comparison to the normal tissue that surrounds it. By triggering oncogenic intracellular signaling, such as Akt, β-catenin, focal adhesion kinase (FAK), and phosphatidylinositol 3-kinase (PI3K) pathways, and simultaneously inhibiting tumor suppressor genes for phosphatase and tensin homolog (PTEN) and glycogen synthase kinase 3/, elevated tumor stiffness strongly influences the growth of cancer. Increased matrix rigidity also promotes the activation of neighboring fibroblasts into a CAF phenotype. This activation is sustained by the mechanosensitive transcription factor yes-associated proteins.[49,52] Fibronectin (Fn) is a mega glycoprotein of 440 kDa, which is constituted of two smaller monomers. It is one of the most prevalent glycoproteins found in the ECM and it is generated by a wide variety of different cell types, including fibroblasts and endothelial cells. Research has shown that the structure of fibronectin provides binding and interaction sites for several other molecules that are also present in the ECM. These molecules include integrins, fibrin, heparin, tenascin, collagen, gelatin, and syndecan. Increased levels of fibronectin have been linked to the growth of tumors, their migration, and invasion, as well as a decreased response to therapy.[45][53,54]

Hypoxia in TME

Hypoxia is a significant characteristic of solid tumors. Intratumoral hypoxia, which results from insufficient oxygen delivery to the tissue, is a common characteristic of the rapid progression of solid tumors. Generally, tissue is considered hypoxic when the oxygen tension decreases below the level of 10 mmHg, as opposed to 40-60 mmHg in normal tissue.[55] Hypoxia in the tumor site can be acute or chronic. Acute hypoxia

is associated with active perfusion and results from the transient opening and closing of tumor vessels. Chronic hypoxia is a consequence of diffusion, as the oxygen demand associated with tumor cell proliferation generates a distance beyond which oxygen cannot diffuse.

Chronic hypoxia is long-lasting or possibly irreversible and typically occurs when tumor cells are located far from functional blood vessels.(56) Tumor hypoxia-induced reactions include altered genomic expressions, inhibition of apoptosis or promotion of autophagy, stimulation of the epithelial-mesenchymal transition (EMT), malignant progression with distant tumor metastasis, increased angiogenesis, and alterations to the anabolic characteristics of core cellular metabolism. In addition, hypoxia is associated with genomic instability due to the increased production of reactive oxygen species (ROS) and changes in the DNA damage repair pathways.(57) The hypoxic condition of the tumor site facilitates the increase in the production and local concentration of ROS and results in impairment of the repair process of the damaged DNAs, hypoxia is also associated with genetic instability.(58)

Hypoxia also enhances the aggressiveness of tumors via clonal selection. The new and more aggressively selected clones result in a vicious cycle of hypoxia, which functions as an impediment to conventional cancer treatments such as radiotherapy, chemotherapy, and phototherapy. Hypoxia in the tumor microenvironment influences the immune system via multiple pathways and contributes to diminished antitumor activity.(57)

IV. Conclusion

The tumor microenvironment is comprised of several individual cellular components grouped with the tumor cells. The complex mechanisms associated with TME can directly influence the behavior and characteristics of a tumor including the growth, invasion metastatic potential, and response to therapy. Understanding the Tumor-associated inflammatory responses and changes in TME is necessary for predicting the disease progression and prognosis. Active research has been carried out in recent years across the globe, to explore the cellular and histochemical changes in the tumor microenvironment which would result in the institution of targeted therapies promoting the survival rates of HNSCC.

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