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Review Article

Tumor Microenvironment of Oral Cancer

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Abstract

Tumor microenvironment decides the fate of tumor progression or regression. Understanding of tumor microenvironment resides and nonresident cells infiltrating and it's interaction with tumor cells especially stromal cells and immune cells. Tumor microenvironment consists of more than 50 percent mass of nonmalignant cells in primary tumor and metastatic tissue. This article describes the role of tumor microenvironment in tumor progression focusing mainly on tumor associated macrophages, endothelial cells and other components such as neutrophils, carcinoma associated fibroblasts in tumor microenvironment of oral cancer.

***Keywords**: Innate Immune Cells; Adaptive Immune Cells; NF-KB; STAT3; IL-1; TNF-α; TGF-β*

Abbreviations

HGF: Hepatic Growth Factor; VEGF: Vascular Endothelial Growth Factor; MMP-9: Matrix Mettaloproteinases-9; COX2: Cyclo-Oxygenase2; INOS: Inducible Nitric Oxide Synthase; ROS: Reactive Oxygen Species; PDGF: Platelet Derived Growth Factor; EGF: Epidermal Growth Factor; FGF: Fibroblast Growth Factor; TNF-Alfa: Tumor Necrosis Factor-Alfa; IFN-Beta: Interferon Beta; IL-10: Interleukin 10; TGF-Beta: Transforming Growth Factor-Beta; CCL17: CC Chemokine Ligand 17; CCL18: CC Chemokine Ligand 18; CCL22: CC Chemokine Ligand 22; PGE2: Prostaglandin E2; IDO: Indole Amine 2,3-Dioxygenase; UPA: Urokinase Plasminogen Activator; UPAR: Urokinase Plasminogen Activator Receptor; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-6: Interleukin-6; IFN-Gamma: Interferon Gamma; COX-1: Cyclo-Oxygenase 1; COX2: Cyclo-Oxygenase 2; NF-KB: Nuclear Factor KB; MCP-1: Macrophage/Monocyte Chemoattractant Protein-1; M-CSF: Macrophage Colony Stimulating Factor; IL-17: Interleukin 17; CD4+ Th17: CD4+ T Helper Lymphocyte17; MDSC: Myeloid Derived Suppressor Cells; SR-A: The Class A Macrophage Scavenger Receptor msr1; GM-CSF: Granulocyte Macrophage- Colony Stimulating Factor; G-CSF: Granulocyte Colony Stimulating Factor; STAT3: Signal Transducer and Activator of Transcription 3; bFGF: Basic Fibroblast Growth Factor; MMPS: Matrix Metallo Proteinases; HIF-1 Alfa: Hypoxia- Inducible Factor Alfa; T reg cell: T Regulatory Cell; T h1: T Helper 1; Th2: T Helper 2; TAM: Tumor Associated Macrophages

Introduction

Cancer is a heterogeneous complex transformed tissue involving numerous tempo-spatial changes in cell physiology. Tumor microenvironment consists of tumor cells, surrounding stroma houses various types of mesenchyme cells and extra cellular matrix. The microenvironment consists of not only tumor cells but the surrounding stroma tunes it with tumor in to an activated state as the tumor evolves through tumor -stromal interactions for acquiring hallmarks are autonomous hyper proliferative, evasion of apoptosis, limitless replicative potential, angiogenesis and invasion [1-4].

Tumor microenvironment of oral cancer

Tumor microenvironment contains various distinct resident and non-resident adaptive, innate immune and other cell types are fibroblast, carcinoma associated fibroblasts, myofibroblast, smooth muscle cells, endothelial cells and their precursors, pericytes, neutrophils, Eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells and antigen presenting cells such as macrophages and dendritic cells. Various data have demonstrated a role of individual component of tumor microenvironment in particularly macrophages, endothelial cells and cancer associated fibroblast in tumor growth and progression [1,2,4,5].

Recent studies have suggested that the tumor stroma provides support is an essential component of tumor microenvironment secretes growth factors and cytokines promotes angiogenesis, tissue invasion and metastasis [6-8].

Endothelial cells are involved in tumor progression in head and neck squamous cell carcinoma by producing various factors and activating signaling molecules. Attachment of oral squamous cell carcinoma cells to endothelial cells is an essential for invasion and metastasis and trigger Notch-1 endothelial signaling pathway promoting capillary formation. Oral squamous cell carcinoma and stromal cells secrete VEGF, PDGF growth factors and IL-8 cytokine promote cell proliferation and angiogenesis. Endothelial cell derived VEGF signals induces BCL-2, CXCL1, CXCL8 proangiogenic chemokines in oral squamous cell carcinoma cells helps in endothelial cell proliferation and angiogenesis. IL-1, TNF-α activates NF-KB a key transcription factor, IL-8, IL-6 cytokines and EGF secreted by endothelial cells induce phosphorylation of transcription factor STAT-3 and AKT in oral squamous cell carcinoma. Transcription of genes such as IL-8, COX-2, IL-1, TNF-α, and VEGF related to angiogenesis by HIF-1 α under hypoxic condition induce angiogenesis [9-13,22] (Figure 1 and 2).

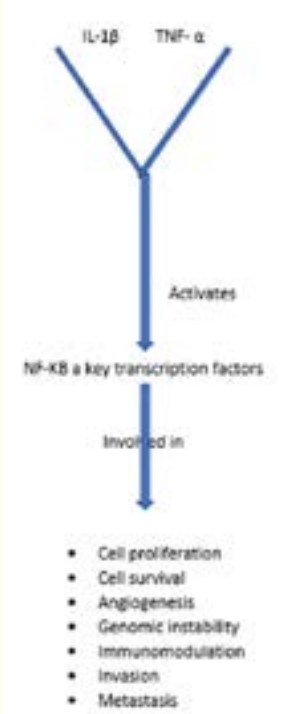

Figure 1: *Shows activation of NF-KB a key transcription factor by inflammatory mediators such as IL-1β, TNF-α involved in tumour progression.*

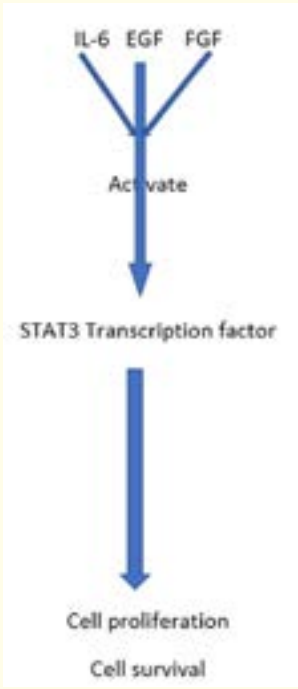

Figure 2: *Shows activation of STAT3 transcription factor by IL-6, EGF, FGF inflammatory mediators involved in cell proliferation and cell survival.*

Immune cells of tumor microenvironment imparts changes in tumor growth and progression. T cell population infiltrate the tumor areas are CD8 T cells supported by CD4 T cells producing IL-2 and IFN- Ɣ associated with good prognosis by killing tumor cells. T cells shows defective activation or function in peripheral blood of patients with oral cancer by various mechanisms.TH2 cells secrete IL-4, IL-5, IL-13 promote tumor growth and antimicrobial tissue inflammation support B-cell response mediated IL-17, IL-21 and IL-22 release increasing angiogenesis. CD4 T regulatory cells have immunosuppressive effects on antitumor CD8 T cells through production of cytokines IL-10 and TGF- β. Mast cells granulocytic leucocyte involved in innate and adaptive immunity present in stroma of oral tumor microenvironment secretes proteases, growth factors promotes angiogenesis, tumor growth and immunosuppression by endothelial proliferation, vascular tube formation and mobilization of Myeloid derived suppressor cells and Regulatory T cells (Tregs) [14-17].

Tumor associated macrophages are predominant leucocytic infiltrating cells in oral tumor microenvironment associated with tumor growth, progression and angiogenesis under hypoxic conditions of growing tumors by upregulation of macrophage chemo attractants such as endothelin-2 and VEGF. Tumor associated macrophages induced tumor cell invasion and migration by colony stimulating factor-1, EGF and macrophage inflammatory protein. These cells are involved in tumor progression by releasing proteases such as cathepsin, cysteine and matrix metalloproteases (MMP9) and also by secreting cytokines such as IL-10, IL-1, IL-6, TGF-β and TNF-α. IL-1, TNF-αproinflammatory cytokines activate NF-KB a key transcription factor involved in tumor progression. EGF, IL-6 inflammatory mediators activate STAT3 transcription factor involved in cell proliferation, and cell survival [4-9].

Tumor stroma is a heterogeneous milieu, houses various cell types and mainly connective tissue and adhesion molecules contributing structural support and functional activity of tumor microenvironment. Fibroblasts are important component of stroma, synthesize

and deposit extracellular matrix by secreting collagen and fibronectin. They are main components in formation of basement membrane separates epithelial and stroma by secreting laminin and type four collagen. Type four collagen was over expressed in head and neck squamous cell carcinoma. Integrins play a role in adhesion of cancer cells to basement membrane components such as laminin and fibronectin also confers polarity by binding to the extracellular matrix. Interleukins overexpressed are IL-1, IL-6, TNF-α and TGF-β after type1 collagen culture with oral squamous cell carcinoma cells in primary and metastatic carcinoma and increase in MMP-2 activity is seen, further activating P-ERK, P-P38, and phosphorylation of MAPKs plays an important role in extracellular cell matrix degradation induced invasion and metastasis by matrix metalloproteases 2,9 (Mmp's2,9) [10-12,14,15].

Carcinoma associated fibroblast (CAF) are the most abundant cells of stromal component of tumor microenvironment origin from fibroblast or mesenchymal stem cells of bone marrow or epithelial cells. These cells primarily originating from activated fibroblast by growth factors produced by tumor are TGF-β, FGF (Fibroblast growth factor), PDGF (Platelet derived growth factor), activate stromal cells in particular fibroblasts, Pericytes and smooth muscle cells mediated by expression of Alfa-SMA, MMP-1,3 and collagens are CAF genes in fibroblast. These cells exhibit rapid growth and proliferation by secreting cytokines and growth factors such as SDF-1 and IL-6, TGF- β, VEGF, COX2, HGF, EGF and also activate plasminogen activator and matrix metalloproteases such as MMP2,9 essential for tumor invasion, expansion and angiogenesis by degrading extracellular matrix and angiogenesis [3,5-9,23] (Table 1).

Cytokines	Transcription factors involved	Role in tumor progression
IL-1 TNF- α IL-8 IL-10 TGF-β	NF-KB AP-1	• Tumour initiation by cell proliferation and cell survival • Tumour promotion by angiogenesis, genomic instability, immunosuppression • Tumour progression by epithelial to mesenchymal transition and invasion
Growth factors EGF FGF VEGF	STAT 3	• Cell survival • Cell proliferation • Angiogenesis
Proteolytic enzymes MMP2,9 UPA		• Invasion and metastasis

Table 1: *Shows chronic inflammatory mediators such as cytokines, growth factors, proteolytic enzymes, transcription factors involved in tumour initiation, tumour promotion and tumour progression.*

Myeloid derived suppressor cells (MDSC) are immature myeloid cells of granulocytic or monocytic origin generated by bone marrow in response to various stimuli such as infection, traumatic stress and cancer exhibit immunosuppression of especially CD8+ T cells through cell to cell contact or nitric oxide synthase 2, ROS, arginase or IL-10 immunosuppressive cytokine expression and also disrupt antigen presentation by dendritic cells, M1 macrophage polarization, T cell activation and inhibit NK cell cytotoxicity [7,9,10,14,15].

MDSC induce skew the differentiation of CD4+ T cells to Tregs (regulatory T cells) and M2 phenotype macrophage, recruited to the site induced by an inflammatory cytokine macrophage migration inhibitory factor expressed by tumor cells. These cells are difficulty in characterization because of diverse phenotype. Tumor growth induced MDSC by VEGF-A pro- angiogenic factor induction [16-21].

Conclusion

Tumor microenvironment favors not only tumor progression by cross talk of tumor cells, stroma and immune cells, but also determines prognosis. It is also a major future therapeutic target by modulation of microenvironment of tumor, rather than concentrating only on tumor cells. Hence, thorough understanding of tumor microenvironment biology, modulation by immune cells, signaling pathway, stroma for future therapeutic and prognostic strategy.

Conflict of Interest

None.

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