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Chronic Inflammation Induced Immunosuppression in Tumor Microenvironment of Oral Cancer

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Abstract- Oral Cancer is a wound that do not heal is a complex disease consists of heterogeneous tissue in their tumor microenvironment. Oral cancer accounts eighth most Common Cancer worldwide. Chronic inflammatory mediators released from immune cells in tumor microenvironment of oral cancer such as macrophages, T lymphocytes, dendritic cells, Natural killer cells release cytokines, Chemokine's and growth factors helps in generation of myeloid derived suppressor cells. Myeloid derived suppressor cells are derived from myeloid progenitor cells of bone marrow secretes inflammatory mediators iNOS, arginase-1, PGE2,IL-10 and IL-4 suppresses adaptive and innate immunity by interacting with macrophages, T-cells, Natural killer cells and dendritic cells favours pro-tumoral activity by activating transcriptional factors (NF-KB,STAT -3,HIF) further progress in to oral cancer. Myeloid derived suppressor cells reduces T cell activation and function by Arginase-1, iNOS, peroxynitrate over expression and cysteine depletion.

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Keywords: myeloid derived suppressor cells, chronic inflammation, oral cancer, granulocytic monocytic colony stimulating factor, natural killer cells, transforming growth factor- beta, vascular endothelial growth factor, prostaglandin E2, hypoxic inducible factor, toll like receptor, lipopolysaccharide, cytokines, chemokines, growth factors.

I. Introduction

Inflammation is the body response to any type of injury, in which various mediators are released in surrounding environment. Recent debated topic is inflammation associated onco -promotion in tumor microenvironment. Inflammatory mediators in oraltumor micro-environment consists of mediators of inflame-mation are Neutrophils, lymphocytes, macrophages, Natural killer cells, Dendritic cells secreting cytokines. Which can induce Immuno-modulation by myeloid derived suppressor cells (MDSC) results in Oral tumor promotion, progression, and metastasis(1).

Immune cells has an important role in preventing or promoting cancer through immune surveivellance of tumor by mechanism of immune-editing, immuneprocessing and immuneevasion. Immunoevasion is one of the hallmark of tumor in order to progress. Immunoevasion mechanism involves the production of cytokines, which are immunosuppressive, T cell apoptosis or loss of HLA class1 and costimulatory molecules. In Immunoediting high immunogenicity tumorseliminate tumor by NK cells, macrophages,T cells. Reduced tumor cell variant immunogenicity favour tumor progression by immunosuppression or resistant to immune attack. Immuno processing stage genetic instability and heterogeneity of cancer cells favour promotion of tumor which, are poorly recognized by immune system or immunosuppression.

Immunoescape stage altered by expression of MHC1 and 11 and costimulatory molecules, antigen processing dysregulation antigen processing, expression of low levels tumor antigen, other mechanisms of immunosuppression are T cell tolerance to tumor antigen and immunosuppressive cytokines IL-10,TGF-Beta or T regulatory cells (Treg). (48)

Oral cancer is an eighth most common cancer in the worldwide. Every year nearly 300,400 new cases have been reporting worldwide and costs 145,400 lives a year. Squamous cell carcinoma involves 90% of head and neck region especially from mucosal epithelium linked to various adverse habits such as smoking form of tobacco, smokeless tobacco, alcohol drinking and also human papilloma virus.

Advance oral cancer locally, management has been a challenging issue involving multidisciplinary approach of surgery, chemotherapy and radiotherapy. Despite recent improvement in management of oral cancer still the prognosis is grave with five year survival rate nearly 50%.

Early stage of inflammation neutrophils are predominant leucocyte and first cell to migrate are regulated by macrophages and mast cells in tissue. As inflammation proceeds various types of leucocytes majority of them are lymphocytes gets activated and recruited to the inflammatory site by a signalling network involving chemokines, cytokines, growth factors for defense against infection. Shifting of antimicrobial tissue damage to tissue repair occurs mediated by PGE2, TGF-Beta and reactive oxygen and nitrogen inter-mediates having dual role in both aggravating and suppressing inflammation. Resolution of inflammation requires macrophages, dendritic cells and phagocytes by apoptosis and phagocytosis, which promote an anti-

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inflammatory response. If inflammation is dysregulated, aggravating to chronic inflammatory cellular respose causing immunosuppression, tissue and DNA damage by cytokines, growth factors, reactive oxygen and nitrogen species released from macrophages and lymphocytes(1,2).

II. Factors Affecting Inflammation Induced Immunosuppression in Tumor Microenvironment of Oral Cancer

Oral tumor microenvironment consists of various heterogeneous inflammatory mediators such as neutrophils, natural killer cells, T and B lymphocytes, mast cells, and antigen presenting cells(APC) such as macrophages, Dendritic cells and other distinct cell types including fibroblasts, Carcinoma associated fibroblast, smooth musclecells, myo-fibroblast, endothelial cells and their precursors, pericytes. Recent data have demonstrated a role of these individual components, in particular carcinoma associated fibroblasts, macrophages and endothelial cells, in promoting tumor growth and progression (1-2). The tumorstroma has an indispensable role in acquiring hallmark capabilities. The stroma provides support with growth factors (GM-CSF,G-CSF,M-CSF; VEGF; TGF), cytokines (IL-1,IL-4,IL-5,IL-6,IL-10,IL-13, TNF-Alfa, Interferon –Gamma), chemokines (CCL2,CCL4,CCL5, CXCL1, CXCL12 and CXCL8) along with COX2 which, secrete prostaglandin E2,promotes the generation of Myeloid derived suppressor cells.

III. Role of mdsc in Immunosuppression

These are immature heterogeneous myeloid cells that fail to terminally differentiate in to granulocytes, dendritic cells or macrophages on chronic inflammatory conditions and exhibit immunosuppressive function by multiple mechanism. Their broadly distinct phenotypical characteristics, Among human MDSCs, the two subsets can be distinguished as Granulocytic and Monocytic(3). which, is responsible for immuno-modulatory activity in tumor microenvironment by evading active immune system by various factors by potent inhibitors of both antigenic –specific and non-specific T-cell activation. These factors are arginase, nitric oxide, Reactive oxygen species (ROS), PGE2, Cystein, peroxynitrate. An important mutagenic factor frequently abundant in an inflammatory microenvironment is ROS (eg. Oxygen ions and peroxides) results from oxidative stress induced by phagocytic cells.ROS are highly reactive, unstable molecules that damage DNA increases the cell mutation rate, thus favouring the appearance of clones with oncogenic properties. Potential key mechanism of MDSC –induced CD8+ T-cell immunosuppression in tumor bearing hosts by increased NADPH oxidase, NOX_2 activity (4-5). Nitric oxide is produced by MDSC by utilising L-arginine as substrate for nitric oxide synthase (6,7). Which, suppresses T-cell activation, adhesion, proliferation and migration (8-13).It also suppresses T-cell function, particularly CD8+ T cells by blocking the activation of signalling molecules in T cells, including JAK1(Janus activated kinase 1), STAT5, ERK and Akt (8,11). It has also been shown to inhibit MHC class 2 expression and promote CD8 T-cell apoptosis (14,15). Other important moderator synthesize by MDSC is Arginase. L- Arginine is a conditionally essential aminoacid and metabolized by arginases and nitric oxide synthases to produce either L- ornithine and urea (16,17,18). L- arginine is an amino acid required for T-cell function and proliferation. L-arginine deprivation has been reported to induce T-cell dysfunction and suppression of T-cell function (19,20,21).These mechanisms seem to contribute to the protumoral function of MDSC(22). MDSC are copious producers of peroxynitrate and increased levels are associated with tumor progression by inhibiting antigen specific, cytotoxic T-cell responses (23). Cysteineis an essential amino acid required for T-cell activation, differentiation and proliferation (24). MDSC mediated cysteine depletion, block activation of T-cell from the local microenvironment results in the inhibition of T-cell activation and function (25). PGE2 is an eicosanoids synthesise by COX2produced and secreted by MDSC, mediated over expression of arginase, Corelated with their pro-inflammatory and immunosuppressive properties, further inhibiting the activity of CD8+ T cells. MDSCs immunosuppressive function, activation and proliferation is activated by IFN-gamma, TLR ligands, IL-13, IL-4, and TGF –beta, which trigger STAT3and NF-kb signalling pathways(26,27,28). These various factors are produced during the course of inflammation following cellular stresses, in response to hormones, growth factors, endotoxin and inflammatory cytokines or by growing tumors which induces angiogenesis, apoptosis, chronic inflammation and immunosuppression(28,29).

IV. Interaction of mdsc with other Immunecells

MDSCs communication network between macrophages and DCs that promotes and maintains an immunosuppressive microenvironment. This communication is mainly mediated by inflammatory mediators IL-1beta, IL-6, IL-10, PGE-2, and TGF – beta (30,31). The activating NK receptors inhibited by IDO (Indoleamine 23-dioxygenase) andPGE2 are counteracted by NKG2A an inhibitory receptor utilized by both T and NK cells (32). An early response of damaged tissue is production of IL-8 by the epithelial cell itself, which together with macrophages and mast cells secrete TNF- alfa and histamine allows neutrophil extravasion to injure site initiating inflammation. Chemokines secreted by

endothelial cells and macrophages brings inflammatory and immune cells to the site of inflammation(33). Among inflammatory factors promoting proliferation are TGF-beta, fibroblast growth factor, epithelial growth factor, TGF-beta synthesized by mast cells, macrophages and lymphocytes as an inactive precursor in inflammatory microenvironment activated by proteases. TGF-beta promotes mesenchymal Cell proliferation and immuno - modulation by promoting N2 neutrophils and M2 macrophages, facilitates tumor invasion and metastasis (34,35). LPS is a known activator of macrophage cross talk with MDSC in the presence of LPS. Later LPS binds to LPS binding protein. Which helps in transfer ofLPS to the membrane bound receptor CD14 through TLR4signalling pathway. TLR4 signalling pathway gets activated by CD14 binds with TLR4 further downstream activation of NF-kb driving MDSC production of IL-10 resulting in immunosuppression and immune evasion by promoting M2 polarization of macrophages(36). Alternatively activated macrophages(M2 type) are an important source of both Fibroblast growth factors, and Endothelial growth factors activated by cytokines such as IL-4, IL-5, IL-6, IL-9, IL-13, IL-17 and TGF-beta acts as a immunosuppressor towards Treg (Regulatory T cell) cells maintain immunosuppressive microenvironment (37,38). Tumor stromacan also suppress immune effector function. Extra cellular accumulation of lactate, adenosine, VEGF under hypoxic condition activated by hypoxia inducible transcriptional factor (HIF) further induces angiogenesis. Cross talk between MDSC and dendritic cells in presence of cytokines such as IL-4, GM-CSF and PGE2 results in decrease in production of mature dendritic cells , blocking T-cell production of IFN-gammaand dendritic cells production of Pro-inflammatory cytokine IL-23driving the proliferation and inflammatory function of Th17 cells. Which suppresses both adaptive and innate immunity, due to immunosuppressive network, the immature dendritic cell fail to activate to become mature dendritic cell on antigenic presentation. So, the activation ofCD4+ and CD8+ T cells don't take place. All together co-operate to inhibit Dendritic cell antigen- processing, presenting activity and dendritic cell tolerance (39-47).All these factors contribute to pro-tumoral activity, tumor progression, invasion and metastasis. Inflammation is considered to be a' Seventh hallmark' of cancer (4).

Myeloid derived suppressor cells are immature myeloid cells of myeloid progenitor cells upon chronic inflammation. They are of two types Monocystic-MDSC and Granulocytic-MDSC. Myeloid derived suppressor cells induce immunosuppression by various mechanisms suppresses both innate and adaptive immunity, it also possess plasticity and the type of MDSC in tumor microenvironment determines the immunesuppression. Complex interactions between MDSC and immune cells and their role in immune-suppression need to be studied. Understanding of MDSC biology, chronic inflammatory mediators, which helps in MDSC recruitment, generation, activation and their role in immunosuppression must be revealed for therapeutic strategy and its role in tumor prognosis.

V. Conclusion

Thorough understanding of immune cells of Oral tumor microenvironment , role of immune cells such as Macrophages, T lymphocytes and natural killer cells which, drive towards tumorigenesis. Role of Inflammatory cells and their mediators such as cytokines, their interactions with myeloid derived suppressor cells are major immunosuppressor and immune evasion cells. Phonotypical and functional role of myeloid derived suppressor cells in oral tumor microenvironment linking between inflammation and oral cancer. Hence, modulating targeted or combined immune cells in oral tumor microenvironment, could possibly hold a future therapeutic opportunity with better survival rate and less possible complications.

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, Tumour 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, Indoleamine 2,3 –dioxygenase,
UPA, Urokinase plasminogen activator,
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 helper1, Th2, T helper 2,
TAM, Tumor associated macrophages,
TLR, Toll like receptor,
DC, Dendritic cells,
NK cells, Natural killer cells,
HLA, Human leucocyte antigen,
MHC 1, Major histocompatibility antigen 1,
Akt, Protein kinase B,
ERK, Extracellular signal-regulated kinase.

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