Myeloid Derived Suppressor Cells in Oral Cancer: An Emerging Concept

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Abstract: Myeloid derived suppressor cells (MDSC) are specialized immunoregulatorycells and major cause of immunosuppression in oral cancer tumor microenvironment. Which are generated by various mediators of chronic inflammation. MDSC exerts its effects by two mechanisms, first is enzymatic mechanism by two enzymes which are elevated in MDSC are arginaseand iNOS2, second is non-enzymatic mechanism by ROS, peroxynitrate ,L-selectin and interaction with other immune cells. It also has a role in progression of oral cancer by secreting inflammatory mediators. This article brief about the MDSC in immune regulation and tumor progression in oral cancer tumor microenvironment.

Keywords: iNOS, Arginase 1, COX-2, HIF-1 Alfa, T regs, Peroxynitrate, S 100 A8/A9, ROS.

INTRODUCTION

Oral cancer is the major cause of concern mainly in South east asian countries and other parts of the world, because of extensive use of tobacco products in the form of chewable or non-chewable form, infections such as HPV, alcohol consumption. Majority of oral cancers are preceded by potentially premalignant lesions and conditions such as leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus. Oral squamous cell carcinoma is the most common carcinoma of oral cavity. Oral cancer along with pharyngeal cancer account 7th most common cancer in the world. Tobacco in the form of chewable or non-chewable form and HPV infection release various inflammatory mediators such as cytokines, chemokines, growth factors and enzymes from chronic inflammatory cells such as neutrophils, macrophages, mast cells and lymphocytes in inflammatory microenvironment activate key transcription factors such as NF-KB and STAT3 involved in tumor progression. IL-1, TNF-α pro-inflammatory cytokines activate NF-KB transcription factor, IL-6 and EGF activate STAT-3 transcription factor, involved in cell proliferation by Cyclin –D, C-MYC, cell survival by BCL-2, BCL-XL, CFLIP, surviving, immunemodulation/ chronic inflammation by MHC-1, MHC-11, cytokines, angiogenesis by IL-8,COX-2,VEGF, and adhesion/ invasion by ICAM-1, upa, ELAM-1, VCAM-1, E-Selectin [1-6].

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MDSC: DEFINITION, GENERATION, EXPANSION AND ACTIVATION

Myeloid derived suppressor cells are heterogeneous population of early myeloid progenitor cells that do not differentiate in to mature dendritic cells, granulocytes and macrophages. These are characterized by the ability to suppress T cell and NK cell function, can play a role in tumor development and chronic inflammation due to potent regulatory role in immune responses. MDSC generation and expansion in the bone marrow in response to cancer is derived from inflammatory factors such as G- CSF, IL-6, GM-CSF, IL-1 Beta, IL-10, TGF-Beta, prostaglandin E2, Hypoxia inducible factor - 1 Alfa (HIF-1 Alfa), Vascular endothelial growth factor (VEGF) and recruited to the tumor site by chemokine's (CCL2, CCL3, CCL4, CCL5, CXCL1, CXCL8) and S100 A8/A9. MDSC activation by TNF- Alfa, IL-10, TGF-Beta, IL-1 Beta, IL-6, IFN-gamma, COX-2, Hypoxia inducible factor - 1 Alfa (HIF-1 Alfa). Myeloid derived suppressor cells is of two types are, granulocytic and monocytic, granulocytic subtype can be characterized as Lin^{-} $HLA\text{-}DR^{-/lo}$ or $CD11b^{+}$ $CD14^{-}CD15^{+}CD33^{+}$ and monocytic subtype can be characterized as $CD14^{+}$ $HLA\text{-}DR^{neg/lo}$ or $Lin^{-}HLA\text{-}DR^{neg/lo}$ $CD11b^{+}$ $CD14^{+}$ $CD15^{-}$ (6-11) (Figure **1**).

MDSC IN IMMUNOSUPPRESSION AND TUMOR PROGRESSION

Myeloid derived suppressor cells mainly involved in immunosuppressive activity, which requires cell to cell contact due to interaction of cell surface markers and secretion of transitory soluble mediators such as ROS, iNOS and arginase 1 as a result of exposure to specific cytokines. MDSCs are induce to express iNOS and arginase 1 enzymes at very high levels, iNOS breaks down L-arginine in to nitric oxide, while iNOS-2 breaks

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down L-arginine in to urea and L-Ornithine. Depleting L-arginine prevents CD3 expression on T-cell, unable to transmit signals required for T lymphocyte activation. Further, it may inhibit cell cycle regulatory proteins cyclinD3 and cyclin dependent kinase 4, which blocks T-cell proliferation. High levels of NO produced by MDSC mediated iNOS2 enzyme, interfere with inhibition of effector T-cell activation through transcriptional factors are JAK (Janus-kinase) and STAT (Signal transducer and activator for transcription pathways) signaling proteins required for numerous Tcell functions, inhibit MHC class 11 expression on antigen presenting cells and induce Tcell apoptosis.

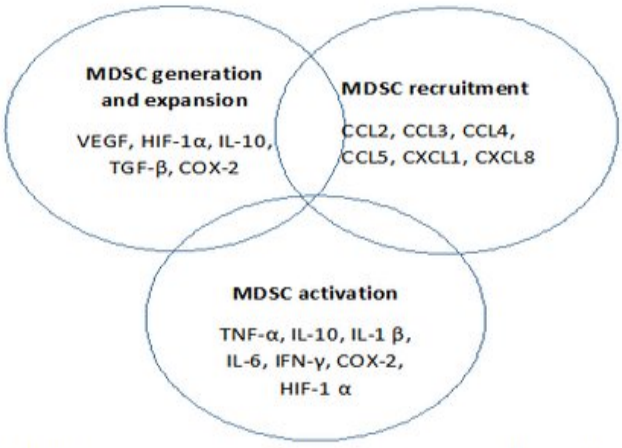

Figure 1: Showing MDSC generation and expansion, recruitment, and activation by various inflammatory mediator in the tumor microenvironment of oral cancer.

The other MDSC mediated immunosuppression mechanism is by L-arginine independent, these includes reactive oxygen species (ROS), TGF-Beta, and cysteine depletion. ROS production likely occurs via the NADPH oxidase pathway present in all phagocytic cells. ROS production plays an important role in MDSC mediated immunesuppression. Its production by MDSC is mediated by interaction of Tcell or by exposure to cytokines such as TGF-Beta, IL-6, IL-10 and GM-CSF. A form of ROS is hydrogen peroxide, prevents cytokine secretion and T-cell apoptosis. ROS and NO production by MDSC at the site of injury induced by immune cells such as IFN-Gamma [11-16].

An aminoacid cysteine, essential for T-cell activation is depleted by MDSC. L-selectin is a plasma membrane molecule belongs to a selectin family member, which facilitates the extravasation of leukocytes from the blood and lymphatics to lymphnodes and inflammatory locales. MDSC mediated down regulation of L-selectin, impaires T-cell activation. Without L-selectin tumor antigen in the lymphnode presented by antigen presenting cells will not be encountered by naïve CD4 and CD8 T cells, thereby further reducing T-cell activation.

One of the most damaging oxidants in the body produced by a reaction of NO with hydrogen peroxide is peroxynitrite, found in at the site of inflammation, where MDSC and immune cells accumulate in cancer causes T cells unresponsiveness to antigen presenting cells [16-18].

MDSC production of inflammatory mediator S100 A8/A9 induced by TGF-Beta and VEGF. S100 A8/A9 helps not only in recruitment of MDSC in tumor microenvironment, but also in immunosuppressive activity by stimulating NF-kB and MAPK (Mitogen activated protein kinases) signaling pathways in tumor cells regulate cell proliferation, cell survival, cell differentiation and cell motility, thereby promoting tumor progression. MDSC mediated immunosuppression by T regulatory cells (Tregs) through direct cell to cell interaction or expansion in the presence of specific production of soluble factors such as IL-10, and TGF-Beta. MDSC interacts with other immune cells such as macrophages, natural killer cells, natural killer T-cells bring about immunosuppression mediated by IL-10, natural killer cell activation receptor (NKG2D), TGF-Beta, and IL-13. Recent evidences suggest that MDSC also involve in tumor promotion and progression by producing MMPs involved in extracellular matrix degradation and also acts as an angiogenic switch by

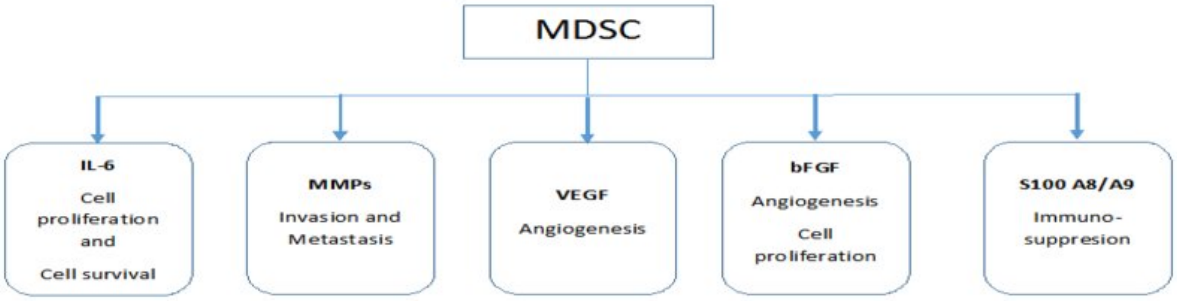

Figure 2: Showing factors secreted by MDSC involved in tumor progression.

releasing VEGF, bFGF (Basic fibroblast growth factors) and recruiting pericytes for angiogenesis [18-22] (Figure **2**).

CONCLUSION AND FUTURE PERSPECTIVE

Myeloid derived suppressor cells are immune regulatory cells present in oral cancer tumor microenvironment bring about immune evasion by interacting with other immune cells producing various inflammatory mediators such as cytokines, chemokine's, growth factors and enzymes. Majority of oral cancer is mainly due to smoking, tobacco chewing, alcohol, infectious agents such as hpv induce release of inflammatory mediators include cytokines, chemokines, growth factors, enzymes, Which involved in generation, expansion and activation of MDSC, involved in tumor progression. We need to understand the molecular biology of these cells and their mechanism of action in tumor microenvironment of oral cancer for future prognostic and therapeutic interventions.

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

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 = Neuclear 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

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