Chronic Inflammatory Mediators in Tumor Microenvironment Induced Tumor Progression

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ABSTRACT

Inflammation is the body's defensive action against noxious stimuli such as physical or chemical or thermal or infectious agents by inflammatory mediators released from the innate and adaptive immune cells. If the inflammation is aggrevated, chronic, nonresolving, and smoldering inflammation in dysregulated immune cells results in releasing various inflammatory mediators such as chemokines, cytokines, growth factors, and proteolytic enzymes produced from chronic inflammatory cells such as neutrophils , macrophages, mast cells, basophils, T cells, and B cells in the tumor microenvironment. IL-1β,TNF-α, and COX-2 pro-inflammatory mediators released from chronic inflammatory cells activate key transcription factors including NF-KB, STAT3, HIF-1α and AP-1 which work together and cause cell proliferation by activation of cyclin D cell cycle regulatory protein, angiogenesis by IL-8,VEGF inflammatory mediators, immuno-suppression by IL-10,TGF-β, cell survival by activation of BCL-2,BCL-XL anti-apoptotic proteins, genomic instability by release of ROS,RNS free radicals, invasion and metastasis by release of proteolytic enzymes such as (UPA, Mmp 2,9). This article described the role of chronic inflammatory innate and adaptive immune cells and their mediators in tumor microenvironment involved in tumor progression.

Key Words: *NF-KB, STAT-3, IL-1β, IL-6, TNF-α, COX-2*

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INTRODUCTION

Inflammation is the body's defensive action against any noxious stimuli such as physical or chemical or infectious agents. Inflammatory cells such as innate and adaptive immune cells release various inflammatory mediators. Innate immune cells are the first line of defensive action against non- specific infection; and the inflammatory cells release inflammatory mediators reaching to the site of injury, and activate the adaptive immune cells resulting in tissue repair and regeneration [1-3].

If the inflammation is aggrevated chronically, the non-resolving and smoldering inflammation causes the dysregulated immune cells to release various inflammatory mediators such as chemokine's, cytokines, growth factors, and proteolytic enzymes which lead to tumor initiation, promotion, and progression [1, 4].

Lichen planus, Oral submucous fibrosis, gingivitis and chronic periodontitis associated oral squamous cell carcinoma, sialadenitis related salivary gland carcinoma, Gastric acid associated Barrett's metaplasia and reflux esophagitis associated esophageal carcinoma, Sjogren's syndrome and Hashimoto's thyroiditis associated mucosa, associated lymphoid tissue lymphoma, UV radiation associated skin inflammation melanoma, Silica, asbestosis, smoking associated silicosis and bronchitis associated lung carcinoma, Prostatitis induced prostate carcinoma, chronic pancreatitis induced pancreatic cancer, Hepatitis B induced hepatocellular carcinoma, HPV induced cervical cancer, and pharyngeal cancer can be named as some inflammatory conditions or injuries that are related with malignancy. Human herpes virus 8 (HHV8) induced Kaposi's sarcoma. 20% of all cancers have been associated with chronic infections, 35% of cancers have been attributed to dietary factors, 20 percent of cancers have been due to obesity, and by increasing chronic inflammation, hepatocellular carcinoma has been

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promoted. Chronic inflammation has been considered as a seventh hallmark of cancer [1, 4-6].

Chronic inflammatory mediators in tumor microenvironment involved in tumor progression

Inflammation mainly involves innate immune cells, triggered by viral structures and foreign microbes known as specialized recognition pattern PAMP (Pathogen associated molecular pattern) or cell death; and tissue injury releases cellular constituents known as DAMP (Damage associated molecular pattern), recognized by PRR(Pattern recognition receptors) which belongs to TLR(Toll like receptor) trans membrane receptor family. TLR transmits the intracellular signal through adaptor protein (My88), which results in further activation of innate and adaptive immune cells, amplifying the inflammatory response. The activation of innate immunity results in secretion of chemokines and cytokines, recruit T cells and MHC class1 and class 11 up regulation [2, 7-9].

Chemokines are chemotactic cytokines that involve in positioning and migratory patterns of immune cells to the site of inflammation. Receptors of chemokines are expressed on all the leucocytes produced by stromal and tumor cells which facilitate the tumor progression. Neutrophil recruitment is mediated by CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8. The recruitment of macrophages, dendritic, and natural killer cells was by CCL2, CXCL12-CXCR4, CCL4, CCL5, and MCP-1. Lymphocyte and natural killer cells were recruited by CXCL12-CXCR4, CXCL9, CXCL10, CXCL11, CCR7-CCL21, CXCL19, and CCL21 [10, 11].

Antitumor N1 phenotype to protumoral N2 phenotypic neutrophils was mediated by TGF-β. Neutrophils in tumor microenvironment produced ROS, RNS, VEGF, HGF, Mmps 2, 9, TGF-β, involved in genomic instability, cell proliferation, angiogenesis, immunosuppression, invasion and metastasis [2, 12-14].

Macrophages in tumor microenvironment produced the growth factors of (EGF, VEGF, FGF), cytokines (IL-1, IL-6, IL-10, TNF-α, TGF-β,TH17), chemokines, and proteolytic enzymes (UPA, MMPs2,9,COX-2) were involved in tumor promotion and progression [12, 15-17].

IL-1β and TNF-α pro-inflammatory cytokines activated NF-KB as a key transcriptional factor , EGF, and IL-6 ,IL-10,IL-4,IL-11,IL-17 activated the transcriptional factor of STAT3, combined with NF-KB which was involved in cell proliferation, cell survival, angiogenesis, genomic instability, immunosuppression, invasion and metastasis(Table1). Mast cells produced by bone marrow involved in innate and adaptive immunity, matured in tissue, had protumoral activity by producing TNF- α, IL-10, IL-1, IL-6 cytokines. The ability to respond to an extrinsic signals depended on the surface expression of array of receptors such as TLR,NOD like receptors and FC, complement receptors, angiopoietin-1, VEGF, TGF-Beta, FGF-2 growth factors, release of proteases such as MMPs activated by tryptase favours degradation of extracellular matrix, angiogenesis, invasion and metastasis in patients with oral squamous cell carcinoma, colorectal, breast, bladder, lung, pancreatic, prostate, melanoma, gastric, esophageal, and ovarian cancer [3, 12, 17-22].

Mast cells recruited eosinophils, T and B cell immune response activity, and MDSC accumulation in tumor microenvironment. CD4 T and CD8T cells mediated immunosuppression by expression of surface receptors of PD-1 and CTLA-4 on their surface [3, 15, 23].

Tumor associated macrophages were functionally and phenotypically divided in to two subtypes of M1 or classically activated (by Th1 cytokines such as IFN-ϒ) secrete TNF-α, IL-1, IL-2, IL-6, IL-12 or IL-23. M2 phenotype or alternatively activated macrophages (by Th2 cytokines) such as IL-4, IL-13, IL-10) in the tumor microenvironment. M1 macrophages shifted towards M2 phenotypic macrophages in tumor microenvironment secrete TGF- β, and produced chemokine CCL22 that attracted T reg cells.Tregs produced IL-10 ,TGF-β, express $CD4^+$ $Fox3^+$ involved in immunosuppression of NK (natural killer) cells and Dendritic cells (Innate and adaptive immune cells) [4-6, 24, 25].

IL-17 pro-inflammatory cytokine is a subtype of CD4T cells produced by Th17 cells, expressed by tumor associated macrophages, induced IL-23 pro-carcinogenic cytokine, mediated IL-6 and TGf-β, promoted tumor progression by activating IL-1,TNF-α,IL-6 in patients with hepatocellular carcinoma, oral squamous cell carcinoma, prostate, colorectal, esophageal , and gastric carcinoma [26, 27].

In hypoxic tumor microenvironment, the recruitment of tumor associated macrophages induced HIF-1 α which acted as a transcriptional factor for IL-8, VEGF, COX-2, and promoted angiogenesis and immunosuppression [4, 6].

B cells producing IL-10 which are called as Bregs, were induced by STAT3 with Erk or P38, elevated the expression of PD-1. B cells induced tumor progression by activation of myeloid and mast cells, and also by production of IL-10 induced immunosuppression [4, 6].

TGF-β is a dual inflammatory mediator produced by tumor associated neutrophils, and tumor associated macrophages acted as tumor protective role in an initial stage, and in later stage acted as tumor promotive role by activating smad, snail, snug, transcription factors, and promoted epithelial tomesenchymal transition which induced invasion and immunosuppression [4, 28].

Transcription factors such as NF-kB ,STAT3 ,HIF-1α acting together promoted malignant changes by cellular proliferation (CyclinD , C-myc) , resistance to apoptosis by (BCL-XL,BCL-2), Immunosuppression /inflammation

(MHC-Class1,II,cytokines IL-1α,TGF-β,NO), angiogenesis (IL-8,VEGF,COX-2), invasion and metastasis (TGF-β , MMP-2,9,upA) [4, 6, 28].

NF-KB transcription factor would have an antagonistic activity against P53 tumor suppressor gene, as a guardian of the genome mutated in majority of cancers; more than 50% of all cancers by NO (Nitric oxide), ROS (Reactive oxygen species), RNS (Reactive nitrogen species) free radicals are induced by NF-kB as a key transcription factor; thus promoting inflammation induced tumor progression. NF-KB induced the activation of enzyme activation of cytidine deaminase (AID), caused DNA damage and mutation in tumor related genes (Fig 1), (Fig. 2) [4, 6, 11, 12].

CONCLUSION

Chronic inflammation and their mediators would induce tumor initiation, promotion and progression in tumor microenvironment. Chronic inflammatory conditions of human body such as oral potential malignant lesions and conditions, prostatitis, esophagitis induced chronic inflammatory mediators such as chemokines, cytokines, growth factors and proteolytic enzymes in tumor microenvironment. Chronic inflammatory mediators released from chronic inflammatory cells activated NF-KB,STAT-3, HIF-1α, and AP-1 key transcription factors, which induced chronic inflammatory mediators such as chemokines, cytokines, growth factors, and proteolytic enzymes involved in tumor initiation, tumor promotion, and tumor progression by cell proliferation, cell survival, angiogenesis, genomic instability, immunesuppression, tumor invasion and metastasis. Chronic inflammation has been considered as a seventh hallmark of cancer. Thorough understanding of chronic inflammatory mediators in tumor microenvironment and their interactions with tumor stroma in tumor initiation, promotion, and progression by chemokines, cytokines, growth factors, proteolytic enzymes, and activation of transcription factors involved in tumor progression, would be helpful for future detection of cancer biomarkers for therapeutic and prognostic purposes.

Conflict of interest: None

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