

## Cytokines - major molecular messengers orchestrate between inflammation and cancer

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### ABSTRACT

Inflammation is the defensive mechanism against physical or chemical or thermal or infectious agents. Acute inflammation is a protective mechanism against any noxious stimuli by various mediators such as cytokines, chemokines, enzymes, growth factors by inflammatory cells. If the inflammation is aggravated chronically, smouldering inflammation results in release of inflammatory mediators such as cytokines, chemokines, growth factors, proteolytic enzymes, from innate and adaptive immune cells results in tumor initiation, tumor promotion and tumor progression. Cytokines are intercellular molecular messengers between immune cells and cancer cells, synthesized from immune cells and stromal cells activate transcription factors bring about tumor progression by cell proliferation, cell survival, angiogenesis, genomic instability, epithelial to mesenchymal transition, invasion and metastasis. This article briefs about the role of IL-1, TNF- $\alpha$ , IL-6, IL-8, IL-10, TGF- $\beta$ , and IL-17 cytokines in progression of cancer.

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**Keywords:** Interleukin-8, interleukin-10, TNF- $\alpha$ , TGF- $\beta$ , STAT-3, NF- $\kappa$ B

### Introduction

Most of all solid tumors have inflammatory cells and their mediators in their tumor microenvironment. External environmental factors play a very important role in cancer. Inflammatory mediators in tumor microenvironment promote tumor initiation, promotion and progression. Chronic inflammatory conditions induced tumor progression are ulcerative colitis and Crohn's disease induced colorectal cancer, hepatitis B and C induced hepatocellular cancer, chronic periodontitis induced oral squamous cell carcinoma, oral potentially premalignant conditions (Lichen planus and oral submucous fibrosis) induced

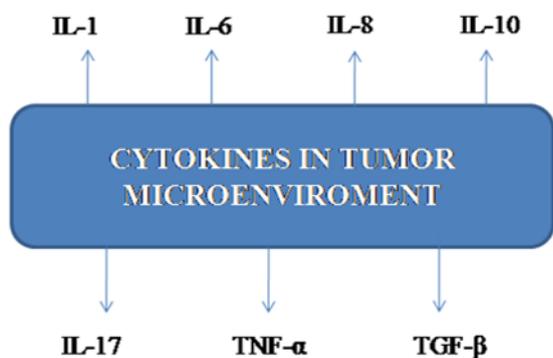
oral squamous cell carcinoma, prostatitis induced prostate cancer, HPV induced oropharyngeal carcinoma and cervical cancer, smoking induced lung carcinoma, gastric cancer associated with chronic gastritis (*H. Pylori*), esophageal cancer associated with Barret's esophagitis, gall bladder carcinoma associated with chronic cholecystitis, endometrial carcinoma associated with endometriosis. Chronic inflammation is considered as a seventh hallmark of cancer.

Interleukins are intercellular messenger molecules discovered in the 1970. Cytokines develop a specific immune response to a target antigen by

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**Figure 1.** Cytokines in inflammatory tumor microenvironment are IL-1, TNF- $\alpha$ , TGF- $\beta$ , IL-6, IL-8, IL-10 and IL-17.

communicating cells of the immune system [1, 2].

Interleukins are secreted by immune cells such as CD4 T helper cells, monocytes, macrophages and endothelial cells. They attach to a surface specific cell receptor, triggers a cascade of events in the target cell alters cell behavior. Interleukins also has immunomodulatory functions through maturation, migration, differentiation and adhesion of the cells of the immune system [3].

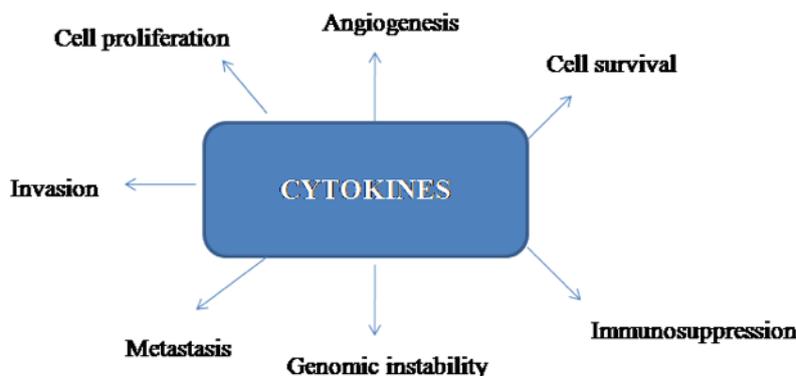
In inflammatory microenvironment recruit immune cells produce cytokines, chemokines, growth factors, activate transcription factors such as NF- $\kappa$ B, STAT-3, recruit chemokines, cytokines, prostaglandins activate transcription factors such as NF- $\kappa$ B, STAT-3, from cancer cells involved in cell proliferation, cell survival, angiogenesis, genomic instability, epithelial to mesenchymal transition, invasion and metastasis. Cytokines are involved in pro-inflammatory or anti-inflammatory action depends on cytokine

concentrations, expression of cytokine receptor content, state of activation of surrounding cells. They stimulate stromal and immune effector cells at tumor site and enhances cytotoxic effects of immune cells to tumor cells. Recent studies has shown that interleukins have major role in tumor driven molecular mechanism. Tumor as it progress and evolve, they evade by the immune system recognition by recruiting inflammatory cells secretes various cytokines in tumor microenvironment, which in turn stimulates biomarkers such as transcriptional factors involved in induction of EMT (Epithelial to mesenchymal transition) markers, anti-apoptotic molecules and cancer stem cells. Cytokines such as TNF- $\alpha$ , TGF- $\beta$ , IL-1, IL-8, IL-10, IL-6 and IL-17 creates a conducive inflammatory environment of tumor driven immunosuppression, tumor growth and metastasis [4-6] (Figure 1).

### Cytokines in tumor microenvironment

Cytokines secreted by immune cells involved in tumor progression by promoting cell proliferation, angiogenesis, genomic instability, cell survival, immunosuppression, invasion and metastasis (Figure 2).

IL-1 is a pleotropic cytokine are of two subtypes IL-1 $\alpha$  and IL-1 $\beta$  with encoding two separate genes have an identical biological activity through same receptor complex produce by variety of cells such as monocytes, macrophages, keratinocytes and endothelial cells activate T cells and B lymphocytes.



**Figure 2.** Cytokines secreted by immune cells involved in tumor progression by promoting cell proliferation, angiogenesis, genomic instability, cell survival, immunosuppression, invasion and metastasis.

IL-1 $\alpha$  is localized in cell membrane, cytosol and regulates intracellular microenvironment binds to IL-1R1 expressed in most cell types and responsible for IL-1 signal transduction. IL-1 $\beta$  is located extracellularly binds to IL-R11 present on neutrophils, monocytes, B lymphocytes and decrease signal transduction of IL-1 produced by human cancer cells. IL-1  $\beta$  activates NF- $\kappa$ B a key transcriptional factor, which in turn induce expression of IL-8, TNF- $\alpha$ , VEGF, IL-6 and TGF- $\beta$  promotes tumor progression in various human cancers. This protein acts through induction of prometastatic genes such as MMPs, angiogenic proteins and growth factors such as VEGF, IL-8, IL-6, TNF- $\alpha$  and TGF- $\beta$ , further activates MAPK-AP-1, NF- $\kappa$ B and P13/AKT signaling pathway, promote tumor growth and metastasis in several human tumors such as melanoma, head and neck squamous cell carcinoma, colon, lung and breast cancer [7-9].

IL-6 is a potent inflammatory cytokine, it is a key growth promoting and anti-apoptotic factor, produced mainly by macrophages, dendritic cells, and B lymphocytes as well as fibroblasts, epithelial cells and endothelial cells. IL-6 stimulates target cells via binding to IL-6R activates transcriptional factor STAT3 acts on malignant cells. It also increases VEGF expression involved in angiogenesis, cell proliferation, cell survival, invasion and epithelial to mesenchymal transition in head and neck cancer cells and increasing their metastatic potential in human cancers such as oral squamous cell carcinoma, gastric cancer and multiple myeloma [10-12].

IL-8 is a cytokine produced by macrophages, epithelial cells also known as neutrophil chemotactic factor induced by variety of stimuli are LPS, cytokines such as IL-1, TNF-  $\alpha$  and bacterial or viral products. Transcriptional factor such as NF- $\kappa$ B is an essential for IL-8 expression was dependent on hypoxia, cellular stress, nitric oxide (NO), acidosis, and a potent promoter of angiogenesis, aggressive growth and metastasis in many human cancers such as head and neck cancer, breast, cervical, prostate, colon, gastric, lung, melanoma, brain, mesothelioma, ovarian cancer and hematological malignancies such as AML, CLL and Hodgkin's lymphoma [13-16].

IL-10 is secreted by alternatively activated T cells phenotype (Th2 cells) acts on macrophages, T cells, B cells, monocytes, dendritic cells, granulocytes, and mast cells inhibits antigenic cell presentation, cell maturation and differentiation allowing evasion of immune surveillance by tumor cells and cytokine

production acts as immunosuppressive and anti-inflammatory role. It inhibits the activation of transcription factor NF- $\kappa$ B and stimulating STAT3 activation, there by inhibiting pro-inflammatory cytokine production such as TNF- $\alpha$ , IL-6, and IL-12. It has also shown to modulate apoptosis, angiogenesis suppression and pro-tumorigenic effect in cancers such as in B cell lymphoma prognosis is poor, promotes head and neck cancer and Burkitt's lymphoma [17-20].

TNF- $\alpha$  involved in chronic inflammatory diseases induced carcinogenesis by promoting angiogenesis, invasion, tumor progression have been demonstrated. It is produced by tumor and stromal cells or inflammatory cells such as macrophages, T cells, B cells and endothelial cells in tumor microenvironment, promotes cancer cell survival by induction of NF- $\kappa$ B encoding genes dependent anti-apoptotic molecules such as BCL-2, BCL-XL, surviving, CFLIP, and TRAF1/2. TNF- $\alpha$  dependent tumor promotion based on direct oncogene activation and generation of genotoxic molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), induce DNA damage and mutations, facilitating tumorigenesis. Other actions of TNF- $\alpha$  include immunosuppression of T cell response, cytotoxic activity of macrophages, and promotion of angiogenesis by its ability to cause differentiation of myeloid progenitor cells in to endothelial cells in tumor microenvironment. Pro-tumoral activity of TNF- $\alpha$  mediated via TNFR1 receptor found on tumor and stromal cells, whereas, TNFR2 receptor found on leucocyte infiltrate, stimulating autocrine growth, acting via cross talk between EtK-VEGFR2. TNF- $\alpha$  also promotes metastasis by inducing epithelial-mesenchymal transition (EMT) and found elevated in plasma of patients with advanced cancer, which helps in prognostic purpose in many cancers such as head and neck cancer, lung carcinoma, skin cancer, ovarian cancer [21-23].

TGF- $\beta$  is a pleiotropic immunosuppressive and anti-inflammatory cytokine produced by tumor cells, stromal cells, including cancer associated fibroblasts and immune cells such as T cells and macrophages in tumor microenvironment. Paradoxical complex role of TGF- $\beta$  in tumor is documented, in an early stage of cancer, it acts as a tumor suppressor, promoting apoptosis and inhibiting cell cycle progression through P21 up-regulation and MYC down-regulation. In later stages of tumor it enhances immunosuppression by converting effector T cells in to regulatory T cells (T

**Table 1.** Role of cytokines in tumor progression

Cytokines	Source	Action
IL-1	Monocytes	Angiogenesis
	Macrophages	Immune suppression
	Endothelial cells	Tumor progression
TNF- $\alpha$	Neutrophils	
	Macrophages	Genetic mutation
	Mast cells	Immune suppression
IL-6	T and B cells	Angiogenesis
		Invasion and metastasis
		Cell proliferation
IL-8	Dendritic cell	Cell survival
	Macrophages	
IL-10	B-lymphocytes	
	Macrophages	Angiogenesis
TGF- $\beta$	Mast cell	Immune suppression
	Macrophages	Cell survival
	Monocytes	Cell proliferation
	Dendritic cells	
	Granulocytes	
IL-17	T and B cells	
	T cells	Epithelial mesenchymal
	Carcinoma associated fibroblasts	Transition (EMT)
IL-17	Tumor cells	Immune suppression
	Macrophages	
	Mastr cells	Immune suppression
IL-17	Macrophages	Chronic inflammation
		Angiogenesis
		Tumor progression

reg), tumor invasion and metastasis by inducing epithelial mesenchymal transition (EMT) through Smad, Slug and snail transcription factors. TGF- $\beta$  receptor mutation or deletion leading to poor prognosis in cancers such as oral squamous cell carcinoma, colorectal, gastric, prostate, non-small cell lung, breast, bladder cancer [24-26].

IL-17 is a pleiotropic, procarcinogenic cytokine is a subtype of CD4 T cells produced by CD4 Th17 cells, expressed by tumor associated macrophages involved in tumor progression, induced by IL-23 pro-inflammatory cytokine in tumor microenvironment. It is involved in promoting inflammation and angiogenesis by production of TNF- $\alpha$ , IL-6 and IL-1 $\beta$  induced activation of STAT3 and NF-KB transcription factors, promotes tumor progression in human carcinomas such as oral squamous cell carcinoma, non-Hodgkin's lymphoma, breast, colon, gastric, hepatocellular, melanoma, ovarian, pancreatic, prostate, renal cell, and small cell lung cancer [27-30] (Table1).

## Conclusion and Future Perspective

Chronic inflammation promotes tumor initiation and progression by releasing inflammatory mediators such as cytokines (IL-1,IL-6, IL-10, TGF- $\beta$ , IL-8 and TNF- $\alpha$ ) from innate and adaptive immune cells. Cytokines are chemical mediators, which acts as a messenger between immune, cancer and stromal cells to bring about cell proliferation, cell survival,

immunosuppression, genomic instability, angiogenesis, invasion and metastasis by activating transcriptional factors such as (NF- $\kappa$ B, STAT3, HIF-1 $\alpha$ ). It acts as a biological markers, therapeutic target and prognostic markers in cancers. So, thorough understanding of cytokines, their role, and interaction with cancer cells needed for future perspective. Understanding of interaction of cytokines with immune cells, stroma and cancer cells in tumor microenvironment, their signaling pathway, role in tumor progression, helps in future diagnostic, therapeutic and prognostic purpose.

### Conflict of interest

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### Abbreviations

HGF = hepatic growth factor, VEGF = vascular endothelial growth factor, MMP-9 = matrix metaloproteinases-9, NO = nitric oxide, ROS = reactive oxygen species, PDGF = platelet derived growth factor, EGF = epidermal growth factor, FGF = fibroblast growth factor, TNF- $\alpha$  = tumor necrosis factor- $\alpha$ , IFN- $\beta$  = interferon-beta, IL-10 = interleukin 10, TGF- $\beta$  = transforming growth factor-beta, PGE2 = prostaglandin E2,IDO = indoleamine 2,3-dioxygenase, IL-2 = interleukin-2, IL-4 = interleukin-4, IL-6 = interleukin-6, IFN- $\gamma$  = interferon-gamma, COX2 = cyclo-oxygenase 2, NF-KB = Neuclear factor kappa B, IL-17 = interleukin-17, CD4+Th17 = CD4+T helper lymphocyte 17, STAT3 = signal transducer and activator of transcription 3, bFGF = basic fibroblast growth factor, MMPS = matrix metallo proteinases, HIF-1 $\alpha$  = hypoxia-inducible factor- $\alpha$ . Treg cell = T regulatory cell, TAM = tumor associated macrophages, AP-1 = activator protein 1, EMT = epithelial mesenchymal transition, MAPK = mitogen-activated protein kinase, P13k = phosphatidylinositol 3-kinase, IL-8 = interleukin-8, LPS = lipopolysaccharide, Th2 cell = T helper 2 cell, IL-1 = interleukin-1

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