

# Inflammation and Cancer: Critical View

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**Abstract:** Inflammation is the physiological response to an injury, it could be chemical, thermal, physical and infectious for reparative activity to injury. Recent data suggest that chronic inflammation leads to cancer development. Inflammatory mediators released to surrounding environment due to inflammation by inflammatory cells acts as a defensive or offensive depends on secretion of chemical mediators of inflammation such as growth factors, cytokines activating various transcriptional pathways bring about cell proliferation, angiogenesis further leads to tumor growth. This article describe the role of inflammatory cells and its mediators to development of cancer, various underlying unanswered future challenge questions in association with inflammation and cancer.

**Keywords:** TLR, PAMPs, DAMPs, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, NF-KB, STAT-3, HIF-1 $\alpha$ , TGF- $\beta$ , Tumor associated macrophages, Tumor associated neutrophils.

## INTRODUCTION

Acute inflammation is a defensive action against chemical or infectious or physical agents release various inflammatory mediators such as innate and adaptive immune cells such as neutrophils, macrophages, NK cells, dendritic cells, T and B lymphocytes, to heal and regenerate the injure tissue by releasing chemokines (IL-8, MCP-1, MIP-1 $\alpha$ ), cytokines (TNF- $\alpha$ , IL-1, IL-6, IL-10, TGF- $\beta$ ), growth factors (EGF, FGF, VEGF), enzymes (upa, Cox-2, caspases).

Neutrophils, macrophages are phagocytic cells, natural killer cells to produce IFN- $\gamma$ , opsonin, granzyme-B, acts as an antiviral, anti-inflammatory, and apoptotic activity. Dendritic cells and macrophages are antigen presenting cells to T and B lymphocytes. CD8 cytotoxic T lymphocytes produce IFN- $\gamma$ , acts as an antiviral activity. Helper CD4 T cells activate B lymphocytes to promote humoral and cytotoxic response. Activation of antigen specific T cells death and T cells and neutrophils apoptosis induced by NF-KB in acute inflammation to reduce inflammation and helps in healing.

Acute inflammation aggravated chronically, smoldering inflammation by persistent infectious agents or chemical agents, cause dysregulated immune cells produce various inflammatory mediators such as chemokines, cytokines, growth factors from innate and adaptive immune cells activates key transcription factors such as NF-KB, STAT3 involved in tumor

initiation, promotion and progression by cell proliferation, cell survival, angiogenesis, immune evasion, genomic instability, invasion and metastasis.

Inflammation is an essential to survival and integrity of multicellular organisms, is a function of innate immune cells to ward off infectious agents to develop specific immunity. The link between inflammation and cancer is not a recent concept was known about 150 years ago that was in 1863, by Virchow proposed that chronic inflammation predispose to development of cancer. Estimation of current data suggests that 25% of cancers are related to chronic inflammation [16]. The epidemiological data clearly shows the association of chronic inflammation or chronic inflammatory conditions lead to malignant transformation in the affected tissue.

Some inflammatory conditions or injury that are associated with malignancy are 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. Human herpes virus 8 (HHV8) induced Kaposi's sarcoma. 20% of all cancers are associated with chronic infections, 35% of cancers are attributed to dietary factors, of which 20 percent of cancers are due

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to obesity, by increasing chronic inflammation promotes hepatocellular carcinoma [1,2,4].

### **INFLAMMATORY CELLS AND THEIR MEDIATORS INVOLVED INTUMOR INITIATION, PROMOTION AND PROGRESSION**

In some cancers, inflammatory conditions precede the development of malignancy or inflammatory mediators in tumor microenvironment milieu drive to tumor progression, invasion and metastasis. Association between inflammation and cancer determined by the fact that inflammatory mediators such as ROS and nitrogen species produced by inflammatory cells are leucocytes recruited to the inflammatory site to kill infectious agents by chemokine's bring about DNA damage and genetic mutation [1-4]. Two pathways linking inflammation and cancer are extrinsic pathway activated by inflammatory cells are leucocytes and their mediators increases cancer incidence or promotion. Other pathway is intrinsic pathway triggered by oncogenic events initiate cancer induce transcription of inflammation related genes such as myc, ras, ret or inactivation of tumor suppressor genes such as PVHL, PTEN, P<sup>53</sup> leads to production of cytokines by neoplastic initiated cells. Inflammatory cells and mediators can disorganize the cancer cell genome directly by DNA damage or affecting repair system of DNA and altering cell cycle check points. Inflammatory mediators down regulates miss match repair family by HIF-1  $\alpha$  induced by TNF- $\alpha$  and IL-1  $\beta$  cytokines in cancer. PGE2 and ROS, nitrogen species, H<sub>2</sub>O<sub>2</sub> inactivates MMR (Miss match repair) DNA repair members by damaging enzymes at protein levels [1,2,5]. Inflammation induced chromosomal instability is due to inactivation of P53, which protect cell by inducing apoptosis upon DNA damage, after oxidative stress and chromosomal instability by ROS, nitrogen species.

Tumor associated neutrophils (TAN) promote genetic instability through RNS and ROS release, angiogenesis by VEGF, MMP-9 or prokinectin-2 (BV8), and invasion by HGF and oncostatin M inflammatory mediators [2,4].

Macrophages are predominant key cells in chronic inflammation accumulating in hypoxic areas due to HIF-1 dependent up regulation of CXCR4 and activation of pro-angiogenic factors including VEGF, IL-8, PDGF and angiopoietin-like 4 [6,7].

PAMPs (Pathogen associated molecular patterns) and DAMPs (Damage associated molecular patterns)

are specialized recognition patterns detect the microbes, microbial products, cell death, cell injury, HSP70, IL-1  $\alpha$ , HMGB-1, S100 calcium binding proteins recognized by pattern recognition receptors belongs to TLR (Toll like receptor) family activates innate and adaptive immune cells mediated NF-KB transcription factor by chemokine's, cytokines involved in tumor progression [5].

Chemokine's are chemotactic cytokines that involve in positioning and migratory patterns of immune cells to the site of inflammation. Receptors of chemokine's are expressed on all leucocytes produced by stromal and tumor cells facilitates tumor progression. Neutrophil recruitment is mediated by CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8. Recruitment of macrophages, dendritic, and natural killer cells are by CCL2, CXCL12-CXCR4, CCL4, CCL5, and MCP-1. Lymphocyte and natural killer cells recruitment by CXCL12-CXCR4, CXCL9, CXCL10, CXCL11, CCR7-CCL21, CXCL19, and CCL21 [6,29].

Mast cells produced from bone marrow involved in innate and adaptive immunity, have protumorigenic activity by producing TNF- $\alpha$ , IL-10, IL-1, IL-6 cytokines activate NF-KB and STAT-3 transcription factors. Ability to respond to an extrinsic signal depends on surface expression of variety of receptors such as TLR, complement receptors, NOD like and Fc receptors. VEGF and angiopoietin, TGF- $\beta$ , FGF-2 growth factors, release of proteases such as MMP activated by tryptase favours extracellular matrix degradation, angiogenesis, invasion and metastasis. It recruits T and B cell adaptive immune response, eosinophils in tumor microenvironment [3,4,8,9].

Based on genetic and functional program changes in microenvironment signals, Th1 lymphocytes activates M1 macrophages by microbial products, microorganism killing by IFN- $\gamma$  and producing nitrogen species and RO intermediates. Th2 lymphocytes activates M2 macrophages are alternate activated leading to production of TGF- $\beta$ , IL-4, IL-13. Inflammation and adaptive immunity promote cell proliferation by producing growth factors, angiogenesis, repair and tissue remodeling [10-12]. Tumor associated macrophages are abundant innate immune cells in inflammatory tumor microenvironment induce cell proliferation, angiogenesis, invasion and metastasis by producing cytokines (IL-1, IL-6, IL-8, IL-10, TNF- $\alpha$ , TGF- $\beta$ , IL-17), chemokines (CCL17, CCL18, CCL22, CXCL8), growth factors (EGF, FGF, VEGF) and enzymes (COX-2, UpA, iNOS, MMPs, Arginase1),

immunosuppressive factors (IDO, iNOS, B7-H1). M2 macrophage have different phenotype IL-12 low/IL-10 high to produce TGF- $\beta$ , IL-4, IL-13 cytokines having pro-tumoral activity, IL-1 $\beta$  and TNF- $\alpha$  activates NF-KB and IL-6, EGF, activates STAT-3 main key transcription factors in cell proliferation, resistant to apoptosis, angiogenesis, immunosuppression, genomic instability, invasion and metastasis. In tumor the macrophage polarized to M2 type recruited to inflammatory site that is called tumor associated macrophages(TAM) by chemokine's (CCL2) sustained by CSFs, VEGF-A cytokines in tumor microenvironment [13-16]. Tumor associated macrophages require TGF-beta, IL-10, and M-CSF to acquire M2 properties. M2 type macrophage promoting tumor proliferation, progression, inhibition of adaptive immunity, remodeling and stromal deposition [17,18].

Tumor associated macrophages suppress antitumor T cell immunity by IDO (Indoleamine 2,3-dioxygenase). Dendritic cell maturation is inhibited by IL-10, TGF-Beta, M-CSF and attraction of T regulatory cells to the tumor site. Suppression of T cells acquire T reg phenotype and other inflammatory mediators such as monocytes via cytokine mediators TGF – Beta and IL-10. IL-6 is a inducer of STAT3 activated in various cancer types. Primary malignant cells are activated by STAT3 play a role in development of cancer in inflammatory microenvironment [19-22].

Dendritic cells are antigen presenting cells, prime T cells, dendritic cells presents antigen to CD8 T cells gets matured, activates CD4 or CD8 T lymphocytes produce IFN- $\gamma$  acts as an antiviral activity. In tumor microenvironment DCs and NK cells become immunosuppressive by IL-10, Tregs, TGF- $\beta$  [2].

IL-17 pro-inflammatory cytokine secreted by Th17 cells, is a subtype of CD4 T cells. CD4 T cells differentiate in to Th17 T cells generates IL-17 and IL-22 produce IL-6, TNF- $\alpha$ , IL-1  $\beta$  cytokines and promote tumorigenesis by activation of STAT3, production of inflammatory angiogenic mediators such as PGE2, VEGF, keratinocyte derived chemokine's, macrophage inflammatory protein-2. IL-23 is a key factor in maintaining and expanding Th17 inflammatory cell populations involved in cell proliferation and cell survival. Th17 involved in tumor growth by antagonizing and counteract the Th1 cells secreting IFN- $\gamma$  [23-29].

HIF-1 $\alpha$  transcription factor for IL-8, COX2, VEGF in hypoxic tumor microenvironment induced by TAM's,

promotes angiogenesis and immunosuppression mediated by NF-KB and STAT-3 [29].

B lymphocytes are anti-tumorigenic, but antigen and antibody complex impairs antitumor activity [2]. B lymphocytes produce IL-10 known as Bregs, mediated by STAT3 and express PD-1 receptor involved in immunosuppression by suppressing CD8 T cells. It activates mast cells and myeloid cells involved in tumor progression [2,29]. T cells and B cells mediated immunosuppression by expression of surface receptors CTLA-4 and PD-1 [4,29].

## FUTURE CHALLENGES

1. Not all chronic inflammatory conditions predispose to malignancy only certain conditions with underlying inflammatory mediators and their mechanism drive to malignant changes need to be identified those inflammatory factors and underlying mechanism of action.
2. At what stage of inflammation, critical factors, does the chronic inflammation tip towards malignancy.
3. What type of patient with chronic inflammatory changes predisposes to malignancy.
4. Complex interaction between Inflammatory – immune cells, their mediators and epithelial cells should be understood. These questions need to be answered before linking inflammation and cancer.
5. Genomic alterations driven by acute or chronic inflammatory mediators need to be studied.
6. Acute or chronic inflammatory mediators and their interaction in progression of cancer.

## CONCLUSION

Inflammation and cancer is a complex concept to understand. We have to understand the thorough mechanism of inflammation, inflammatory cells and their mediators, and their interactions and above mystery linking the inflammation and cancer. Then probably, we could co-relate inflammation and cancer in a better way.

## 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	=	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
IL-17	=	Interleukin 17
CD4+ Th17	=	CD4+ T helper lymphocyte17
MDSC	=	Myeloid derived suppressor cells
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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