

## Inflammation-related cancer or cancer-related inflammation

**Shrihari T.G**

*Department of Oral Medicine and Oral Oncology, Krishna Devaraya College of Dental Sciences and Hospital, Karnata, India*

### ABSTRACT

Inflammation is the body's defensive action against various stimuli such as physical or chemical or infectious agents. Acute inflammation and their mediators help in tissue repair and healing. If the inflammation aggravates chronically, non-resolved, dysregulated immune system, results release of various inflammatory mediators such as free radicals (ROS and RNS), cytokines, chemokines, growth factors and proteolytic enzymes produced by innate and adaptive immune cells activate transcriptional factors (NF-KB, STAT3 and HIF-1 $\alpha$ ) results in cell proliferation, angiogenesis, immunosuppression, genetic instability, invasion and metastasis. Oncogenes related to cancer activate inflammatory mediators such as chemokines and cytokines, which alters the inflammatory tumor microenvironment, promotes tumor progression. This article highlights about the role of inflammation and oncogenes activate inflammatory mediators in tumor progression.

*Eur Res J 2018;4(1):1-5*

**Keywords:** Inflammation, cancer, myeloid-derived suppressor cells, inflammatory mediators, tumor associated macrophages, lymphocytes, tumor associated neutrophils, NF-KB, STAT3, HIF-1 $\alpha$ , oncogenes, cytokines, chemokines, growth factors, COX-2

### Introduction

Inflammation is the complex biological response to physical or chemical or infectious stimuli. Acute inflammatory response to tissue injury results in tissue repair by various mediators such as neutrophils, macrophages, and dendritic cells release mediators such as COX-2, ROS, TGF- $\beta$ . If the inflammation is aggravated chronically, no resolving, chronic smoldering inflammation results in dysregulated immunity mediated release of cytokines, chemokines, growth factors, proteolytic enzymes by innate and adaptive immune cells. External environmental factors

contribute very important roles in cancer. Single gene mutation is insufficient to transform in to neoplastic cell, instead it require four to five somatic cells genetic mutations [1, 2].

In extrinsic pathway of inflammation-related cancer, 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

*Address for correspondence:*

*Shrihari T.G, Assistant Professor, Krishna Devaraya College of Dental Sciences and Hospital, Department of Oral Medicine and Oral Oncology, Bangalore-562157, Karnata, India E-mail: drshrihariomr@gmail.com*

*Received: May 15, 2017; Accepted: July 18, 2017; Published Online: August 1, 2017*

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 to obesity, by increasing chronic inflammation promotes hepatocellular carcinoma [1-7].

#### *Inflammatory mediators involved in tumor progression*

Most of all tumors are associated with inflammatory microenvironment triggered by inflammatory response, which is protumorigenic. In intrinsic pathway of cancer-related inflammation, some oncogenes such as RAS, RET and MYC induce transcriptional program by activating signaling pathways results in remodeling of the tumor microenvironment through leucocytes and lymphocytes recruitment, expression of protumorigenic chemokines, cytokines (IL-6, IL-8, IL-1 $\beta$ , CCL2, CCL20) induce an angiogenic switch leading to tumor progression and immune escape by recruitment of Tregs or Th2 immunosuppressor cells [1, 8-10].

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 leukocytes 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 [11-13].

In initiative phase ROS, RNI and RNS free radicals produced by neutrophils, macrophages and TNF- $\alpha$  in tumor microenvironment cause DNA damage and genetic instability. In promotive phase growth factors (EGF, FGF, VEGF), Cytokines (TNF-

$\alpha$ , IL-1, IL-6, IL-8, IL-10, TGF- $\beta$ ), proteolytic enzymes (MMP-2 and 9, UPA) produced by tumor associated neutrophils, tumor associated macrophages, mast cells and T and B lymphocytes. IL-1 induced by chemicals and TNF- $\alpha$  activates NF- $\kappa$ B key transcriptional factor and also AP-1. IL-6, IL-10, IL-22, IL-11, HGF and EGF activates STAT3 transcriptional factor for cellular proliferation, cell survival, angiogenesis, immunosuppression, invasion and metastasis in patients with oral squamous cell carcinoma, prostate, hepatocellular, lung, colorectal, gastric, bladder, ovarian, and esophageal cancers [14-22].

Damage associated molecular patterns (DAMP) and pathogen associated molecular patterns (PAMP) activated in response to Hsp70, HMGB-1, S100 calcium binding protein, IL-1 $\alpha$ , LPS, microbes and their microbial products recognized by pattern recognition receptor (PRR) family belongs to Toll like receptor family activates cytokines induced transcriptional factors such as NF- $\kappa$ B, STAT3 favours tumor progression. Cytokines induced over expression of activation induced cytidine deaminase (AID) causes genomic instability in critical genes such as TP53, C-MYC and BCL-6 involved in cancers such as liver, gastric and lymphoma [5, 12, 23-25].

In hypoxic tumor microenvironment recruitment of tumor associated macrophages induce HIF-1  $\alpha$  acts as a transcriptional factor for IL-8, VEGF, COX-2 promotes angiogenesis and immunosuppression. MMP-2,9, UPA, prokineticin 2 (BV8) and TGF- $\beta$  produced by tumor associated neutrophils (TAN) involved in tumor invasion and metastasis including oncostatin M (OSM) and HGF, which induce tumor progression. 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). B cells producing IL-10 are called as Bregs induced by STAT3 with ERK or p38 and elevated expression of PD-1. CD4 T cells expressing CD25 and FOXP3 are called Tregs, mediated by TGF- $\beta$ , IL-10 and IL-4, produce IL-10, TGF- $\beta$  [26]. Alternatively activated Th2 cells activates TAM (M2) phenotypic macrophages, eosinophils through cytokines and B cells, which activates phagocytes, mast and NK cells,

produce IL-10, IL-4, IL-13 and TGF- $\beta$ , increased expression of arginase 1, programmed death ligand (PDL1) acts as immunosuppressive on dendritic cells, natural killer cells, T and B lymphocytes in patients with oral squamous cell carcinoma, lung, pancreatic, colorectal, breast, melanoma, esophageal, prostate, ovarian, renal cell cancer. Th1 cells activate macrophages through IFN- $\gamma$  secretion and cell to cell contact [6, 11, 27-46].

B cells induced tumor progression is by activation of myeloid and mast cells, and also production of IL-10 induced immunosuppression. Mast cells are produced by bone marrow involved in innate and adaptive immunity, matured in tissue, have protumoral activity by producing TNF- $\alpha$ , IL-10, IL-1, IL-6 cytokines. Ability to respond to an extrinsic signals depends on 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. Mast cells recruit eosinophils, T and B cell immune response activity and MDSC accumulation in tumor microenvironment. CD4 T and CD8 T cells mediated immunosuppression by expression of surface receptors PD-1 and CTLA-4 on its surface [47, 48].

IL-17 proinflammatory cytokine is a subtype of CD4 T cells produced by Th17 cells, expressed by tumor associated macrophages induced IL-23 procarcinogenic cytokine, mediated IL-6 and TGF- $\beta$ , promotes tumor progression by activating IL-1, TNF- $\alpha$ , IL-6 in patients with hepatocellular carcinoma, oral squamous cell carcinoma, prostate, colorectal, esophageal, gastric cancer [1, 8, 12, 24, 49].

Myeloid derived suppressor cells (MDSC) are heterogeneous population of immature myeloid cells that are precursors of dendritic cells, macrophages and/or granulocytes derived from bone marrow is of two types granulocytic or monocytic. Myeloid-derived suppressor cells has a potent regulatory immune response and have a major role in chronic inflammation and tumor development by activation of tumor-derived mediators or cytokines such as IL-1 $\beta$ , IL-4, IL-6, IL-10, COX-2 and TGF- $\beta$  induce expression of arginase-1, inducible nitric oxide synthase (iNOS) or ROS immunosuppressive factors.

Which, can initiate apoptosis in T cells, programmed cell death and immunosuppression of effector cells such as adaptive and innate immune cells.

Expansion of myeloid-derived suppressor cells by factors such as GM-CSF, G-CSF, M-CSF, stem cell factor and VEGF. Myeloid-derived suppressor cells activates STAT3 and matrix metallo-proteases (MMPs) there by promoting angiogenesis, invasion, and cell proliferation by further activation of STAT3 induces the secretion of bFGF and VEGF. Myeloid-derived suppressor cells activate MMPs, facilitate cancer cell invasion and intravasation by disruption of endothelial cadherins, degradation of extracellular matrix, adhesion proteins or basement membrane vessels in patients with head and neck cancer, prostate, bladder, esophageal, and oral squamous cell carcinoma.

MDSC also facilitate epithelial to mesenchymal transition in cancer cells by using factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and TGF- $\beta$  [12, 50-54].

In extrinsic pathway, external environmental factors play an important role such as tobacco, alcohol, dietary factors, viruses, chemical ingestion, induced inflammatory cells and their mediators such as cytokines, chemokines, growth factors, enzymes, released from innate and adaptive immune cells activate transcriptional factors (NF-KB, STAT-3), in majority of cancer, which is inflammation-related cancer. In intrinsic pathway of cancer-related inflammation the oncogenes-mediated activation of inflammatory mediators induced tumor progression in tumor microenvironment.

In tumor microenvironment, both intrinsic and extrinsic pathway is activated or whether intrinsic and extrinsic pathway activated individually need to be known for future diagnostic, therapeutic or prognostic purpose.

### *Conclusion and future prospective*

Chronic inflammatory cells and their mediators have a role in tumor initiation, promotion and progression of cancer. These mediators are ROS, RNS free radicals, chemokines, cytokines, growth factors and proteolytic enzymes produced by chronic inflammatory cells in tumor microenvironment such as innate and adaptive immune cells. Oncogenes-related cancer induced activation of inflammatory mediators, promote tumor progression. Both intrinsic and extrinsic pathways are activated simultaneously or individually in tumor microenvironment need to be

known. In future, identification of inflammatory mediators will be suitable for cancer biomarkers, therapeutic strategy and prognostic purpose.

## Abbreviations

HGF=hepatic growth factor, VEGF=vascular endothelial growth factor, MMP-9=matrix metalloproteinases 9, COX2=cyclo-oxygenase 2, INOS=inducible nitric oxide synthase, 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- $\beta$ , 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, NF-KB=nuclear factor KB, MCP-1=macrophage/Monocyte chemoattractant protein1, 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 $\alpha$ =hypoxia-inducible factor  $\alpha$ , T reg cell=T regulatory cell, Th1=T helper 1, Th2=T helper 2, TAM=tumor associated macrophages

### Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

## References

[1] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation and cancer. *Cell* 2010;140:883-99.

[2] Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest* 2015;125:3347-55.

[3] Maciel TT, Moura IC, Hermine O. The role of mast cells in cancers. *F1000Prime Rep* 2015;7:9.

[4] Shrihari TG. Dual role of inflammatory mediators in cancer. *Ecancermedicalscience* 2017;11:721.

[5] Korniluk A, Koper O, Kemona H, Dymicka-Piekarska V. From inflammation to cancer. *Ir J Med Sci* 2017;186;57-62.

[6] Okada F. Inflammation-related carcinogenesis: current findings epidemiological trends, causes and mechanisms. *Yonago Acta Medica* 2014;57:65-72.

[7] Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 2015;347:78-81.

[8] Allavena P, Germano G, Marchesi F, Mantovani A. Chemokines in cancer related inflammation. *Exp Cell Res* 2011;317:664-73.

[9] Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073-81.

[10] Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science* 2015;348:69-74.

[11] Chai EZ, Siveen KS, Shanmugam MK, Arfuso F, Sethi G. Analysis of the intricate relationship between chronic inflammation and cancer. *Biochem J* 2015;468:1-15.

[12] Katoh H, Watanabe M. Myeloid-derived suppressor cells and therapeutic strategies in cancer. *Mediators Inflamm* 2015;2015:159269.

[13] Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* 2014;41:49-61.

[14] Nagasaki T, Hara M, Nakanishi H, Takahashi H, Sato M, Takeyama H. Interleukin-6 released by colon cancer-associated fibroblasts is critical for tumour angiogenesis: anti-interleukin-6 receptor antibody suppressed angiogenesis and inhibited tumour-stroma interaction. *Br J Cancer* 2014;110:469-78.

[15] Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, et al. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell* 2014;26:638-52.

[16] Houghton AM. The paradox of tumor-associated neutrophils: fueling tumor growth with cytotoxic substances. *Cell Cycle* 2010;9:1732-7.

[17] Putoczki TL, Thiem S, Loving A, Busuttill RA, Wilson NJ, Ziegler PK, et al. Interleukin-11 is the dominant IL-6 family cytokine during gastrointestinal tumorigenesis and can be targeted therapeutically. *Cancer Cell* 2013;24:257-71.

[18] Necula LG, Chivu-Economescu M, Stanciulescu EL, Bleotu C, Dima SO, Alexiu I, et al. IL-6 and IL-11 as markers for tumor aggressiveness and prognosis in gastric adenocarcinoma patients without mutations in Gp130 subunits. *J Gastrointest Liver Dis* 2012;21:23-9.

[19] Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* 2009;15:103-13.

[20] Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. *Gastroenterology* 2010;138:2101-14.

[21] Karin M. Nuclear factor- $\kappa$ B in cancer development and progression. *Nature* 2006;441:431-6.

[22] Speiser DE, Utzschneider DT, Oberle SG, Munz C, Romero

- P, Zehn D. T cell differentiation in chronic infection and cancer: functional adaptation or exhaustion? *Nat Rev Immunol* 2014;14:768-74.
- [23] Candido J. Cancer-related inflammation. *J Clin Immunol* 2013;33:579-84.
- [24] Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell* 2010;141:39-51.
- [25] Woo SR, Corrales L, Gajewski TF. Innate immune recognition of cancer. *Annu Rev Immunol* 2015;33:445-74.
- [26] Yang L, Pang Y, Moses HL. TGF- $\beta$  and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends Immunol* 2010;31:220-7.
- [27] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;454:436-44.
- [28] Chen L, Gibbons DL, Goswami S, Cortez MA, Ahn YH, Byers LA, et al. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. *Nat Commun* 2014;5:5241.
- [29] Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. *Nat Rev Cancer* 2012;12:307-13.
- [30] Spranger S, Spaepen RM, Zha Y, Williams J, Meng Y, Ha TT, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. *Sci Transl Med* 2013;5:200ra116.
- [31] Kitamura T, Qian BZ, Pollard JW. Immune cell promotion of metastasis. *Nat Rev Immunol* 2015;15:73-86.
- [32] Castello G, Scala S, Palmieri G, Curley SA, Izzo F. HCV-related hepatocellular carcinoma: from chronic inflammation to cancer. *Clin Immunol* 2010;134:237-50.
- [33] Kim PS, Ahmed R. Features of responding T cells in cancer and chronic infection. *Curr Opin Immunol* 2010;22:223-30.
- [34] Tan W, Zhang W, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM, et al. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. *Nature* 2011;470:548-53.
- [35] Bos PD, Plitas G, Rudra D, Lee SY, Rudensky AY. Transient regulatory T cell ablation deters oncogene-driven breast cancer and enhances radiotherapy. *J Exp Med* 2013;210:2435-66.
- [36] Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, et al. IL-17-producing  $\gamma\Delta$  T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* 2015;522:345-8.
- [37] Deng W, Gowen BG, Zhang L, Wang L, Lau S, Iannello A, et al. Antitumor immunity. A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection. *Science* 2015;348:136-9.
- [38] Waldhauer I, Steinle A. NK cells and cancer immunosurveillance. *Oncogene* 2008;27:5932-43.
- [39] Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity* 2014;41:14-20.
- [40] Gocheva V, Wang HW, Gadea BB, Shree T, Hunter KE, Garfall AL, et al. IL-4 induces cathepsin protease activity in tumor-associated macrophages to promote cancer growth and invasion. *Genes Dev* 2010;24:241-55.
- [41] Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell* 2010;141:39-51.
- [42] Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A, Jaillon S. Tumor associated macrophages and neutrophils in cancer. *Immunobiology* 2013;218:1402-10.
- [43] Makkouk A, Weiner GJ. Cancer immunotherapy and breaking immune tolerance: new approaches to an old challenge. *Cancer Res* 2015;75:5-10.
- [44] Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, Mauger S, Bindea G, et al. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, th2, treg, th17) in patients with colorectal cancer. *Cancer Res* 2011;71:1263-71.
- [45] Chaudhry A, Rudensky AY. Control of inflammation by integration of environmental cues by regulatory T cells. *J Clin Invest* 2013;123:939-44.
- [46] Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. *Nat Immunol* 2015;16:343-53.
- [47] Ohnishi S, Ma N, Thanam R, Pinlaor S, Hammam O, Murata M, Kawanishi S. DNA damage in inflammation-related carcinogenesis and cancer stem cells. *Oxid Med Cell Longev* 2013;2013:387014.
- [48] Diakos C I, Charles CA, Mcmillan DC, Clarke SJ. Cancer related inflammation and treatment effectiveness. *Lancet Oncol* 2014;15:493-503.
- [49] Wang K, Kim MK, Di Caro G, Wong J, Shalapour S, Wan J, et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* 2014;41:1052-63.
- [50] Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. *Semin Cancer Biol* 2012;22:33-40.
- [51] Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res* 2014;2014:149185.
- [52] Marvel D, Gabrilovich DI. Myeloid-derived suppressor cells in tumor microenvironment: expect the unexpected. *J Clin Invest* 2015;125:3356-64.
- [53] Condamine T, Gabrilovich DI. Can the suppressive activity of myeloid-derived suppressor cells be "chop"ped? *Immunity* 2014;41:341-2.
- [54] Shrihari TG. Inflammation related cancer-Highlights. *J Carcinog Mutagen* 2016;7:269.