Review article

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A SYSTEMATIC REVIEW AT THE CROSSROADS OF POLYMORPHISMS IN PRO INFLAMMATORY CYTOKINE GENES AND GASTRIC CANCER RISK

Zareen Sultana[1], Srikanta Guria[2],Madhusudan Das[1]*

[1]Department of Zoology, University of Calcutta, 35 Ballygunge Circular Road, Kolkata-700019
[2]Post Graduate Department of Zoology,Barasat Govt. College, Barasat, Kolkata-700124

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ABSTRACT:

Acute inflammation is a response to an alteration induced by a pathogen or a physical or chemical insult, which functions to eliminate the source of the damage and refurbish homeostasis. However, chronic inflammation triggers cellular events that can promote malignant transformation. Several inflammatory mediators, such as TNF-α, IL-6, TGF-β, IL-1β and IL-10, have been shown to participate in both the initiation and progression of cancer. In this review, we investigate the role of these cytokines in carcinogenesis, such as their capacity to generate reactive oxygen and nitrogen species, their potential mutagenic effect, angiogenesis and metastasis. Finally, we will provide an in-depth analysis of the participation of these cytokines in gastric cancer (GC) attributable to chronic inflammatory disease. Polymorphisms in interleukin-1 (IL1) and tumour necrosis factor α (TNFA) gene clusters are associated with an increased risk of gastric cancer. However, their role in gastric precancerous lesions remains poorly understood. Our objective was to perform a review addressing the association between IL1B-and TNFA gene polymorphisms and gastric precancerous lesions. In this article we have provided a rationale for the use of cytokine and chemokine blockade and further investigation of non-steroidal anti-inflammatory drugs, in the chemoprevention and treatment of malignant diseases.

KEY WORDS: Inflammation, Cytokine, Tumour, Cancer

* Corresponding author

Zareen Sultana**,**
Email:madhuzoo@yahoo.com
Tel: +91 – 9831281756

INTRODUCTION:

Gastric cancer (GC) is the second most common cause of death from cancer, with an estimated 700,000 deaths each year worldwide (Parkin *et al*., 2005). Gastric adenocarcinoma arises from the glandular epithelium (mucosa) of the stomach (Marimuthu*et al*., 2011). Chronic gastritis is a histopathologic entity characterized by chronic inflammation of the stomach mucosa.

It has been reported that approximately 15-20% of all malignancies are exacerbated by inflammation (Ono *et al*., 2008). Inflammation in the form of chronic superficial gastritis is one of the early phases in the development of gastric cancer (Kamangar*et al*., 2006). More than 90 % of gastric cancers have been reported to be adenocarcinomas, leiomyosarcomas, gastro intestinal stromal tumours and carcinoid tumours (Hamilton *et al.,* 2006*).* Various factors contribute to this inflammation-induced gastric cancer. Infection with *Helicobacter pylori* induces chronic inflammation of the stomach (Wroblewski*et al*., 2010). Even a single episode of heavy drinking can induce mucosal inflammation and hemorrhagic lesions. Other factors include diet comprising smoked food, salted fish and meat, pickled vegetables, smoking etc (Nagini, 2012). Although a number of factors probably influence an individual's predisposition to gastric cancer and course of progression to gastric cancer, it is clear that chronic inflammation is a feature that links this cancer to many other types of malignancy (Lauren *et al*., 1965). Investigators also recognized that areas of gastric adenocarcinoma were frequently found in areas of chronic inflammation, as well as in settings of atrophic gastritis. The common features essential to inflammation-associated carcinogenesis include pro inflammatory cytokines such as IL-1β, TNF-α, etc. (Tsujimoto*et al*., 2010). Chronic inflammation results in the up regulation of diverse cytokines and chemokines and the recruitment of numerous hematopoietic populations to inflamed tissues (Fox *et al*., 2007). These are involved in the pathogenesis of gastric ulcer. Polymorphisms in human IL-1β and TNF-α genes have been reported to influence cytokine expression. A biallelic polymorphism at positions -31 and -511 in the promoter of the IL-1β gene has been associated with the development of gastric cancer (El-Omar *et al*., 2003; Furuta*et al*., 2002). An increased risk for gastric cancer associated with pro inflammatory IL-1β polymorphisms has now been confirmed in many populations throughout the world. Mutation in another cytokine gene TNF-α has been associated with chronic inflammation and gastric cancer (Perez-Perez *et al*., 2005). Polymorphisms in IL-1β (Chr. 2q14) gene have been associated with an increased risk of hypochlorhydia, gastritis and non-cardia gastric cancer development (El-Omar *et al*., 2000; Camargo *et al*., 2007). Polymorphisms in the promoter region of TNF-α (Chr. 6p21.3) has been found to be associated with an increased production of this cytokine resulting in a high-risk genotype with a 27-fold or greater risk of developing gastric cancer (El-Omar *et al.,* 2003; Wroblewski*et al*., 2010).

The response of the body to a cancer is not a unique mechanism but has many parallels with inflammation and wound healing. Moreover cancer susceptibility and severity may be associated with functional polymorphisms of inflammatory cytokine genes, and deletion or inhibition of inflammatory cytokine inhibits development of experimental cancer. If genetic damage is the "match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames". It was in 1863 that Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the "lympho reticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Over the past ten years our understanding of the inflammatory microenvironment of malignant tissues has supported Virchow's hypothesis and the links between cancer and inflammation are starting to have implications

for prevention and treatment (Balkwill*et al*., 2001). Moreover, increased risk of malignancy is associated with the chronic inflammation caused by chemical and physical agents, and autoimmune and inflammatory reactions of uncertain etiology (Ekbom A 1990).

Inflammatory cells in tumour microenvironment

The inflammatory microenvironment of tumours is characterised by the presence of host leucocytes both in the supporting stroma and in tumour areas (Negus R 1997). Tumour infiltrating lymphocytes may contribute to cancer growth and spread and to the immunosuppression associated with malignant disease.

Tumour-associated macrophages (TAM) are a major component of the infiltrate of most, if not all, tumours (Mantovani A 1992). When appropriately activated, TAM can kill tumour cells or elicit tissue destructive reactions centred on the vascular endothelium. However, TAM also produces growth and angiogenic factors as well as protease enzymes which degrade the extracellular matrix. Hence, TAM can stimulate tumour-cell proliferation, promote angiogenesis and favour invasion and metastasis (Mantovani A 1992) This dual potential of TAM is expressed in the "macrophage balance" hypothesis (Mantovani A 1992). Tumour-associated dendritic cells (TADC) usually have an immature phenotype with defective ability to stimulate T cells (Allavena P 2000). In breast cancer, immature TADC are interspersed in the tumour mass, whereas mature dendritic cells are confined to the peritumoural area (Allavena P 2000). There is now evidence that inflammatory cytokines and chemokines, which can be produced by the tumour cells and/or tumour-associated leucocytes and platelets, may contribute directly to malignant progression.

Pro inflammatory Cytokine

Tumour necrosis factor (TNF)

TNF is a major mediator of inflammation, with actions directed towards both tissue destruction and recovery. While inducing death of diseased cells at the site of inflammation, TNF stimulates fibroblast growth. It can destroy blood vessels but also induce angiogenic factors (Kollias G 1999) Likewise, in malignant disease, high-dose local TNF selectively destroys tumour blood vessels, (Lejeune FJ 1998) but when chronically produced this cytokine may act as an endogenous tumour promoter, contributing to the tissue remodelling and stromal development necessary for tumour growth and spread. TNF can be detected in malignant and/or stromal cells in human ovarian, breast, prostate, bladder and colorectal cancer, lymphomas and leukaemias, often in association with ILs 1 and 6 and macrophage colony stimulating factor. (Naylor MS 1993) In epithelial ovarian cancer, TNF mRNA is found in epithelial tumour islands, where there is a positive correlation with tumour grade (Naylor MS 1993). TNF is also implicated in the induction of a chemokine called monocyte chemotactic protein-1, which can regulate the macrophage and lymphocyte infiltrate, and of matrix metalloprotease-9, in the ovarian tumour microenvironment. In breast cancer, infiltrating macrophages are a major source of TNF, which may regulate thymidine phosphorylase, a key angiogenic enzyme in the tumour epithelium (Leek RD 1998).

Interleukins 1 and 6

In mouse models of metastasis, treatment with an IL-1 receptor antagonist (which inhibits the action of IL-1) significantly decreased tumour development suggesting that local production of this cytokine aids development of metastases. Moreover, mice deficient in IL-1ß

were resistant to the development of experimental metastases (Vidal-Vanaclocha F 2000).

Angiogenesis

Angiogenesis is important in the evolution of both cancer and inflammatory diseases that may predispose to cancer (O'Byrne KJ 2000). Once a tumour is established it may attain further characteristics, via mutations or hypoxia, which stimulate new blood vessels. The inflammatory cell infiltrate, particularly TAM, may contribute to tumour angiogenesis, and there are many reports of associations between macrophage infiltration, vascularity and prognosis (Leek RD 1999). Moreover, TNF, IL-1 and IL- 6 can stimulate production of angiogenic factors such as VEGF. Cytokines and chemokines affect various stages in the process of metastasis. TNF and CC chemokines can induce production of proteases important for invasion in both tumour cells and macrophages. Indeed, monocytes infiltrating the tumour tissue may provide cancer cells with a ready-made path for invasion (the "countercurrent invasion theory") (Opdenakker G 1992).

Gastric inflammation

Persistent association of microaerophilic, gram-negative enteric bacteria results in chronic gastric inflammation which in turn leads to gastric cancer. Accumulating evidences suggest that *H. pylori*-induced inflammation is initiated both by host and bacterial factors. In addition, environmental factors also play a potent role in disease progression. However, the actual pathogenesis behind chronic inflammation is not well understood. *H. pylori* enters inside the stomach via the fecal-oral route mainly through contaminated food and water (Klein *et al*., 1991, Hopkins *et al*., 1993). The most probable mode of transmission is via direct contact with the infected patient within the family or a common source of contaminated water or food of a locality (Hopkins *et al*., 1993, Nurgalieva*et al*., 2002). Gastric inflammation is accompanied by induction of oxidative stress by reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS) and subsequent secretion of proinflammatory cytokines like interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α (Yamaoka *et al*., 1996). Gastric epithelial cells also secrete IL-8 (Jung *et al*., 1997) which attracts the polymorphonuclear (PMN) cells. Moreover, *H. pylori* infection stimulates iNOS and other enzymes including myeloperoxidases, NADPH oxidases, eosinophil peroxidases. These enzymes trigger ROS and reactive nitrogen species (RNS) production, which induce DNA damage (Wang *et al*., 2005).

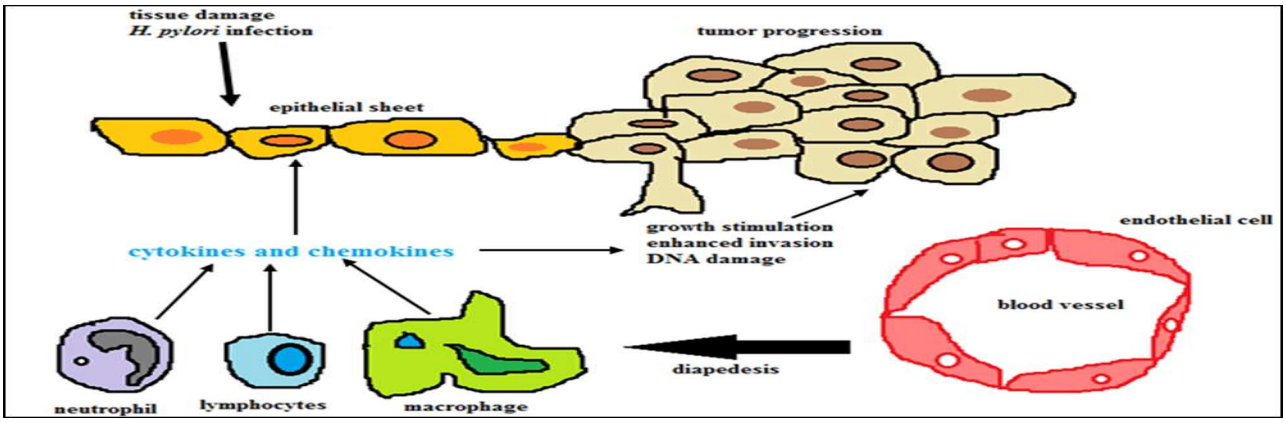

Figure 1: Inflammatory responses stimulate excess cytokine and chemokine production that leads to the progression of malignancy

Inflammation and cancer risk: An overview

Accumulating clinical data for solid tumours show a correlation between high-density leukocytic infiltration into tumours and poor outcome of patients with malignancies of different origins, such as breast (Pollard JW,2008, Shabo I 2008), bladder (Hanada T 2000), rectum (Shabo I 2009) and endometrium (Salvesen HB 1999) . In addition, deficient monocyte recruitment at tumour sites in mice lacking CSF-1 expression was shown to attenuate late-stage progression and metastasis formation, suggesting that monocytes contribute to tumour progression (Lin EY 2001). Nevertheless, the presence of inflammatory cells can be an indicator of favourable prognosis in some tumour types, as for example, the presence of macrophages in colorectal cancer (Forssell J 2007, Zhou Q 2010), gastric (Ohno S 2003) carcinomas . These latter data suggest, that, at least in some situations, inflammatory cells may be able to eliminate tumour cells just as they can destroy normal cells. Leukocyte infiltrate includes a variable representation of leukocytes, including macrophages, neutrophils, mast cells and T and B lymphocytes (Lin EY 2004). Therefore, inflammatory cells and immune modulatory mediators present in the tumour microenvironment polarize host immune response towards specific phenotypes impacting tumour progression. Macrophages are often the most abundant immune cell population in the tumour microenvironment. Recruitment of monocyte precursors circulating in the blood leads to their differentiation into tumour-associated macrophages. It has been reported, that, once recruited into tumours, macrophages can assume two different phenotypes: M1 or M2, based on environmental stimuli and each expressing specialized functional properties (Allavena P 2008). The M1 phenotype is associated with inflammation and microbial killing activity, whereas the M2 phenotype is associated with activities which are predominant and key events in cancer, including inhibition of T helper 1 adaptive immunity by immunosuppressive mediators [TGFβ, IL-10 or prostaglandin E2 (PGE2)], production of growth and survival factors (EGF, IL-6 and CXCL8), secretion of angiogenic factors (VEGF, TGFα or PGE2), production of matrix metalloproteases (MMPs) which degrade extracellular matrix, and chemokines which are able to recruit more inflammatory cells (CCL17, CCL18 or CCL22), (Allavena P 2008).

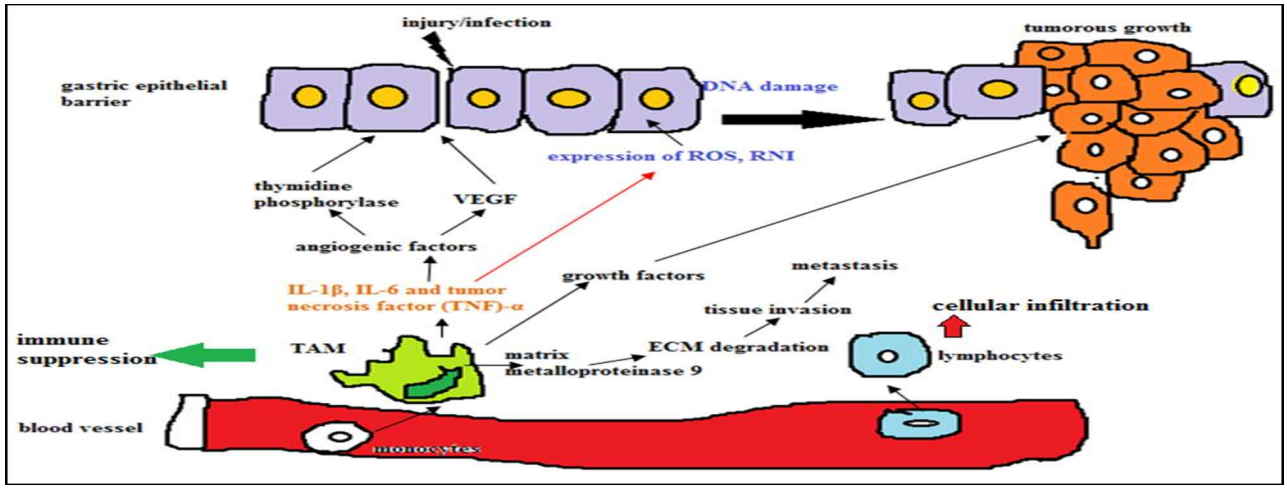

Figure 2: central role of tumour associated macrophages **(TAM)** in gastric cancer risk

National status

The incidence of gastric cancer in India is overall less compared to worldwide incidence. The regional variation in incidence and presentation can be ascertained by the fact that gastric cancer in South Indian males has been reported to be more common and occurring a decade before their North Indian counterparts (Malhotra*et al*., 1967). In a case-control study from Trivandrum, a high consumption of rice and chilli, and consumption of high-temperature food were found to be independent risk factors for gastric cancer in multivariate analysis (Mathew *et al*., 2000). In a study from Hyderabad comparing 94 gastric cancer patients and 100 normal age- and sex-matched controls, smoking and alcohol were significantly associated with gastric cancer (Ponnala*et al*., 2010). The incidence of gastric cancer in Mizoram has been reported to be the highest in India (Phukan*et al*., 2005). In another report from Chennai, alcohol consumption and use of pickled food were found independent risk factors for gastric cancer (Sumathi*et al*., 2009).

International status

There is a worldwide variation in the incidence of gastric cancer. A high incidence of gastric cancer has been reported from Southeast Asia, most commonly from Japan, China, and South Korea, and this has been attributed to the consumption of preserved food containing carcinogenic nitrates (Alberts*et al*., 2003). Low-risk population is seen among whites in North America, India, Philippines, most countries in Africa, some Western European countries and Australia (Mohandas *et al*., 2000). In addition, gastric cancer has been found in men more than in women. However, the factors leading to this variability among countries, races and sex may be the genetic polymorphisms (Crew *et al*., 2006). At the international level, most of the research work carried out in this field is based on the polymorphism/mutation profile associated with the disease. The association study in most of the cases has been found to vary with populations across the world. For example, in 2007, a meta-analysis study conducted amongst the Caucasians detected a moderate but statistically significant association between IL1B-511T and gastric cancer risk in Caucasians, but not in Asians (Camargo *et al*., 2007). This shows that even though this particular genotype has a close association with gastric cancer in the Caucasians, it has no significance amongst the Asians. Therefore, there is a need to study the genetic etiology of this disease in our population to find out whether the gene polymorphisms (associated with gastric cancer) that have been detected in different parts of the world and have been published in various literature also holds true for our population. In India also, most of the work that has been done is based on epidemiology and survey studies. Very few studies have been reported on the genetic causes of gastric cancer in the Indian population, especially in West Bengal. Hence, it is important to conduct the genetic analysis of our population to find out genetic markers for the predisposition of gastric cancer. In our lab we are trying to screen polymorphism (s)/ mutation (s) of the genes IL-1β (Interleukin 1 beta) and TNF-α (Tumour necrosis factor alpha) and their association with development of gastric cancer in the population of West Bengal.

Polymorphisms in Pro inflammatory Cytokine Genes and Gastric Cancer Risk

A possible candidate gene IL-1β for its polymorphisms has been proposed as a key factor in determining the pattern of gastritis and risk of malignant transformation (El Omar *et al*., 2001) in several populations i.e. Chinese (Zeng*et al*., 2003); Japanese (Kai *et*

al., 2005); Irish (Murphy *et al*., 2009); United Kingdom (Macarthur *et al*., 2004); Italy (Perri*et al*., 2010). A biallelic polymorphism at positions -31 and -511 in the promoter of the IL-1β gene has been associated with the development of gastric cancer and its precursors (El-Omar *et al*., 2003; Furuta*et al*., 2002). An increased risk for gastric cancer associated with pro inflammatory IL-1β polymorphisms has now been confirmed in many populations throughout the world (Perez-Perez *et al*., 2005). Three polymorphisms in the promoter region of this gene have been studied more than the other polymorphisms. TNF-α -308G>A is associated with an increased production of TNF-α (Jang *et al*., 2001), which is a central mediator of the immune response. The function and significance of TNF-α -238G>A is less clear, but because a putative repressor site is located in a 25-base stretch that includes position -238, this polymorphism may be functional (Jang *et al*., 2001). TNF-α -857C>T is also associated with higher transcriptional activity of TNF-α (Hohjoh and Tokunaga, 2001). Consolidated panels of polymorphisms associated with gastric cancer risk were identified in Asians and Caucasians. The results caution against the assumption that genetic risk factors are consistent between races.

DISCUSSION:

The tumour microenvironment formed by stromal cells, infiltrating immune cells, and tumour cells contain factors that can promote carcinogenesis. Ample evidence supports the involvement of cytokines in events leading to the initiation, promotion, invasion and metastasis of cancer. In a chronic inflammatory process, cytokines such as TNF-α and IL-6 induce the generation of free radicals that can damage DNA, potentially causing mutations that lead to tumour initiation. Tumour growth is also favoured by proinflammatory cytokines that stimulate cell proliferation and reduce apoptosis, while anti-inflammatory cytokines, such as IL-10 and TGF-β, contribute to tumour immune evasion. The invasive properties of tumours are related to the activation of the epithelial-mesenchymal transition program triggered by TGF-β and enhanced by proinflammatory cytokines, such as TNF-α and IL-6. Proinflammatory cytokines also play an important role in angiogenesis and metastasis. In the latter, chemokines such as IL-8 have an important role in cell migration to other tissues. Although we observed that many cytokines contribute to carcinogenesis, their pro- or antitumoural roles depend on the balance of these different inflammatory mediators and the stage of tumour development. For this reason, studying the role of these mediators in different tumours or stages of development is essential for designing new personalized treatments using these potential therapeutic targets. In this line, the potential role of cytokines has been reported, as a diagnostic marker for cancer. The determination of the serum levels of cytokines, such as IL-6 or IL- 10, might be associated with a tumourigenic process or poor prognosis. However, further prospective studies are needed to determine trusted cut-off values of circulating cytokines to establish a direct relationship with cancer. In the field of therapy, several clinical trials have been implemented in order to evaluate the inhibitors of cytokine receptors or neutralizing antibodies that prevent the sustained exposure to these inflammatory mediators that promote tumour progression. While progress has been made in the understanding of the mechanisms of these cytokines in the tumorigenic process, establishing a relationship between cytokine expression and disease progression, survival and response to therapy remains a major challenge.

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