Review Article

Role of Inflammatory Markers in Tumorogenesis

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ABSTRACT

Inflammation is considered to be the initiating event of tumorogenesis in the case of chronic immune related disorders. Chronic inflammation that results due to exogenous chemicals or exposure to harmful radiation also induces drastic DNA damage. This is often witnessed by change in expression of proteins involved in both immune system and inflammation. The inflammatory markers can thus help us in early diagnosis of cancer so that the severity of the disease can be controlled by radiotherapy or chemotherapeutic treatment. Hence, this review widely focused on the correlation that exists between inflammation and cancer. The inflammatory pathways, markers of chronic inflammation and observable changes in specific transcription factors associated with different types of cancer were also discussed.

Keywords: Inflammation, Tumorogenesis, Cytokines, Chemokine

INTRODUCTION

The relationship between inflammation and cancer is not new which was first indicated by Rudolf Virchow in 19th century who observes the presence of leukocytes. The recent evidence has obtained that inflammation plays a critical role in tumorigenesis and some of the underlying molecular mechanisms have been elucidated.[1] Inflammation and cancer are connected by two pathways: extrinsic pathways from conditions that cause non-resolving smouldering inflammatory responses and intrinsic pathways driven by oncogenes or tumor suppressor genes that activate the expression of inflammation-related programmes. [2, 3] Cancer is the second prominent cause of deaths all over the world. Worldwide 7.6 million deaths are caused by cancer which represents 13 % of all global deaths. [4] Although many evaluations have been made between inflammation and cancer, the liaison concerning different inflammatory factor associated with different cancer types has be expounded in this review.

Inflammation

Inflammation is physiologic improvements in response to tissue destruction bring about microbial pathogen infection, chemical irritation, and/or wounding. [5] Towards the starting time of inflammation, neutrophils are the main cells to transfer to the inflammatory area under the directive of molecules created by rapidly reacting macrophages and mast cells prestationed in tissues. [6, 7] As the inflammation advances, different sorts of leukocytes, lymphocytes, and other inflammatory cells are initiated and fascinated to the inflamed site by a signalling network involving incredible number of growth factors, cytokines, and chemokines. [6, 7]

Acute inflammation is a transient reaction essentially portrayed by a leukocytes infiltrate of the damaged tissue, eradicating of the stimulus and tissue repair. It generally results in healing and the cellular and molecular events tangled have been largely identified in the most recent years as affirmed by the development of numerous drugs that objective them precisely. Chronic inflammation, then again, is a drawn out and dysregulated reaction at the same time portrayed by active inflammation, tissue destruction and attempts at tissue repair. It can be the advancement of an acute inflammatory reaction which fails to eradicate the noxious stimulus but is characterized by peculiar types that makes the two processes entirely discrete. [8]

Cancer and its Types

Cancer describes malignant neoplasms characterized by metastatic development. It may happen in practically every organ and tissue concerning to a variety of etiologic factors, example, genomic instability and environmental stress.[5] Cancer results from the outgrowth of a clonal population of cells from tissue. The headway of growth, alluded to as carcinogenesis, can be shown and depicted in different ways. One approach to illustrate this procedure is to delineate the basic highlights of both disease cells and tumors: the "hallmarks" of malignancy.[9] Cancer development requires the securing of six major properties: self-sufficient proliferation, insensitivity to anti-proliferative signals, evasion of apoptosis, unlimited replicative potential, the maintenance of vascularization, and, for malignancy, tissue invasion and metastasis.[9]

Cancer can likewise be considered as to a stage savvy advancement practically assembled into three stages: initiation, promotion, and progression.[10] Initiation is described by genomic changes inside the "cancer cell," for

example, point mutations, gene deletion and amplification, and chromosomal relocations leading to irreversible cell changes. Tumor enlargement is stimulated by the survival and clonal expansion of these "initiated" cells. Progression includes a generous development in tumor dimension and either growth-related or mutually exclusive metastasis. Vital to the development of cancer is the gathering of genetic lesions in cells. Such occasions are perceptibly required for initiation yet may likewise be associated with the promotion or progression of tumor development.[10]

Inflammatory diseases (e.g., inflammatory bowel disease) could increase the risk of developing different types of cancer including bladder, cervical, gastric, intestinal, esophageal, ovarian, prostate and thyroid tumors.[2] The most commonly diagnosed cancer was lung cancer (1.8 million, 13 % of the total), breast cancer (1.7 million, 11.9%) and colorectal cancer (1.4 million, 9.7 %). The widespread causes of cancer death were lung cancer (1.6 million, 19.4% of total) liver cancer (0.8 million, 9.1%) and stomach cancer (0.7 million, 8.8%). It has been estimated that there would be significantly increase to 19.3 million new cancer cases per year by 2025.[11-13]

Inflammation and Cancer

- Chronic inflammation increases malignancy risk.
- Subclinical, often untraceable inflammation may be as important in increasing cancer risk (for instance, obesity-induced inflammation).
- Various types of immune and inflammatory cells are frequently present within tumors.
- Immune cells affect malignant cells through production of cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species.
- Inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression.
- In developing tumors antitumorigenic and protumorigenic immune and inflammatory mechanisms coexist, but if the tumor is not rejected, the protumorigenic effect dominates.
- Signalling pathways that facilitate the protumorigenic effects of inflammation are often subject to a feed-forward loop (for example, activation of NF-kB in immune cells induces production of cytokines that activate NF-kB in cancer cells to induce chemokines that attract more inflammatory cells into the tumor).
- Certain immune and inflammatory constituents may be expendable during one stage of tumorigenesis but absolutely critical in another stage.[1]

Inflammation that promote cancer

In spite of the interpretations that an acute inflammatory response might exert a tumor inhibition or an antitumor effect, there are no doubts that the chronic inflammation can rather stimulate a tumor development acting at all phases of the procedure from initiation to progression.[2] Numerous types of cancer have been correlated to chronic infection or to chronic inflammatory conditions not related with pathogens and it has been projected that chronic infection and inflammation contribute to about 25% of all cancer cases worldwide.[14] To comprehend the connection between chronic inflammation and cancer it can be useful to start considering the foremost features of cancer cells and how they can be correlated to the inflammatory process.[15] As previously mentioned, chronic inflammation is simultaneously characterized by active inflammation, tissue destruction and attempts at tissue repair. The chronic inflammatory state can foster the accumulation of genomic lesions in multiple ways.[16]

The relationship between inflammation and cancer is clearly demonstrated by several experimental evidence showing that the development of experimental cancers only occurs or is favoured in wounded sites. In reality, tumor promotion requires the survival of initiated cells, as well as their expansion and many inflammatory mediators (i.e., cytokines, chemokines, and eicanosoids) can advance proliferation of initiated cells and to trigger signal transduction pathways that are implicated in carcinogenesis.[17] Numerous particles and pathways, for example, the Wnt/β-catenin pathway and the COX-1 and -2 enzymes, have been exposed to play a part in both inflammation and tumorigenesis. Another particle lately involved in the association between inflammation and cancer is NF-κB. Its stimulation is essential in mediating epithelial cell survival in protection from noxious stimuli in intestinal epithelium during an inflammatory response and is similarly essential in survival and resistance to apoptosis of initiated cells as well as in the promotion of several cancer-related pathways.[18,19]

It is important that NF-κB plays a vital role in the production of several inflammatory mediators.[19] One of these key chemical mediators implicated in inflammation-associated cancers is tumour necrosis factor alpha (TNF-α), which is involved in the immune response and in inflammation. This cytokine can be produced by different cell types and its receptor is omnipresent. TNF-α assumes a focal part in initiating the inflammatory reactions and is essential in its evolution. Conversely, when left unregulated it can cause chronic inflammation and substantial evidence has confirmed that TNF-α is involved in promotion and progression of experimental and human cancers mainly through its ability to activate NF-κB and other transcription factors convoluted in tumorigenesis.[20] Consistent with its name, high doses of loco-regional TNF-α can cause haemorrhagic necrosis by means of selective destruction of tumour blood vessels. Nonetheless, when formed in the tumour microenvironment, TNF-α can act

as an endogenous tumor promoter and available data suggest that its effects on both initiated cells and inflammatory cells in the surrounding stroma are important in promoting the early stages of cancer.[17,18]

Finally, it has to be kept in mind that in some types of viral infection, virally encoded proteins can directly contribute to cellular transformation, as is the case for the E6 and E7 oncoproteins of human papillomaviruses (HPV). Several cell types take part into the inflammatory response but macrophages are the major players in chronic inflammation being involved in tissue remodelling and repair. Several similarities can be identified between the process of wound repair and tumor development and tumor has been compared to a wound that does not heal.[21] Tumor-associated macrophages (TAMs) are derived from peripheral blood monocytes recruited into the tumor. Upon activation by cancer cells, the TAMs can release the same set of chemical mediators involved in wound repair including growth factors, proteolytic enzymes and cytokines which can affect several aspects of the tumorigenetic process such as: i) invasion and metastasis: macrophages secrete a variety of proteases, such as matrix metalloproteinases (MMPs), urokinase-type plasminogen activator and cathepsin B, able to breakdown the basement membrane and facilitate escape of proliferating tumor cells into the surrounding stromal tissue, thus predisposed to invade surrounding tissue and metastasize; ii) angiogenesis: macrophages cooperate with tumor cells to induce a vascular supply by producing angiogenic factors.

This statement has allowed the development of a "biphasic control" model of angiogenesis during tumorigenesis. According with this model, tumor cells would not initially produce by themselves angiogenic growth factors, as they learn to do in the later phases, but would exploit the ability of inflammatory cells (mainly macrophages but also mast cells) to release angiogenic factors; iii) immunosuppression: macrophages secrete factors that suppress the anti-tumor functions of innate immune system. With all these activities, TAMs play an important role in tumor development and the presence of extensive TAM infiltration has been shown to correlate with cancer metastasis and poor prognosis in a variety of human cancers.[20, 22]

It is noteworthy that most of macrophages activities are triggered by TLRs activation thus complicating the effects that can be obtained using TLR agonists, as previously mentioned. More recently, TAMs have been also implicated in the epidermal-mesenchymal transition (EMT) of cancer cells. EMT is a process that allows epithelial cells to separate from their neighbours and migrate to distal regions. It plays an important role during embryonic development but also occurs during the process of wound repair when it is induced by macrophage-produced stimuli. TAMs are likely also important in the EMT of epithelial cancer cells during cancer progression thus favouring invasion and metastasis of carcinoma cells.[19]

Cancer related inflammation

The connection between inflammation and cancer can be viewed as consisting of two pathways: an extrinsic pathway, inflammatory conditions would just help to facilitate tumor development. Chronic inflammation acts as a trigger to increase cancer risk or progression. Chronic inflammatory conditions associated with cancer development include chronic infections (e.g., *Helicobacter pylori* for gastric cancer and mucosal lymphoma; papilloma virus and hepatitis viruses for cervical and liver carcinoma, respectively), autoimmune diseases (e.g., inflammatory bowel disease for colon cancer) and inflammatory conditions of uncertain origin (e.g. prostatitis for prostate cancer) ; and an intrinsic pathway, internal genetic events which cause neoplasia, at the same time, would trigger the expression of inflammation-related programs and then guide the construction of an inflammatory microenvironment inside tumor tissue. RET (rearranged during transfection) oncogene in papillary carcinoma of the thyroid is a typical example for this intrinsic pathway.[23] It should be noticed that although those oncogenes might be representative of different pro-inflammatory molecular classes and actions, they will share the capacity to orchestrate all cancer related inflammation circuits.[24]

The two pathways converge, resulting in the activation of transcription factors, mainly nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3) and hypoxia-inducible factor 1α (HIF1α), in tumour cells. These transcription factors coordinate the production of inflammatory mediators, including cytokines and chemokines, as well as the production of cyclooxygenase 2 (COX2) (which, in turn, results in the production of prostaglandins). These factors recruit and activate various leukocytes, most notably cells of the myelomonocytic lineage. The cytokines initiate the comparative key transcription factors in inflammatory cells, stromal cells and tumour cells, producing more inflammatory mediators has been created and a malignancy-related inflammatory microenvironment being delivered. Smouldering malignancy-related inflammation has numerous tumour-promoting impacts.[2] (Fig. 1)

Inflammation and Various types of Cancer

Inflammation and lung cancer

Lung carcinogenesis is a multifaceted process requiring the acquisition of genetic mutations that confer the malignant phenotype as well as epigenetic modifications that may be manipulated in the course of therapy. Inflammatory signals in the lung cancer microenvironment can promote apoptosis resistance, proliferation, invasion, metastasis, and secretion of proangiogenic and immunosuppressive factors.

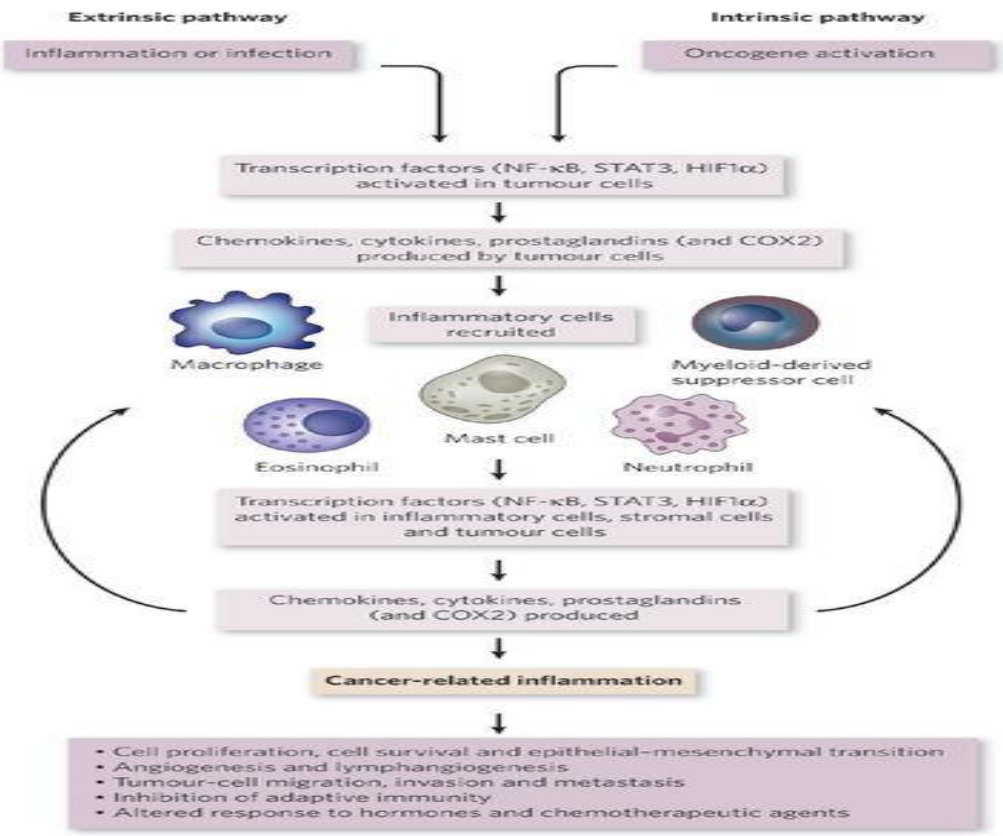

Figure 1: Cancer related inflammation

Cytokines, growth factors and small-molecule inflammatory mediators released in the mounting tumor microenvironment pave the way for epithelial–mesenchymal transition, the shift from a polarized, epithelial phenotype to a highly motile mesenchymal phenotype that becomes dysregulated during tumor invasion. Inflammatory mediators within the tumor microenvironment are derived from neoplastic cells as well as stromal and inflammatory cells; thus, lung cancer develops in a host environment in which the deregulated inflammatory response stimulates tumor progression.

Inflammation-related metabolic and catabolic enzymes (prostaglandin E_2 synthase, prostaglandin I_2 synthase and 15-hydroxyprostaglandin dehydrogenase), cell-surface receptors (E-type prostaglandin receptors) and transcription factors (ZEB1, SNAIL, PPARs, STATs and NF-κB) are differentially expressed in lung cancer cells compared with normal lung epithelial cells and, thus, may contribute to tumor initiation and progression. These newly discovered molecular mechanisms in the pathogenesis of lung cancer provide novel opportunities for targeted therapy and prevention in lung cancer.[25]

Inflammation and epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is a very deadly gynecological cancer for which overall prognosis has stayed poor in the course of recent decades. A number of concepts have been postulated in an effort to explain the aetiology of EOC. Noteworthy, these theories likely are not fundamentally unrelated, as they all converge more or less on the part of inflammation in promoting ovarian tumorigenesis and cancer progression. The tumor milieu in which ovarian carcinoma improved with an expansive range of spectrum of pro-inflammatory cytokines and chemokines. Specifically, several of these cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, produced by tumor itself or/and activated immune cells, besides stimulating cancer cell growth, have been presented to influence clinical disease status and prognosis, by reducing responsiveness to chemotherapy and inducing symptoms such as anorexia, altered energy metabolism, anemia, weight loss, depression and fatigue.

Recent data demonstrate that cytokine antagonists may have a role to play in the treatment of ovarian cancer. Their activity by restraining both generation and movement of provocative cytokines appears to acquire the control of angiogenetic and apoptotic events, the reversal of chemo resistance, the improvement of systemic symptoms and prognosis.[26]

Inflammation and colorectal cancer

Colorectal cancer (CRC) is the one of the foremost causes of cancer-related deaths in the world. CRC causes more than 600,000 deaths yearly and occurrence rates are increasing in most of the developing countries. Epidemiological and laboratory examinations suggest that environmental factors such as western style dietary habits, tobacco-smoking, and lack of physical activities are

considered as risks for CRC. Molecular pathobiology of CRC implicates pro-inflammatory situations to encourage the tumor malignant progression, invasion, and metastasis. It is well recognized that patients with inflammatory bowel disease are at higher risk of CRC. Many evidences exist reiterating the link between Inflammation and CRC.

Inflammation involves interaction between various immune cells, inflammatory cells, chemokines, cytokines, and pro-inflammatory mediators, such as cyclooxygenase (COX) and lipoxygenase (LOX) pathways, which may lead to signalling towards, tumor cell proliferation, growth, and invasion. Thus, the mechanisms pro-inflammatory mediators and reactive oxygen/nitrogen species play a role in promoting CRC.[27,28]

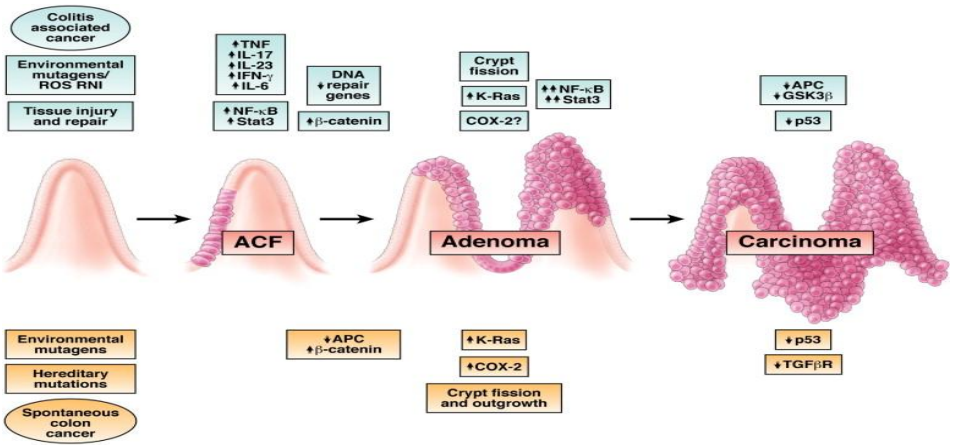

Figure 2: Mechanisms of colorectal cancer (CRC) and colitis-associated cancer (CAC) development.

CRC is initiated by accumulation of mutations in oncogenes and tumor suppressor genes; some of these lead to aberrant activation of β-catenin signaling. Mutations in *adenomatous polyposis coli* (APC), β-catenin, or other components of this pathway mediate the transition of single pre-neoplastic cells to aberrant crypt foci (ACF) and then to adenoma and colorectal carcinoma. Chronic inflammation, which prompts CAC, is portrayed by creation of pro-inflammatory cytokines that can instigate mutations in oncogenes and tumor suppressor genes (APC, p53, K-ras) and genomic precariousness through different mechanisms. Persistent inflammation enables tumor promotion by stimulating proliferation and anti-apoptotic properties of premalignant cells, and in addition tumor progression and metastasis. There is considerable overlap in mechanisms of CRC and CAC pathogenesis. Glycogen Synthase Kinase-β (GSK-β); Reactive Nitrogen Intermediates (RNI); Transforming Growth Factor (TGF) were also involved in the formation of carcinoma.[27,28]

Inflammation and prostate cancer

During the time of inflammation and prostate tumor progress, the role of NF-*κ*B has been valued. The nuclear factor NF-*κ*B is related with the upregulation of tumor promoting cytokines, for example, IL-6 and TNF-*α*. However, NF*κ*B is a ubiquitous transcription factor and poses a challenge as a potential target to control inflammation-associated tumor growth studies. To decide a potential focus of inflammation, various examinations have proposed the role of inflammatory cytokines and chemokines in prostate growth.

Clinically, the estimation of IL-1*β*, IL-18, IL-6, and MIC-1/GDF-15 relates with the danger of carcinoma and the forecast of established cancer. However, the role of IL-6 in prostate tumor is well predicted, studies on serum IL-18 for its diagnostic utility in cancer are limited. Concentrate on a companion of 149 patients showed that serum IL-18 level was essentially higher in privately propelled prostate malignancy when contrasted with solid control and BPH. Expression of IL-18 binding protein (IL-18 BP) was significantly upregulated in patients with large volume disease, and a high serum level of IL-18 BP was correlated with Gleason score.

In the same way, MIC-1/GDF15 is controlled by the inflammatory cytokines and clinical confirmation supports the notion that serum MIC-1/GDF-15, in mishmash with PSA, may enhance the specificity for prostate cancer identification. It has been proposed that IL-1*β* and IL-18 apply immunosuppressive impacts and support tumor promoting microenvironment. In this manner, recognizing the regulators of inflammation-associated cytokine/chemokines as a molecular target of cancer progression may deliver a chance to additionally comprehend the part of inflammation in prostate disease.[29]

Inflammation and thyroid cancer

The relationship between inflammation and thyroid cancer and the pathophysiology of chronic inflammation that induces papillary thyroid carcinoma (PTC). Several studies have strongly suggested an increased risk of papillary thyroid carcinoma (PTC) in patients with Hashimoto's thyroiditis (HT), the most common autoimmune disease in thyroid cancer. Furthermore, an intense immune infiltrate is often associated with PTC, and might play a critical role in the regulation of carcinogenesis and in carcinoma progression.

Molecular studies have identified activation of the RET/PTC rearrangement-induced MAPK signaling pathway as the driving force in the development of PTC in the context of HT. These genetic alterations may be favored by chronic inflammation. In this regard, the RET oncoprotein and its downstream effectors, such as those implicated in the activation of the MAPK pathway, as well as inflammatory molecules of the tumor microenvironment could be promising molecular targets for new therapeutic strategies for thyroid cancer.[30-32]

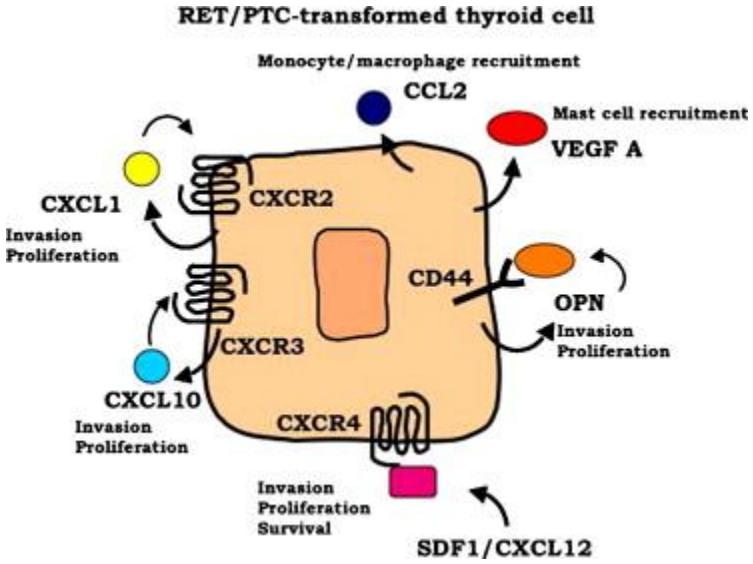

Figure 3: RET/PTC transformed thyroid cell

Inflammation and bladder cancer

Bladder cancer is a highly immunogenic malignancy. Urothelial cancer cells plan to control the immune system by restricting its cytotoxic role while motivating the secretion of growth promoting factors. Cytokine-induced irregular characteristics in the dissemination and separation of tumor-infiltrating cytotoxic cells can induce bladder sarcoma cell proliferation. Tumor-induced release of excessive amount of cytokines causes an "inflammatory storm" which drives metastasis formation via degradation of extracellular matrix proteins. Tumor-related selective cyclooxygenase-2 (COX-2) upregulation suppresses the cell-mediated immune response via aberrant prostaglandin metabolism resulting in failure of differentiation of myeloid cell progenitors into mature antigen-presenting cells. T cells are capable of increasing the oxidative stress on bladder cancer cells via induction of COX-2 and STEAP expression.

Some evidence also suggests that COX-2 activation may be also involved in inflammation-mediated cancer stem cell proliferation. Antibodies against the VEGF-co-receptor neuropilin decrease the angiogenetic potential of bladder cancer cells. Inflammation-based predictive bladder cancer models have demonstrated to accurately predict response to treatment both in the curative and palliative setting. While randomized trials do not support a clinical benefit for the use of anti-inflammatory drugs (i.e., celecoxib, atorvastatin) in preventing recurrence of low-grade bladder cancer, further investigations are warranted in the setting of high-grade tumors since the immune response to cancer stimuli is most probably more pronounced in advanced stages.[33]

Inflammation and pancreatic cancer

Pancreatic cancer has tremendously poor anticipation and the cellular mechanisms contributing to pancreatic cancer are moderately unidentified. Inflammation has been distinguished as a huge factor in the improvement of other solid tumor malignancies. Both genetic and sporadic types of chronic pancreatitis are related with an improved risk of developing pancreatic cancer. The collective increase in genomic damage and cellular proliferation, both of which are seen with inflammation, powerfully favours malignant transformation of pancreatic cells. Cytokines, reactive oxygen species (ROS), and mediators of the inflammatory pathway such as NF-κB and COX-2 have been revealed to rise cell cycling, grounds loss of tumor suppressor function, and excite oncogene expression; all of which may prompt to pancreatic malignancy.[34,35]

Pathways involved in pancreatic cancer

Signal transduction pathways via Ras and P13K/Akt cause cell proliferation and survival

- Epidermal Growth Factor Receptor (EGFR)
- Insulin like Growth Factor -1Receptor (IGF-1R)
- Hepatocyte Growth Factor Receptor (HGFR)
- Vascular Endothelial Growth Factor Receptor (VEGFR)

Development signalling pathways that can cause tumor progression and resistance to chemotherapy

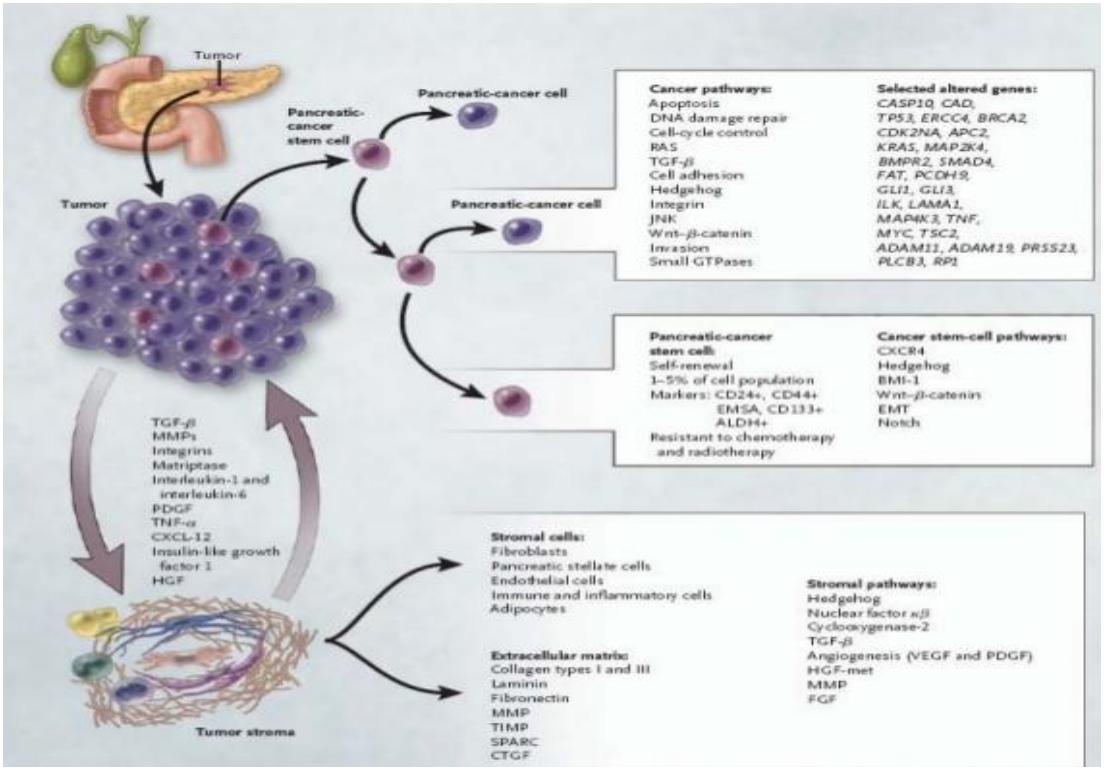

Figure 4: Pathway involved in pancreatic cancer

- Hedgehog
- Notch
- Wnt

Tissue invasion and neovascularization

- Matrix Metalloproteinase

DNA damage control and impaired apoptosis

- p53
- p14 ARF/p16INK4A

SMAD4/Transforming Growth Factor-β (TGF-β)

Inflammation and cervical cancer

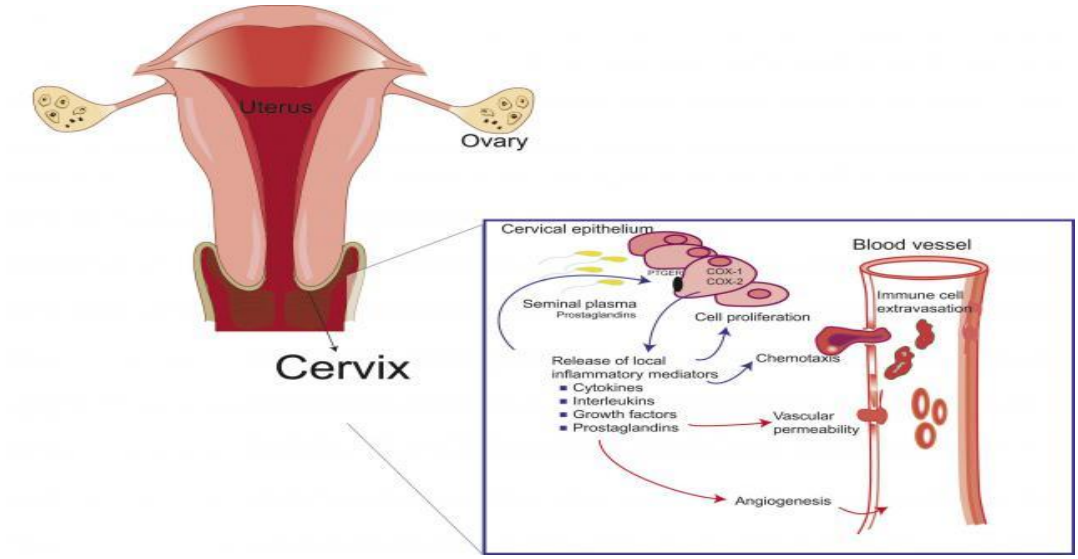

Figure 5: A schematic diagram highlighting pathways involved in inflammation and cervical cancer progression

Cervical cancer is the most common gynaecological cancer among women in developing countries. Virtually all cases of cervical cancer follow after infection of the cervical epithelium with oncogenic human papilloma virus (HPV) types. The majority of anogenital cancers in humans are associated with the high-risk HPV16 and 18 and there is correlation between percentage of HPV 16 and 18 integration and severity of the cervical lesions. Although it is necessary to have infection of the cervix with oncogenic HPV to develop cancer, HPV itself may not be sufficient. Other associated cofactors including compromised immune system or infections with herpes virus II, Chlamydia trachomatis, Neisseria gonorrhoeae, or bacterial vaginosis have been associated with cervical inflammation and increased risk of cervical cancer [36]. COX-1 and COX-2 expression were both significantly elevated in the neoplastic epithelial and vascular endothelial cells of cervical cancers of all grades and stages.[37]

Inflammation and liver cancer (hepatocellular carcinoma)

Hepatocellular carcinoma (HCC) is one of the most aggressive human cancers and the third leading cause of death worldwide. HCC is an example of inflammation-related cancer, as the chronic inflammatory state appears to be necessary for the initiation and development of liver cancer. Several studies have shown that chronic infections with hepatitis viruses (hepatitis B virus, HBV and hepatitis C virus, HCV) are major risk factors for HCC development. Other risk factors to liver carcinogenesis include chronic alcohol abuse, biliary disease, metabolic disorders, drugs, toxins, and genetic conditions, such as hereditary hemochromatosis and 1-antitrypsin deficiency. Thee chronic inflammation is characterized by the continued expression of cytokines and recruitment of immune cells to the liver. Moreover, Tumor-Necrosis-Factor-alpha (TNF-α) - induced Nuclear Factor kappa B (NF-κB) activation plays a key role in hepatocarcinogenesis. Among a wide range of cytokines involved in liver inflammation, TNFα, interleukins (IL6, IL1α, IL1βα and IL10), and TGFβ (transforming growth factor beta) are thought to play major roles. It is therefore clear that the crosstalk between tumor cells and their surrounding microenvironment is required for HCC development. The molecular links that connect cancer cells and TAMs are not completely known, but recent studies have demonstrated that NF-κB, STAT-3, and HIF-1 signalling pathways play key roles in this crosstalk.[38]

TAMs promote hepatocellular carcinoma (HCC) growth, angiogenesis, invasion, and metastasis, as well as the suppression of antitumor immune response by interacting with both stromal and cancer cells within the tumor microenvironment. TAMs are recruited in HCC milieu by Macrophage Colony-Stimulating Factor (M-CSF), Chemokine (C-C motif) Ligand 2 (CCL2), Vascular Endothelial Growth Factor (VEGF), and Transforming Growth Factor β (TGFβ), and they, in turn, release many cytokines, chemokines and growth factors, which are implicated in such crosstalk. In particular, Interleukin 6 (IL-6) and Transforming Growth Factor β (TGFβ) favour tumor growth, whereas Tumor Necrosis Factor α (TNF α), Osteopontin (OPN), Matrix Metalloproteases (MMPs), and Interleukin 6 (IL-6) are involved in invasion and metastasis; TGF β, in concert with Interleukin 10 (IL-10), promotes the suppression of antitumor immune response. Finally, angiogenesis is induced by several molecules, including VEGF, Epidermal Growth Factor (EGF), Platelet Derived Growth Factor (PDGF), and TGF β.[39]

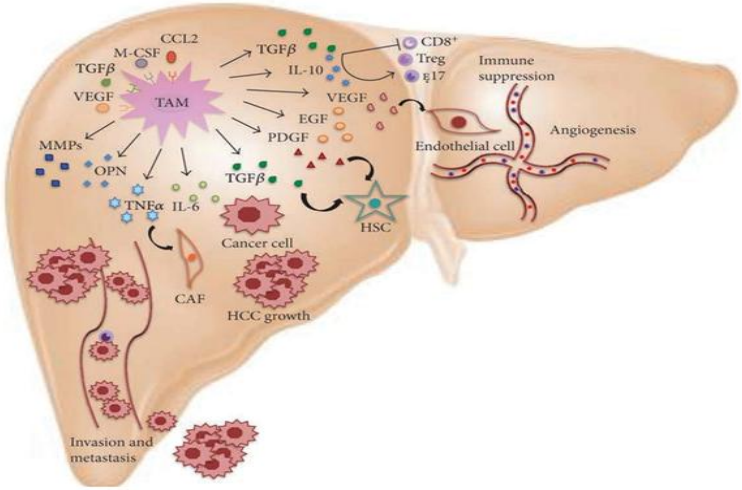

Figure 6: The roles of tumor-associated macrophages (TAMs) in liver cancer.

Inflammation and breast cancer

Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer. Despite extensive study, whether inflammation contributes to the tumorigenicity or aggressiveness of IBC remains largely unknown. In this chapter, we will review the potential role played by inflammation in IBC based on the results of in vitro, in vivo, and patient studies. Current evidence suggests that several major inflammatory signalling pathways are constitutively active in IBC and breast cancer. Among

them, the NF-κB, COX-2, and JAK/STAT signalling systems seem to play a major role in the tumorigenesis of IBC. Inflammatory molecules such as interleukin-6, tumor necrosis factor alpha (TNF-α), and gamma interferon have been shown to contribute to malignant transformation in preclinical studies of IBC, while transforming growth factor-β, interleukins 8 and 1β, as well as TNF-α appear to play a role in proliferation, survival, epithelial-mesenchymal transition, invasion, and metastasis.[40,41]

Inflammation and gastric cancer

Inflammation of gastric epithelium is known to be related with the improvement of gastric malignancy. There are a few systems by which aggravation may advance malignancy improvement and the acceptance of the cyclooxygenase-2/prostaglandin E2 (COX-2 / PGE2) pathway and activation of NF-κB and STAT3 have all the earmarks of being major pathways. Actually, it has been demonstrated that all the gastric tumors shows an induction of COX-2 expression and *H. pylori* disease is known to prompt COX-2 acceptance. In this way, IL-8 and IL-11 expression is overwhelmingly incited in gastric malignancy, while in gastritis generally TNF-α articulation is expanded. Gastric malignancy shows regular increments in inflammatory cytokines chemokine (C-X-C motif) Ligand 1 (CXCL1), CXCL2, CXCL5, Chemokine (C-C motif) Ligand 3 (CCL3), CCL4, and Toll Like Receptor -2 (TLR-2).[42]

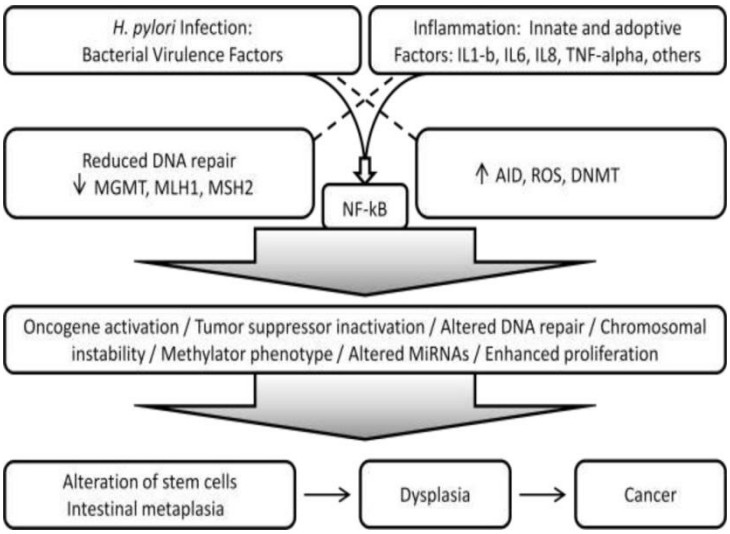

Figure 7: *H. pylori* virulence factors and inflammation mechanisms leading to gastric cancer.

CONCLUSION

Inflammatory responses play extensive roles at different stages of cancer cell growth and proliferation which includes initiation, promotion, malignant conversion, invasion, and metastasis. Inflammation is a key component of the tumor microenvironment. Recent efforts have thrown various drug targets on molecular and cellular pathways linking inflammation and cancer. Thus, this review focused on critical molecular players during the development from inflammation to carcinogenesis. These protein markers have functions in both inflammatory responses and cancer development. Future therapies should also take notice of these natural genetic variation and change in expression of these markers that reflects the severity of inflammation. Moreover, these studies also help in the determination of prognosis of cancer upon treatment with heterogeneous anti-inflammatory and anticancer drugs. Such considerations are extremely important in the design of new therapeutic approaches leading to the reduction of cancer risk.

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