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The Role of Cytokines, Chemokines and NFkB in Inflammation and Cancer

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Abstract

Previous researches have suggested that chronic inflammation plays a critical role in cancer pathogenesis as it has been assessed that underlying infections and inflammatory responses have been associated with 25% of all cancer cases, whereas the inflammatory microenvironment is an essential component of all tumors. Moreover, some of the molecular mechanisms that link the mentioned association have been clarified. Cancer pathogenesis has been associated with physical mutations and environmental factors, whereas a limited rate has been associated with germline mutations. The special role of environmental factors in cancer pathogenesis has been associated with diverse types of chronic inflammation. It has been recorded that 30% of cancer cases can be attributed to smoking and inhaled pollutants, such as asbestos and carbon dioxide silicon, 20% are associated with chronic infections, and 35% are related to nutrition factors. Common bacterial and viral infections increase the risk of cancer development, however smoking acts as a promoter due to its ability to cause chronic inflammation. Similarly, advanced age and cellular senescence has been recorded to have the same role, as cancer pathogenesis promoters, because act through inflammatory mechanisms. Cellular senescence and damaged DNA accumulation are able to enhance chronic inflammation which promotes tumorigenesis. Inflammation-induced cancer contributes to tumor development through different pathways, such as epigenetic alterations and subsequent inappropriate gene expression, gene instability induction, increased proliferation and resistance to apoptosis of the initial cells, immuno-suppression, induction of tumor angiogenesis, tissue remodeling, and eventually development of metastasis.

Keywords: Cytokines; Chemokines; NF-kappaB signaling; Inflammation; Cancer

Abbreviations: TIL: Tumor-Infiltrating Lymphocytes, NPN: Neutrophils Polymorphonuclear, BMC: Bone Marrow Cells, NK: Natural Killer, MHC: Major Histocompatibility Complex, iNOS: Inducible Nitric Oxide Synthase, AP: Protein-Activator-, ROS: Reactive Oxygen Species, RNI: Reactive Nitrogen Intermediates, Cy: Cysteine Residues, MDSC:

Myeloid-Derived Suppressor Cells, VCAM: Vascular Cell Adhesion Molecule, CAF: Cancer-Associated Fibroblasts, cHL: Classic Hodgkin Lymphoma, EGFR; Epidermal Growth Factor Receptor, SDF: Stromal Cell-Derived Factor, RHD: Rel Homology Domain, ERG: ETS-Related Gene, IKK: IKB Kinase, MT: Metallothionein, AOM: Azoxymethane, DSS: Dextran Sodium Sulfate, HCC: Hepatocellular Cancer, LPS: Lipopolysaccharide

Introduction

Cancer is the 2nd leading cause of death worldwide after cardiovascular diseases and is responsible for high rates of morbidity and mortality **[1]**.

Cancer risk factors include advanced age, male gender, cigarette smoking, genetic predisposition, exposure in inhaled particles, pollutants and gases, whereas in its pathogenesis are implicated pre-existing diseases such as chronic obstructive pulmonary disease, chronic pancreatitis, chronic hepatitis, ulcerative colitis, etc. Those findings resulted in the hypothesis that the systematic chronic inflammation may be involved in cancer initiation and/or promotion, as it is possible to enhance cell proliferation and mutagenesis, reduce adaptation to oxidative stress, promote angiogenesis, inhibits apoptosis and increases secretion of inflammatory mediators **[2]**. Chronic inflammation seems to play a critical role in tumorigenesis, as mentioned. In response to injury, a complex integrated system of mechanisms is activated to eliminate the stimulus, repair damaged tissue, and promote wound healing through measured and organized cellular proliferation. Under normal circumstances, this host's physiological response recedes once repair is completed. However, in case that usually tightly regulated self-limiting mechanism becomes disturbed, a state of chronic inflammation may result **[3]**.

Inflammatory cells are implicated in cancer pathogenesis, whereas it has been observed that tumors often are infiltrated by inflammatory cells derived from the bone marrow, that have an active role in cell invasion-infiltration, angiogenesis, lymphangiogenesis and its metastatic spread. Tumor's and host's inflammatory, endothelial and parenchymal cells interact via contact with integrins, cytokines and chemokines contributing to the disease progression **[4]**.

Virchow **[5]** first suggested the association between inflammation and neoplasia as observed that cancer seemed to occur at previous chronic inflammation locations. The initial suggestion that tumor-infiltrating lymphocytes (TIL) may represent an expression of anti-tumor activity was supported by evidence linking TIL with improved prognosis in solid cancers **[6,7]**. Previous and recent reports accumulated data to support the hypothesis that organs affected by chronic inflammation provide the perfect microenvironment in which an abnormal clone or clones of cells are able of evading detection by the host immune system and proceed to invasive carcinoma.The current review provides data concerning the role played by chronic inflammation in carcinogenesis.

Carcinogenesis induced by Chronic Inflammation Cells

Chronic inflammation can contribute to cancer development and progression, as associations have been recorded between inflammatory diseases and cancer, such as the infection with HBV /HCV viruses and hepatocellular carcinoma, chronic reflux esophagitis in Barrett's esophagus and esophageal cancer **[8]**, Crohn's disease/ulcerative colitis and colon cancer, the infection of the cervix by HPV virus and cervical cancer **[9]** chronic pancreatitis and pancreatic cancer **[10]**, chronic prostatitis and prostatic cancer, despite the fact that the latter relationship is unclear and controversial **[11]**.

Carcinogenesis induced by chronic inflammation could be attributed to dysregulation of the immune system and autoimmunity, as in inflammatory bowel disease which increases the risk for colon cancer **[12]**. However, there are inflammatory diseases such as psoriasis which do not increase the risk of cancer development **[13]**.

Cancer-induced inflammation differs from chronic inflammation that results in cancer development. Almost all solid malignancies characterized by an internal inflammatory reaction that produces a pro-tumorigenic microenvironment **[14]**. Based on continuous cellular renewal and the proliferation induces from tumor-associated inflammation, tumors have referred to ''as wounds that do not heal'' **[15]**. In fact, it is a disturbed wound healing and regeneration response of tissue observation based on the finding that

oncogenes such as V-Src or K-ras presuppose the presence of injury and tissue regeneration to induce cancer in adult experimental animals **[16]**.

The tumor microenvironment consists of innate immune cells such as neutrophils polymorphonuclear (NPN), lymphocytes, macrophages, suppressor bone marrow cells (BMC), adaptive immune cells, such as B- and T-lymphocytes, dendritic cells and natural killer (NK) cells, as well as malignant neoplastic cells and their environment substrate, consisting of fibroblasts, endothelial cells, pericytes and mesenchyme cells **[17]**. Those cells communicate and they interact with each other and through production growth factors, cytokines and chemokines affect the tumor development. Through those effects the tumor microenvironment determines whether the inflammatory response will promote tumorigenesis or whether immunity will be established against it **[18,19]**. After tumor establishment the type of inflammation will promote its development. It is possible that the inadequate antitumor immune response is due to the ability of cancer cells to escape from immune cells in combination with the undifferentiated nature of cancer cells **[20]**.

In addition, the inflammatory reaction related with tumor is characterized by pro-inflammatory and anti-inflammatory signals that allow the tumors to grow and escape the immune surveillance **[21]**. It is considered that inflammation, tumor progression and immunity against it co-exist in different sections in its progression pathway, and those environmental and micro-environmental conditions determine the balance between them **[22,23]**. The majority of tumors is characterized by leukocytes infiltration, varying in composition and distribution, that is implicated in carcinogenesis, tumor development, invasion and metastasis. In the tumor microenvironment are mainly observed macrophages associated with the tumor (TAMs) and T-cells that constitute the most important factors of inflammation and cancer as well as an important source of cytokines **[14,24]** TAMs mainly promote tumor development and maybe they are essential for angiogenesis, invasion and metastasis **[25]**.

In particular, macrophages are distinguished into M1 and M2 types **[24]**, activated by IFN-γ, microbial products, and cytokines and express high levels of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12 or IL-23, molecules of the major histocompatibility complex(MHC), inducible nitric oxide synthase (iNOS), and are able to destroy pathogenic and contribute to anti-cancer immune responses **[24]**. M1 macrophages, activated by IFN-γ and bacterial products, express high levels of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12 or IL-23), MHC molecules and iNOS and are capable of killing pathogens and priming anti-tumor immune responses. Conversely, M2 or "alternatively" activated macrophages, which are induced in *vitro* by IL-4, IL-10 and IL-13, down-regulate MHC class II and IL-12 expression and show increased expression of the anti-inflammatory cytokine IL-10, scavenger receptor A, and arginase. Most TAMs are considered to have an M2 phenotype whereas promote tumor angiogenesis and tissue remodeling **[24]**. However, most confirmed tumor-promoting cytokines are "M1 cytokines", whereas IL-10, an M2 cytokine, may be tumor suppressive as shown in colorectal cancer. Furthermore, unlike Th (helper)1 and Th2 cells, M1 and M2 macrophages are plastic and their phenotype is defined by their gene expression prolife rather than by deterministic differentiation pathways and lineage choices **[18,26]**.

Similarly, T-cells exhibit both tumor suppressor and tumor-promoting action **[19]**. Their deficiency or the disruption of specific cytotoxic mechanisms can make experimental animals more susceptible to spontaneous or chemical carcinogenesis **[27]**. However, many of T-cells subsets present in solid tumors participate in the promotion, progression of the tumor or metastasis, including CD8+ T-cells **[28]**, Th1-cells **[29]**, Th2-cells **[30]** and Th17-cells **[31]**. The NK cells are the only type of inflammatory cells that have no pro-tumorigenic role. Similar to TAMs, tumor promoters functions of T-lymphocytes are mediated by cytokines, whereas cytokines and cytotoxic mechanisms mediate the anti-tumorigenic functions of T-lymphocytes **[27]**.

In addition, mast cells and B-lymphocytes contribute to tumor growth and the conventional macrophages and dendritic cells are important for antigen-presentation and T-cell activation during immunity against the tumor as well as for the cytokine production and inducing immune-suppression in established tumors **[32]**.

Tumor development is supported by macrophages, mast cells

and NPNs resulting in up-regulation of non-specific pro-inflammatory cytokines such as INF-γ, TNF-α, IL-1a, IL-1b and IL-6 **[33,34]**. Especially, NPNs influence oncogenesis as act as tumor promoters and suppressors, depending on their differentiation state **[35]**. Critical regulators, such as the transcription factor NF-kB, STAT and SMAD, protein-activator-1 (AP-1), caspases, and cytokines are able to control immune and inflammatory environment through anticancer immunity (IL-12, IFN-γ, TRAIL) or to enhance tumor progression (IL-6, IL-17, IL-23) and have also direct effects on survival and development of cancer cells (TRAIL, IL-6, FasL, TNF-α, EGFR ligands, TGF-b) **[18]**.

Inflammation mechanisms fight pathogenic factors and result in healing of injured tissue. However, an unresolved inflammation leads to loss of balance between two biologically opposing arms of acute inflammation, 'Yin' (tumoricidal) and 'Yang' (tumorigenic) processes that cause disruption of protective mechanisms of immune system **[36]**. That inflammation type due to any failure of accurate control of the immune response may continue to disrupt the cellular micro-environment, leading to genes alterations related to cancer and post-translational modifications in critical proteins of cell cycle signaling pathways, DNA repair and apoptosis **[37]**.

Similarly, the activated NF-kB factor is one of the main links between inflammation and tumorigenesis and seems to allow pre-neoplastic and malignant cells to escape apoptosis. Chronic inflammation can result in genetic alterations through molecules such as cytokines, chemokines, the NF-kB factor, and prostaglandins **[38]**.

Inflammatory response often is followed by an increased production of reactive oxygen species (ROS) in tissues **[39]**, that is possible to alter the signal transduction cascades and induce transcriptional alterations in factors, such as NF-kB, NF-E2/rf2 or Nrg2 (nuclear factor erythroid 2/ related factor 2) and in AP1 factor, which mediate immediate responses in cellular stress **[40,41]**. ROS and reactive nitrogen intermediates (RNI), can act directly or indirectly, through reactions with other chemicals or structural components of cells, whereas their derivatives can also activate NF-kB factor, leading to production of others pro-inflammatory cytokines which in turn they enhance inflammation and therefore more production of ROS as well as recruit others inflammatory cells with secondary enhancement of tissue damage **[42]**.

Activated inflammatory cells also act as ROS and RNI sources and are able to induce DNA damage and genomic instability. ROS-induced DNA damage may result in disruption or induction of transcription, transcription errors, genomic instability, proto-oncogenes activation, tumor suppressor genes inactivation and mitochondria oxidative damage, processes related with carcinogenesis **[43,44]**.

Inflammatory cells may use cytokines, such as TNF-α to stimulate the accumulation of ROS in neighboring epithelial cells and to secrete a large amount of chemokines that promote the production of neoplastic cells, except autocrine growth factor production from the tumor cells themselves. Proinflammatory cytokines through activation of protein kinase signaling affect cells of the immune system resulting in ROS and RNI production. Therefore, TNF-α increases ROS generation by NPN and other inflammatory cells **[45]**.

ROS are produced by mitochondria, the CytP450 and peroxisomes **[42]** and under normal conditions there is a constant endogenous production of reactive ROS and RNI that interact as signaling molecules involved in cellular metabolism, cell cycle and intercellular communication pathways. The balance between the beneficial and/or of damaging effects of ROS is a critical event in living organisms as homeostasis redox is, in *vivo*, the main protective process from cell death **[46]**.

Protective molecules and systems, known as 'antioxidants' defenses' are responsible for controlling of the balance between production and removal of ROS and RNI **[47]**. Oxidative stress occurs in case the production of ROS and RNI in a system exceeds the system's ability to neutralize and eliminate them **[48]**. Under oxidative stress conditions ROS and RNI act as toxic substances that can react with proteins, carbohydrates and lipids leading to subsequent alterations in intra-cellular and in intercellular homeostasis, resulting in possible cell death and regeneration. The cells could react either through amplification of their antioxidant potential or through activation of the caspases system that can induce programmed cell death-apoptosis **[46]**.

The failure of the above pathways and due to the effect of

ROS and RNI in the cell nucleus, the possibility of causing mutation through oxidation, nitration, halogenation of nuclear DNA, RNA and lipids is increased or may be mediated by ROS and RNI products as well as proteins, carbohydrates and lipids that can generate complexes with DNA. ROS can also increase the expression of transcription factors, such as c-fos, c-jun and oncogenes involved in neoplastic transformation **[42]**.

Therefore all these factors are possible to act as initiators and promoters of carcinogenesis through the direct increase of proliferation of epithelial cells **[49,50]**.

The role of cytokines and chemokines in inflammation and cancer

Inflammatory or pro-inflammatory cytokines are signaling molecules secreted from immune cells like Th cells and macrophages, and certain other cell types that promote inflammation. Different cytokines can either promote or inhibit tumor development and progression, regardless of their source **[18]**. Through activation of various downstream effectors, such as NF-κB, AP-1, STAT and SMAD transcription factors, as well as caspases, cytokines control the immune and inflammatory microenvironment to either favor anti-tumor immunity (IL-12, TRAIL, IFNγ) or enhance tumor progression(IL-6, IL-17, IL-23) and also have direct effects on cancer cell growth and survival (TRAIL, FasL, TNF-α, EGFR ligands, TGF-β, IL-6).

Chemokines are soluble chemotactic cytokines that are divided into 4 categories based on positions of the basic cysteine residues (Cys) and are C, CC, CXC, CX3C. Previous studies have shown the involvement of those proteins and their receptors in cell proliferation, migration, invasion, metastasis and angiogenesis in various tumors as well as in cellular uptake, immigration and in regulation of leukocyte recruitment and trafficking to inflammation locations **[33,51]**.

Cytokines and chemokines are involved in many aspects of growth, differentiation and cell activation. Main cytokines play some role in the activation or regulation of the inflammatory response and that contribute in some way to the process of tumorigenesis. Chemokines are key players of the cancer-related inflammation, whereas their respective receptors and ligands are the downstream genetic events that cause neoplastic transformation and which are abundantly expressed in chronic inflammation, increasing susceptibility to cancer. The components of the chemokine system affect different routes of tumor progression, including leukocyte recruitment, neo-angiogenesis, proliferation, survival, invasion, and metastasis of tumor cells **[51]**. Preclinical and clinical trials indicate that the intervention in the chemokine system can be a valuable tool for the development of future therapeutic strategies against cancer **[52]**.

A similar circuit can be executed by myeloid-derived suppressor cells (MDSC) that produce arginase1 and indoleamine-2,3-dioxygenase, which are enzymes that decrease anti-tumor immunity through interference with T cell activation **[53]**. Taken together, tumor associated inflammation drives tumor growth, angiogenesis and can preserve itself through an extensive network of cytokines and chemokines, which are produced by immune, stromal and malignant cells in response to diverse signals. Given that several cytokines (IL-1, TNF, IL-6, IL-23) and transcription factors (AP-1, NF-κB, STAT3) are critical for both inflammation and tumor growth, they control hubs of pro-tumorigenic signaling that may be targeted to curtail both tumor associated inflammation and tumor growth **[54]**.

Pharmacological interference with cytokine signaling decreases tumorigenesis as well as cancer growth **[55-57]** and may therefore serve as a basis for preventive and therapeutic approaches. Altogether, cytokine production by immune and inflammatory cells is an important tumor promoting mechanism that provides malignant cells with a continuous supply of growth and survival signals in an initially hostile microenvironment. In most cases, tumor promoting cytokines act in a paracrine manner, yet several types of cancer cells produce their own cytokines, including IL-6, to achieve the same effect **[58]**.

The special role of TNF-α and other cytokines and chemokines in inflammation and cancer

TNF-α, was identified as an anticancer cytokine, but when tested its anticancer effect in cancer cases, a paradoxical tumor-promoting role was recorded **[59,60]**. Currently the pro-inflammatory role of TNF-α has been associated with all stages that are involved in tumorigenesis including cell transformation **[61]**, survival **[62]**, tumor promotion **[62,63]**, proliferation **[33,63]**, angiogenesis **[63,64]**, infiltration **[65]**

and metastasis **[60,62,63,66]**. It has also recorded that TNF-α is produced by a wide variety of cancer cells, such as in B-lymphomas, megakaryoblastic leukemia, breast, colon, lung, pancreas, ovaries cancer, etc. **[51]**. In addition, Rossi et al. **[67]** found that TNF-α could increase the invasiveness of melanoma cells, and Tan et al. **[68]** found that TNF-α could be a potential therapeutic target for hepatocellular carcinoma. TNF-α also can be used to predict the occurrence and recurrence of liver cancer **[69]**.

When TNF-α is locally expressed by the immune system cells has therapeutic role. However, when it is deregulated and secreted in blood circulation can participate in a wide diversity of diseases, including cancer **[70]**. Various interleukins have been linked to inflammation and the subsequent development of cancer including IL-1, IL-6, IL-8 and IL-17. It appears that they mediate different stages in the pathway leading to carcinogenesis.

IL-1 is a cytokine of the chemokine family and is produced primarily by macrophages. Under normal physiological conditions, IL-1 has an anti-tumor effect, but when the body is in persistent chronic inflammation, IL-1 has a tumor-promoting effect, at which time IL-1β supports tumor development**[71,72]**. IL-1 is involved in the angiogenesis and proliferation of cancer cells, which may promote the development of cancer **[73,74]**. IL-1 also can promote the expression of vascular cell adhesion molecule-1(VCAM-1), thereby promoting adhesion and metastasis of cancer cells **[75]**. Han et al. **[76]** recorded that IL-1 is implicated in the invasion of gastric cancer in a mice model.

So far, the IL-1 family has 11 members, but the most important ones are IL-1α and IL-1β. IL-1α is also expressed by normal tissues and diverse tumor cells, is a regulatory cytokine that can induce the activation of NF-κB and AP-1 transcription factors and can promote various genes expression implicated in cellular survival, proliferation and angiogenesis **[77]**.

The most investigated subtype of IL-1 is IL-1β **[78]**. The study of IL-1α is few, but it is also implicated in tumor progression and metastasis, which can activate NF-κB and promote tumor growth **[79]**.

IL-1β is mainly produced by tissue macrophages, skin dendritic cells, and blood mononuclear cells. The biological activity of the IL-1β precursor is biologically active after being subjected to enzymatic treatment and is mainly present in the microcirculation system **[80]**.

Similar to IL-1α, the role of IL-1β has demonstrated in diverse human cancers in the stomach, cervix, pancreas and lung **[33,51,81,82]**. IL-1β also up-regulates HIF-1α (hypoxia-inducible factor-1 alpha) factor through the classical inflammatory signaling pathway involving NF-κB factor and COX-2, leading to the up-regulation of VEGF, that is required for tumor development and metastasis **[83]**. VEGF activation promotes blood vessel growth and provides nutrients for tumor growth **[84,85]**. At the same time, IL-1β can also induce chronic inflammation and activate blood endothelial cells, thereby promoting the invasiveness and metastasis of cancer cells **[86]**. IL-1β activates the NF-κB signaling pathway of myeloid cell lines (MDSCs), and NF-κB is a critical link between inflammation and cancer. MDSCs can secrete IL-6 and TNF-α, which can promote tumor growth **[87]**. When IL-1β binds to its corresponding receptors, it can activate MyD88 and IL-1 receptor-associated kinase-4 (IRAK4), which results in IRAK2 and IRAK1 phosphorylation and then activates NF-κB. Activated NF-κB can enter the nucleus and promote the transcription of some inflammatory genes **[88]**.

In conclusion, the pro-inflammatory cytokine IL-1 is closely related to the occurrence, development, metastasis, and invasion of tumors, and may be used as a biomarker for tumor diagnosis and prognosis in the future.

IL-5 promotes the invasion and metastasis of lung cancer and bladder cancer cells **[89,90]**. IL-6 is a protein of 184 amino acids with a molecular weight of 21-28 kDa **[91]**. IL-6 is mainly produced by macrophages, T-lymphocytes, B-lymphocytes, monocytes, and other cells **[92]**. It is a multifunctional pro-inflammatory cytokine that promotes tumor cell proliferation, invasion, and metastasis, inhibits tumor cell apoptosis, and promotes blood vessel growth **[93]**. IL-6 is implicated in inflammation-induced carcinogenesis **[94]**, whereas its secretion is associated with multiple myeloma, Non-Hodgkin's lymphoma, renal cell carcinoma, bladder and colon cancer **[33]**. In addition it regulates the expression of genes implicated in the survival, proliferation, and angiogenesis, as mentioned, through the JAK - STAT

signaling pathway **[18]**.

Especially, it mainly relies on the activation of multiple signaling pathways to participate in the development of tumors, such as the JAK2/ STAT3 signaling pathway, RAS/MAPK signaling pathway, and PI3K/AKT signaling pathway **[95]**. Upon binding of IL-6 to its receptor (IL-6R), GP130 is activated to form a dimer, which induces JAK1 and JAK2 phosphorylation leading to STAT1 and STAT3 phosphorylation. Phosphorylated STAT3 can enter the nucleus and induce a variety of gene transcription, such as c-FOX, Bcl-2, IRF-1, etc., which are implicated in cell development, differentiation, inhibition of apoptosis, and promotion of vascular formation and cell adhesion **[91,96-98]**. STAT3 can also induce oncogenes that are associated with cell proliferation and metastasis. Moreover, IL-6 binds to IL-6R to activate the PI3K/AKT signaling pathway, which induces JAK and PI3K phosphorylation and activates AKT, to regulate several genes involved in cell survival **[99]**.

In conclusion, IL-6 is implicated in the proliferation, metabolism, metastasis, invasion, and angiogenesis of various tumors and has been found to have high expression of IL-6 in various tumors, such as breast, colorectal, prostate, lung, and ovarian cancer. Xu et al. **[100]**, suggested that serum IL-6 might be a potential biomarker for colorectal cancer and inhibitors of IL-6, IL-6R, GP130, JAK, and STAT3 may be targets for tumor treatment in the future.

IL-8 is mainly produced by endothelial cells, epithelial cells, fibroblasts, etc., its active form is composed of 69,72,77, and 79 amino acids, respectively, and has a molecular weight of about 8 kDa **[101]**. Their receptors are CXCR1 and CXCR2, and generally only undergoes biological function when it binds to a receptor. Yung et al. **[102]** found that IL-8 binds to CXCR2 and activates transforming factor-β-activating enzyme 1 (TAK1)/NF-κB signaling, which in turn increases the invasiveness of ovarian cancer cells. In another research, Sharma et al. **[103]** observed that IL-8 binds to CXCR1/ CXCR2 and indirectly promotes proliferation, angiogenesis, and invasion of cancer cells and promotes glioblastoma multiforme progression, and the level of IL-8 was higher and the patient's prognosis was worse. Moreover, Zheng et al. **[104]** recorded that M2 macrophages produced IL-8, which activated STAT3 and phosphorylated it, leading to increased expression of lung adenocarcinoma transcript-1 that was associated with lung adenocarcinomas metastasis.

IL-8 can induce PI3K phosphorylation and then can activate AKT phosphorylation, which in turn increases cancer cell survival, blood vessel development, and migration **[105]**. IL-8 also regulates survival, cell proliferation, and invasion by activating MAPK and ERK1/2 phosphorylation**[105]**. IL-8 is highly expressed in many types of cancers, such as lung, colon breast cancer, etc. **[106]**, and is closely related to tumor invasion, development, and metastasis **[107-109]**.

Moreover, is involved in proliferation, angiogenesis and in the metastasis of cancer cells in melanoma, ovarian cancer, astrocytomas, anaplastic astrocytomas and glioblastomas **[33,110]**. IL-11 is a stromal cell-derived cytokine, acts widely in hematopoietic and non-hematopoietic systems. It acts with IL-3 in shortening the Go period of early progenitors, facilitates the development of certain types of plasmacytoma and hybridoma cells, and megakaryocyte colony formation and maturation, and acts as an autocrine growth factor in megakaryoblastic cell lines. It is also responsible for erythrocytopoiesis stimulation, enhances antigen-specific antibody responses, induces acute phase proteins synthesis, inhibits lipoprotein lipase activity and adipocyte differentiation, and promotes neuronal development. Its receptor and signal transduction share partially those of IL-6 **[111]**.

Yang et al. **[112]** and Lay et al. **[113]** found that IL-11 is involved in the development of esophageal squamous cell carcinoma and endometrial cancer.

IL-15 is a pleiotropic cytokine with many biological functions in many diverse cell types. It plays a critical role in the development of inflammatory and protective immune responses to microbial invaders and parasites by modulating immune cells of both the innate and adaptive immune systems **[114]**. It seems to be also a controversial cytokine that most researchers have found to show anticancer activity, however Gupta et al. **[115]** recorded that it promoted colonal expansion of B cell chronic lymphocytic leukemia.

IL-17, also known as IL-17A, links T cell activation to NPN mobilization and activation, and can mediate protective innate immunity to pathogens or contribute to the pathogenesis of inflammatory diseases, such as rheumatoid

arthritis and psoriasis. Moreover, has an emerging role in periodontal disease pathogenesis, as evidence from human and animal model studies suggests that the net effect of IL-17 signaling promotes disease development. In addition to promoting neutrophilic inflammation, IL-17 has potent pro-osteoclastogenic effects that are likely to contribute to the pathogenesis of periodontitis, rheumatoid arthritis, and other diseases implicating bone immunopathology **[116]**.

Concerning its role in cancer, IL-17 acts as a growth factor in cutaneous T-lymphoma as well as an angiogenesis key regulator **[117]**. In addition, some researchers found that IL-17A can promote the formation of tumor blood vessels **[118,119]**, thereby contributing to the proliferation and invasion of tumor cells.

IL-23 is another tumor-promoting cytokine **[120]**. It is mostly expressed by TAMs in a manner dependent on STAT3 and NF-κB **[121]**. IL-23 blockade with neutralizing antibodies or genetic inactivation of the IL-23p 19 gene dramatically decrease tumor multiplicity and development in the two-stage model of skin carcinogenesis **[120]**.

Partially, the pro-tumorigenic effects of IL-23 may be mediated by IL-17 and IL-22 production by Th17 cells, but other effects of IL-23 on CTLs, Tregs, and myeloid cells should be noticed. A close relative of IL-23 is IL-12, which shares with IL-23 the IL-12p40 subunit and is implicated in Th1 differentiation, IFN-γ production, and activation of anti-tumor immunity **[122]**. Secretion of IL-23 and IL-12 are mutually regulated and the alteration from IL-12 to IL-23 production may be an important tumor promoting event. STAT3 activation, ATP, PGE2, and lactic acid increase IL-23 production by TAMs **[121,123]**. The latter two agonists link cancer cell necrosis, induced by hypoxia or therapy, and the Warburg effect (the switch from oxidative phosphorylation to glycolysis) to IL-23 production, thereby shifting antitumor immunity to tumor promotion.

Wang et al. found that IL-23 promotes the development of gastritis, which might lead to gastric cancer **[124]**, and Li et al. found that IL-23 can also promote the metastasis of liver cancer **[125]**. IL-33 is a new member of the IL-1 superfamily of cytokines that is expressed by mainly stromal cells, such as endothelial and epithelial cells, and its expression is up-regulated following proinflammatory stimulation. It can function both as a traditional cytokine and as a nuclear factor regulating gene transcription. It is considered to act as an 'alarmin' released following cell necrosis to alerting the immune system to tissue damage or stress. IL-33 mediates its biological effects via interaction with the ST2 receptors (IL-1RL1)and IL-1 receptor accessory protein(IL-1RAcP), both of which are widely expressed, particularly by innate immune cells and Th2 cells. It strongly induces Th2 cytokine production from these cells and can promote Th2-related disease pathogenesis such as anaphylaxis, asthma, and atopic dermatitis. On the other hand, IL-33 has shown various protective effects in cardiovascular diseases such as atherosclerosis, cardiac remodeling, obesity, and type 2 diabetes mellitus. Consequently, the effects of IL-33 are either proor anti-inflammatory depending on the disease and the model **[126]**.

Concerning its role in cancer, IL-33 can inhibit the growth of lung adenocarcinoma **[127]**, it is also involved in glioma cells invasion and migration **[128]**, promotes the proliferation of colorectal cancer cells **[129]**, and ovarian cancer **[130]**.

Besides cytokines, chemokines are also implicated in the development of inflammatory tumors. CCL11 plays an important role in ovarian cancer cells proliferation and invasion **[131]**, and glioblastoma progression **[132]**. It has been revealed that the CXCR2 chemokine receptor and its ligands promote leukocyte infiltration in the tumor microenvironment, and angiogenesis. In the tumor microenvironment acidic and hypoxic conditions, up-regulating the CXCR4 expression forms a gradient prepared by CXCL12 for migration of cancer-associated fibroblasts (CAF). The axis CXCL12-CXCR4 facilitates metastasis to distant locations and organs and the CCL21-CCR7chemokine ligand-receptor pair supports metastasis to lymph nodes. Those two chemokine ligand-receptor systems are main key mediators of tumor cell metastasis for several malignancies **[133]**. It has been observed that cancer cells secrete, or induce fibroblasts to secrete the CCL5 chemokine, that acts in an autocrine or paracrine manner on tumor cells, which express their receptor (CCR5). That pathway promotes tumor cells proliferation and recruitment of T-reg cells and monocytes to induce osteoclasts activation and bone metastases, by inducing neo-angiogenesis, and to facilitate tumor cells

spread in distant organs. It is considered that CCL5, produced by classic Hodgkin lymphoma (cHL) cells may represent an autocrine growth factor of the tumor cells by creating a microenvironment contributory to tumor progression, whereas CCL5 secreted by fibroblasts or T cells may represent a paracrine growth factor. TCD4+ cells expressing CD40L increase the secretion of CCL5 by cHL cells and induce secreting CCL5 by fibroblasts, which promote activated fibroblasts recruitment by cHL cells, which in turn recruit T-reg cells, mast cells, and eosinophils **[52]**.

It has been recorded that a chemokine of the CXC family, CXCL8, exercises its effects through signaling two G-coupled receptors, CXCR1 and CXCR2 protein. Elevated CXCL8 signaling-CXCR1/2 within the tumor microenvironment of diverse types of cancers promotes tumor progression through the activation of signaling pathways implicated in activation of survival, proliferation, angiogenesis, migration, and cell invasion, through the epidermal growth factor receptor transactivation (EGFR) **[134]**.

Tumor angiogenesis and development stimulation, directly or indirectly through recruitment of TAMs, are typical conditions in which chemokines promote tumor development. On the other hand chemokines may be useful in cancer patients, as they act on the recruitment of dendritic or effector cells or in their vasostatic properties **[135]**. The CXCR4 and CCR7 chemokine receptors are expressed at high levels in breast cancer cells and its metastases, whereas CXCR 4 receptor and stromal cell-derived factor-1 (SDF 1), induce proliferation in ovarian cancer cells, and they are expressed at high levels in prostate cancer and melanoma**[27]**.

In conclusion, chemokines and their receptors have a critical role in determining the metastatic destination of tumor cells.

NF-κB pathway in inflammation and cancer pathogenesis

Besides IL-1, IL-6, and IL-8, other pro-inflammatory biomarkers are also associated with the occurrence and development of cancer, such as TNF-α, TGF-β, BCA-1, etc. Those pro-inflammatory biomarkers generally promote the development of cancer by activating signaling pathways.

The transcription factor NF-κB was discovered as a nuclear factor that binds to the enhancer element of the immunoglobulin kappa light-chain of activated B cells **[136]**. The next observation was that proteins which harbor this specific DNA binding activity are expressed in all cell types and regulate many target genes with a whole variety of functions **[137]**.

Five members of NF-κB have been identified, designated as NF-κB1/p105, NF-κB2/p100, RelA/ p65, RelB and c-Rel, which can form various heterodimers or homodimers and bind to consensus DNA sequences at promoter regions of responsive genes. In contrast to the other family members, NF-κB1 and NF-κB2 are synthesized as pro-forms (p105 and p100) and are proteolytically processed to p50 and p52, respectively**[138,139]**. All members of the family form homo- or heterodimers and share some structural features, including a Rel homology domain (RHD), which is essential for dimerization as well as binding to cognate DNA elements **[140]**.

Transcription factors NF-κB family has an essential role in inflammation and innate immunity. Moreover, NF-κB is increasingly recognized as a crucial factor in many stages of cancer initiation and progression **[141]**. NF-κB has been shown to be a linker of inflammation and cancer in mouse models **[142]**.

NF-κB signaling pathway is activated by a number of stimuli, such as cytokines, and cooperates with multiple other signaling molecules and pathways. Prominent nodes of crosstalk are mediated by other transcription factors such as p53 and STAT3 or the ETS related gene ERG. Those transcription factors either affect NF-κB target genes or directly interact with NF-κB subunits. Crosstalk can also be observed through different kinases, such as GSK3-β, P38 or PIK3 which modulate NF-κB transcriptional activity or affect upstream signaling pathways. Molecules that act as nodes of crosstalk are ROS and miRNAs **[143]**.

NF-κB is able to be activated by a number of stimuli, as mentioned, and more than 100 genes are induced on its activation **[144]**. The NF-κB signaling pathways **[145]** concern the classic pathway that is activated by inflammatory signals including TNF-α, IL-1, TLRs, NODs, viruses, and antigen receptors, resulting in the coordinated expression of multiple inflammatory and innate immune genes. Signal transduction pathways from receptors to NF-κB have been extensively investigated, and a number of adaptor molecules

are implicated in that process. The alternative pathway is strictly dependent on IKK-β homodimers and is activated by lymphotoxin β, B cell-activating factor belonging to the TNF family (BAFF), and CD40 ligand (CD40L). That pathway is important for survival of premature B cells and development of secondary lymphoid organs, however, may have a limited importance in inflammation-associated tumors. The classic NF-κB pathway activates the tripartite IKK complex, resulting in phosphorylation-induced I-κB degradation **[145]**. The classic IKK complex main components are I-κB-kinase-1 and the NF-κB essential modulator (NEMO) also known as inhibitor of NF-κB kinase subunit gamma (IKK-γ). IKK-2, the essential kinase for the classic pathway, phosphorylates Iκ-B, followed by ubiquitination and potential proteasomal degradation. Following I-κB degradation, NF-κB translocates to the nucleus, where it binds and activates κB motif-containing promoters. NF-κB classic pathway is responsible for the activation of the most predominant NF-κB dimer, p65:p50 **[143]**.

Translocation of p65:p50 to the nucleus leads to the transcription of pro-inflammatory genes, such as cytokines (IL-1, IL-6, TNF-α, GM-CSF, IL-4), chemokines (IL-8, RANTES, macrophage inflammatory protein-1$^{\alpha}$, monocyte chemotactic protein-1), adhesion molecules (E-selectin, vascular cell adhesion molecule-1, intercellular adhesion molecule-1), pro-angiogenic factors (VEGF), anti-apoptotic proteins (Bcl2, Bcl-XL, FLIP, cIAP) and inducible enzymes (COX-2, iNOS, MMP-9). Most of those genes overlap with the STAT1 and STAT3 target genes activated by inflammatory stimuli, as the promoter region of many of those genes contains GAS or ISRE sites (STAT-binding elements or IRF binding elements) in addition to κB (NF-κB binding element) regions **[143,145]**.

Consequently, those target genes are often additively or synergistically activated in combination with NF-κB activating stimulation and STAT-activating cytokines. TNF signaling pathway is the substance of extensive cross-talk between apoptosis, NF-κB and JNK signaling**[143,145]**. In case of absence of NF-κB activity, cellular susceptibility to TNF-induced apoptosis increases,whereas the enforced activation of NF-κB protects against apoptosis. In addition, TNF-induced JNK activation is stronger and more prolonged in cells lacking NF-κB, resulting in apoptosis promotion **[145]**.

Transcription factors NF-κB family has been revealed to be a critical factor in many stages of cancer pathogenesis including initiation and progression, cooperating with multiple other signaling molecules and cellular signaling pathways. NF-κB action is mediated by transcription factors such as p53 and STAT3 or the ETS-related gene (ERG), which directly interacts with NF-κB subunits or affects NF-κB target genes. Diverse kinases, such as p38, GSK3-β, or PI3K, are able to modulate NF-κB transcriptional activity or affect upstream signaling pathways. Other categories of molecules that can also act in the integration of those mechanisms implicating NF-κB are ROS and miRNAs **[38]**. NF-κB also regulates many cytokines expression and adhesion molecules which are critical components implicated in the immune responses regulation **[146]**.

Inflammatory mediators such as interleukins, TNF-α, COX-2, 5-lipooxygenase (5-LOX) and MMP-9 are regulated by the factor NF-κB. Although NF-κB is expressed in an inactive status in many cells, the cancer cells express an activated form of NF-κB. That activation is induced by many inflammatory stimuli and carcinogens and the gene products regulated by NF-κB mediate tumorigenesis. NF-κB activity is triggered in response to infectious agents and pro-inflammatory cytokines through the IKB kinase (IKK) complex **[147]**.

It seems that cigarette smoke that contains diverse carcinogens, that care able to initiate and promote carcinogenesis and metastasis, are also able to activate NF-κB factor in many cells and this may play a crucial role in smoking-induced carcinogenesis **[148]**. Its activation has been implicated in malignancies such as nasopharyngeal carcinoma and melanoma. Previous researches have recorded that cancer cells show an increase in pro-inflammatory cytokines production such as TNF-α, IL-1α and IL-6. The regulation those pro-inflammatory cytokines expression involves the NF-kB factor that can be activated by cytokines such as TNF-α. It has been revealed that RET-mediated carcinogenesis depends significantly on IKK activity and subsequent NF-κB activation. The anti-apoptotic response and increased cellular proliferation found in neoplasms cells overexpressing metallothionein (MT) is also mediated by the

NF-κB signaling pathway **[33]**.

NF-κB target genes have many functions and a close association between NF-κB and cancer has been extensively recorded **[149-151]**. An inflammation-dependent colon tumor-model inmice, in which tumors developed after a single dose of genotoxic colonic carcinogen, azoxymethane (AOM), followed by dextran sodium sulfate (DSS) was recorded**[152]**. In that model, IKK-β deletion in intestinal epithelial cells did not decrease inflammation, but rather, resulted in a dramatic decrease in tumor incidence without affecting tumor size **[153]**. On the contrary, IKK-β deletion in myeloid cells resulted in a significant decrease in tumor size. IKK-β deletion re-duces pro-inflammatory cytokines expression that may serve as tumor growth factors. Especially, IL-6 has been shown to be involved in tumor growth, whereas TGF-β has been shown to antagonize IL-6 function **[55]**.

Consequently, the IKK/NFκB pathway specific inactivation in both epithelial and inflammatory cells can attenuate the inflammation-associated tumors generation.

An extra role of NF-κB in inflammation-associated cancer was also recorded in Mdr2- deficient mice, which develop cholestatic hepatitis followed by hepatocellular cancer (HCC) **[154]**, as in that model, the inflammatory process triggered chronic activation of NF-κB in hepatocytes, most likely through the TNF-β enhanced production by adjacent inflammatory cells. NF-κB activity suppression in Mdr2-/- mice from birth to 7 months of age revealed no effect on the early stages of carcinogenesis. In contrast, NF-κB inhibition in tumor development later stages resulted in apoptosis of transformed hepatocytes and failure to progress to HCC. Consequently, NF-κB suppression in tumors, that was associated with TNF-β increased levels could induce cancer cells apoptosis. This is possibly because the caspase and JNK pathways downstream of TNF-R1 be-come predominant in the absence of NF-κB activation.

NF-κB activation is also implicated in inflammation driven tumor progression, as confirmed in a syngeneic colon and mammary cancer xenograft mouse model **[155]**. After metastasized tumors were established, a sub-lethal dose of lipopolysaccharide (LPS) were given to the mice to get systemic inflammation, that stimulated tumor development. LPS-induced metastatic growth response was depended on both TNF-β from host hematopoietic cells and NF-κB activation in tumor cells. Specifically, the NF-κB inhibition in cancer cells transforms the LPS- induced growth response to LPS induced tumor regression. The mentioned transformation was not dependent on TNF-α but on TRAIL, a member of the TNF superfamily, whose receptor is induced in NF-κB-deficient cancer cells by IFNs from host inflammatory cells **[143]**. Consequently, NF-κB inhibition in tumor cells in combination with IFN administration may promote the TRAIL activity to achieve enhanced tumor apoptosis. It is possible that the inhibition of NF-κB in both tumor and inflammatory cells seems to be an effective therapeutic way to prevent cancer progression.

The activation and interaction between NF-κB and STAT3 have been widely investigated in cancers such as stomach, liver, and colon cancers, and it has been observed that the interaction between those transcription factors is important for controlling the communication between inflammatory and cancer cells. NF-κB and STAT3 are the main factors that control the capacity of pre-neoplastic and malignant tumor cells to resist immune surveillance by regulating tumor invasion, angiogenesis and apoptosis. It is possible that the perception of the molecular mechanisms of NF-κB and STAT3 cooperation in cancer development will result in design of new chemopreventive and chemotherapeutic approaches **[156]**.

Moreover, NF-κB synchronizes the central signaling pathways of the innate and adaptive immune responses activation and that STAT3 regulates the various genes expression in response to cellular stimuli, playing an important role in cell development and apoptosis. It has also been revealed that STAT3 is constitutively activated in many cancers, including gastric cancer and is implicated in modulating proliferation, survival of cancer cells and creating a favorable microenvironment to the metastasis formation **[157]**.

Conclusion

Therefore, since so many inflammatory and pro-inflammatory factors are associated with tumors, whether

these factors can be used as biomarkers for specific tumor prediction, prevention, and prognosis is worthy of further study.

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