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Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer

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Abstract

Inflammatory cytokines are highly inducible small glycoproteins or regulatory proteins of low molecular weight secreted by different cell types. They regulate intercellular communication and mediate a number of physiological functions in the human immune system. Numerous prospective studies report that inflammatory cytokines strongly predict coronary artery disease, myocardial infarction, heart failure and other adverse cardiac events. Inflammatory cascade is believed to be a causative factor in the development of atherosclerotic process. Several aspects of atherogenesis are accelerated by cytokines. This article provides an overall overview of current understanding of cytokines in various cardiovascular events. Besides, inflammatory cytokines trigger cellular events that can induce malignancy and carcinogenesis. Elevated expression of several cytokines such as interleukin-1, interleukin-6, interleukin-10, tumor necrosis factor-α, macrophage migration inhibitory factor and transforming growth factor-β are involved in tumor initiation and progression. Thus, they exert a pivotal role in cancer pathogenesis. This review highlights the role of several cytokines in various events of tumorigenesis. Actually, this article summarizes the contributions of cytokines in the pathogenesis of cardiovascular disease and cancer.

Keywords

Cytokines, inflammation, cardiovascular diseases, cancers

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Introduction

Inflammation is a normal response of body's tissue to injury.[1] It is a basic process whereby the body reacts to injury or infection.[2] It is a tissue-destroying localized biological reaction initiated by various factors ranging from microbial infection and chemical injury that result in cell death or cell injury.[3,4] Actually, it is a nonspecific immune response. The main features of inflammation are redness, pain, warmth and swelling.[2] There are mainly two types of inflammation, that is, acute and chronic.[3] Acute inflammation is of a short duration and this inflammatory response is characterized by rapid onset. It is caused by the migration of neutrophils and exudation of plasma proteins and fluids into the injured part of the body.[3] Chronic inflammation manifests by the presence of macrophages and lymphocytes. It is of a prolonged duration.[3] This inflammatory response may be a causative factor in the development of a variety of degenerative diseases like cancer, Alzheimer, rheumatoid arthritis, multiple sclerosis, asthma, congestive heart failure (CHF), diabetes, inflammatory bowel disease, atherosclerosis, gout, aging, acquired immunodeficiency syndrome and central nervous system (CNS) depression.[5,6] Besides, it is mentioned that prolonged action or exaggeration of inflammation may directly harm the body in many ways.[2]

It has been described that inflammatory mediators such as cytokines contribute a significant role in inflammation.[7,8] Inflammatory responses are coordinated by cytokines.[4]

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Cytokines are glycoproteins or regulatory soluble proteins of low molecular weight secreted by different cell types including WBC (white blood cell) in the body. Various cytokines modulate the proliferation and differentiation of immune cells.[4,9] Cytokines are also known as lymphokines, monokines and interleukins as they are secreted by lymphocytes, monocytes and leukocytes accordingly. Moreover, one particular type of cytokines such as monocyte inflammatory protein (MIP-1α and MIP-1β), monocyte chemoattractant protein (MCP-1) and growth-related oncogene (GRO/KC) is known as chemokines as they induce chemotaxis.[10] Pober and Cotran[11] in 1990 reported that lymphocytes and activated tissue macrophages primarily secrete inflammatory cytokines in response to various inflammatory stimuli, such as endotoxin, chemical and physical injury. There are two major groups of inflammatory cytokines: those responsible for acute inflammation and those involved in chronic inflammation. Acute inflammation is caused by cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-11, TNF-α (tumor necrosis factor-α), IL-16, IL-17, G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor).[12] Besides, involvement of cytokines in chronic inflammation can be subdivided into two classes: cytokines coordinating humoral responses are IL-4, IL-5, IL-6, IL-7 and IL-13, and those for cellular responses are IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons, and TNFα and β. Few cytokines significantly play a role in both acute and chronic inflammation, such as IL-1, IL-6, IL-11, IL-17 and TNF-α.[12] Besides, the IL-1 family of cytokines also comprises two ligands with anti-inflammatory activity (IL-37, IL-38).[13]

This review highlights the role of inflammatory cytokines in the pathogenesis of cardiovascular diseases (CVDs) and cancer.

Inflammatory cytokines and CVDs

CVD is a chronic inflammatory state of the blood vessels. It is a major socioeconomic problem and also a threat of public health throughout the world, since they significantly contribute to the global morbidity. Some common CVDs, including atherosclerosis, vascular disease and heart disease, occupy a strong position in the structure of disability and mortality worldwide.[14,15]

Different heart diseases, including coronary heart disease (CHD), atherosclerotic heart disease and CHF, are associated with increased levels of proinflammatory cytokines such as interferon-γ (IFN-γ), IL-1β, IL-6 and TNF-α.[16] These cytokines contribute a significant role in the formation of atherosclerotic plaque. The atheroma, an accumulation of macrophages, lipid-laden cells, mast cells, T cells and other degenerative material, occurs in the inner layer (also known as "tunica intima") of artery walls (endothelium) by a fatty streak.[16–19] Then various inflammatory molecules, cytokines and chemokines are released by the action of activated macrophages which lead to tissue damage and, ultimately, to inflammation. Thus, the formation of atherosclerotic plaque is promoted.[19–21] Actually, inflammatory cytokines contribute a great role in the development of atherosclerotic plaques. Importantly, such plaques or lesions induce endothelial dysfunction. Thus, normal function of endothelium is disrupted and primary stage of atherosclerotic process stimulated.[14] Besides, inflammatory cytokines are also well known to induce numerous chronic inflammatory disorders. Recent study has reported that increased release of cytokines, including TNF-α, IL-6 and IL-1, promote the expression of proatherogenic gene.[22] The retention and infiltration of the tunica intima of endothelium stimulate an inflammatory process in the vessel wall.[19] Modification of lipoprotein LDL (low-density lipoprotein), through enzymatic attack or oxidation in the inner layer, stimulates the release of phospholipids. Thus, endothelial cells can be activated which may accelerate the expression of inflammatory genes. Hence, the accumulation of lipid-laden cells or lipids may start an inflammatory cascade in the artery.[23,24] Within the tunica intima, chemokines recruit monocytes which differentiate into macrophages that trigger the development of foam cells. The macrophages also multiply and secrete various inflammatory cytokines and growth factors, thus amplifying proinflammatory signals.[25] This step is very much essential for the proper development of atherosclerotic lesions.[26] Besides, this step upregulates toll-like receptors.[19] Such type of receptors through stimulating a signal cascade leads to cell activation. The activated macrophage releases cytotoxic oxygen, proteases, nitrogen radical molecules and inflammatory cytokines.[27] Mast cells, dendritic cells and endothelial cells also show similar effects. Numerous toll-like receptors recognize bacterial toxins, DNA motifs and stress proteins.[27] Furthermore, oxidized LDL particles and heat-shock protein 60 of human being may stimulate toll-like receptors.[28,29] Cells in atherosclerotic plaques show a spectrum of these receptors and inflammation of atherosclerosis may be dependent on this pathway.[30,31]

T cells, the immune cells, also contribute in atherogenesis.[25] Natural killer T cells are available in early atherosclerotic plaques. Lipid antigens are recognized by these cells. The activation of these killer cells induces atherosclerotic lesions in ApoE knockout mice.[32] This type of cells also recognizes various viral antigens, which may be available in the plaques. Moreover, activation of these cells in knockout mice may promote the arterial cell death and initiate or stimulate atherosclerosis.[33] T-cell activation also triggers the secretion of a set of inflammatory cytokines. Two stereotypical responses in inbred mice can be obtained: response of the type 1 helper T cells (Th1) activates inflammatory macrophages and type 2 helper T cells (Th2) accelerates allergic inflammatory processes.[19,34] Cytokines which induce a Th1 response are available in the atherosclerotic plaques.[19,35] Therefore, activated T cells mature into Th1 effector cells and start releasing a macrophage-stimulating cytokine, IFN-γ, which in turn

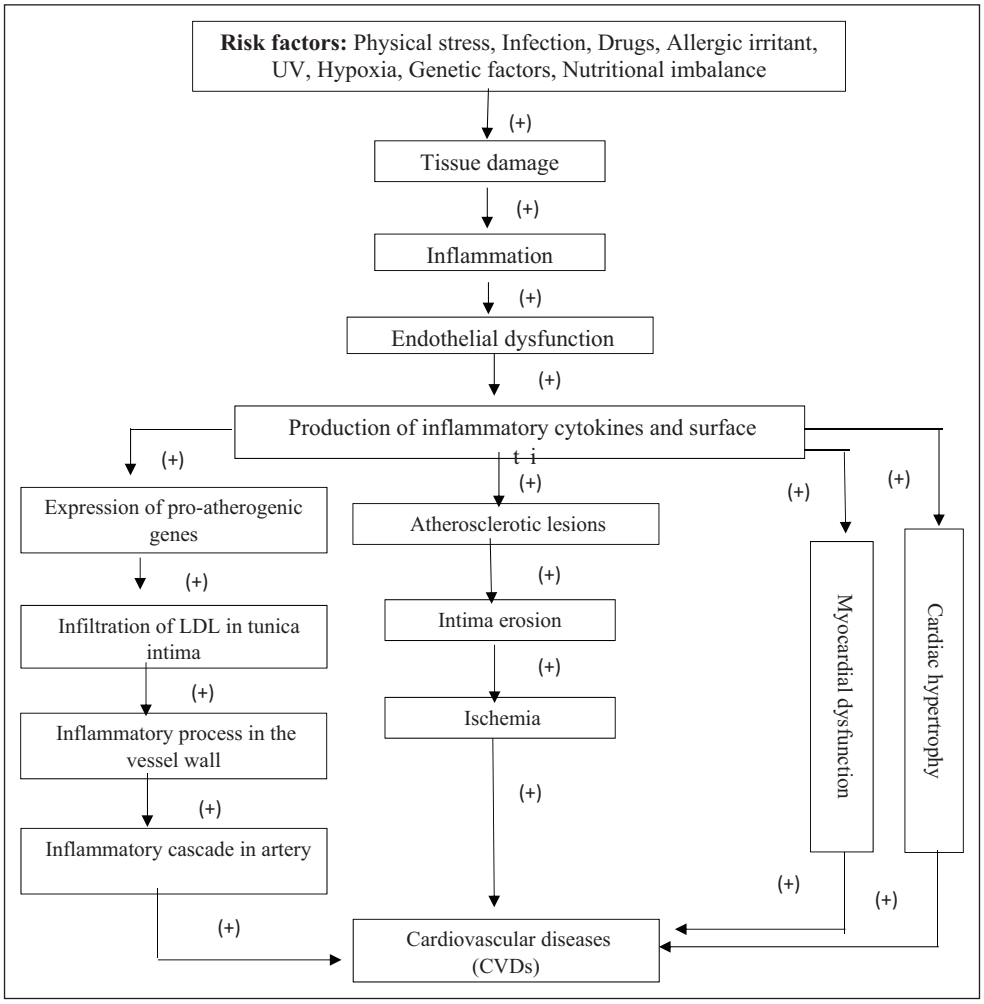

Figure 1. Mechanism of CVDs induced by inflammation ("+" = increased).

promotes the synthesis of inflammatory TNF and IL-1.[34] These cytokines synergistically contribute a role in the production of different cytotoxic and inflammatory molecules in vascular cells.[36] All these effects trigger the formation of atherosclerotic lesions (Figure 1). Smoking, hypercholesterolemia, hypertension, diabetes and obesity are well-recognized atherogenic risk factors.[36,37]

Cytokines in the development of myocardial infarction and coronary artery disease

Inflammation contributes a significant role in the etiology of myocardial infarction (MI), hypertension, angina pectoris (AP), and ischemic heart disease (IHD) or coronary artery disease (CAD).[19,38] MI is caused by atheromatous process, since this process blocks coronary artery inhibiting proper blood flow through it.[19] Atherosclerosis is the major cause of IHD. Intima erosion is caused by atherosclerosis, which leads to subsequent ischemia.[38] Chemokines, including MCP-1, MIP-α, IFN-γ-inducible protein (IP-10) and eotaxin, play a significant role in the pathogenesis of CAD.[39] MCP-1, also known as CCL2 (MCP-1/CCL2), is chemotactic to monocytes and contributes a role in the development of disorders associated with infiltration of monocytes.[40,41] Besides, several studies have reported that elevated levels of C-reactive protein (CRP) and IL-6 are strongly associated with the risk of CAD.[38] CRP is a plasma protein which comes from the liver. The synthesis of CRP is generally regulated by IL-6, which in turn is upregulated by IL-1 and TNF-α.[42] Moreover, smooth muscle cells (SMCs) and monocytic cells also produce CRP in atherosclerotic plaques, more specifically in the tunica intima of endothelium, where it co-localizes with lipoproteins, inflammatory monocytes and monocyte-derived macrophages. This localization ensures a significant contribution to the atherosclerosis.

Furthermore, CRP directly facilitates and amplifies innate immunity, which in turn initiates CHD.[41] Therefore, there is a strong relationship between increased level of high-sensitivity CRP (hsCRP) and inflammatory coronary events.[38] CRP is a causative factor and also an independent predictor

of MI, peripheral arterial disease, stroke and other cardiac events.[14] Cytokines contribute a cytoprotective role in the primary stage of MI, by decreasing cell apoptosis. CRP facilitates further inflammatory incidence of myocardial cells.[43] Besides, different types of pathogens, including herpes family viruses, have a contribution to CAD. Cytomegalovirus induces atherosclerosis through modulating vascular cell activity. It contributes to atherosclerotic lesions causing graft rejection.[19]

Cytokines in the development of heart failure

Heart failure (HF) is a multistep disease. Gullestad et al.[44] in 2012 stated that "Heart failure (HF) is a highly complex multistep disorder in which a number of physiological systems participate." Inflammation participates in the development of HF.[44] Numerous studies have described increased expression and secretion of inflammatory cytokines including IL-1, IL-6, IL-18, TNF-α and cardiotrophin-1 (CT-1), as well as various chemokines such as monocyte chemoattractant peptide (MCP)-1/CCL2, IL-8/CXCL8, CXCL16 and CCL21 in HF patients. Levels of these inflammatory molecules in plasma appear to be increased in direct proportion to deterioration of cardiac performance.[44] Increased expression of these inflammatory mediators or molecules has also been shown within the failing myocardium.[45,46] Numerous researches have explored that the biological effects of inflammatory mediators, including cytokines, may explain different aspects of the syndrome of chronic HF. Furthermore, the pathogenic role of these cytokines in HF is supported by many transgenic animal models.[44] Recently, many researches in gene-modified mice have revealed a link between IL-6, as well as several chemokines (e.g. MCP-1), and the development or progression of HF.[47] Various inflammatory mediators and cytokines are upregulated in HF.[44] By directly acting on cardiomyocytes and fibroblasts, cytokines stimulate hypertrophy and fibrosis. Cytokines impair myocardial contractile function through acting on intracellular calcium transport. They may also stimulate genes involved in myocardial remodeling. Thus, cytokines or inflammatory mediators may modulate myocardial functions.[48] Besides, numerous studies have observed increased CRP levels in HF. Hence, CRP is believed to contribute to chronic HF.[44]

Inflammatory cytokines and cancers

Cancer is a genetic disorder. It is mainly characterized by uncontrolled proliferation of abnormal cells.[49,50] Chronic inflammatory responses are directly associated with different types of cancers. The inflammatory response is a cascade of physiological and immunological processes. Various cytokines and chemokines are involved in the inflammatory mechanism.[51] Besides, proinflammatory mediators recruit inflammatory response–related immune cells such as natural killer (NK) cells, macrophages, activated T-cytotoxic cells and neutrophils to the inflammatory region. These mediators also induce the production of several acute phase reactive proteins including CRP and serum amyloid A (CAA). All of these accelerate the inflammatory processes.[16] Furthermore, epidemiological evidence suggests that chronic inflammation is responsible for up to 25% of all cancers.[52]

How cytokines contribute to cancer development?

Cytokines regulate differentiation, proliferation, cell migration, cell death and immune cell activation.[53] TNF-α is a carcinogenic cytokine and it has two receptors, known as TNF-α receptor-1 (TNF-α R-1) and TNF-α R-2.[54] This cytokine induces tumor cell survival by promoting antiapoptotic mechanisms through the stimulation of certain genes. TNF-α also triggers the production of various genotoxic molecules such as reactive oxygen species (ROS) and nitric oxide, which can lead to DNA damage and ultimately to tumorigenesis.[54,55] IL-6 is another cytokine that participates in carcinogenesis.[56] It is a potent antiapoptotic and growth-promoting factor.[55] By attaching to its receptor (IL-6Rα), IL-6 phosphorylates the STAT (signal transducers and activators of transcription) proteins: STAT1 and STAT3. STAT proteins contribute a significant role in the tumorigenic processes. STAT3 protein is an oncoprotein that is available in different types of cancers. It proliferates malignant cells. Actually, it exerts its activity by directly binding to target genes.[54–58] Furthermore, IL-17 and IL-23 can initiate tumorigenesis by stimulating IL-6/STAT3 pathway in an experimental animal model.[58] Besides, transforming growth factor-β (TGF-β) is a well-documented pleiotropic cytokine. It has three isoforms such as TGF-β1, TGF-β2 and TGF-β3. TGF-β contributes an important role in cell proliferation, invasion, embryogenesis, apoptosis and differentiation.[59,60] TGF-β, IL-6 and TNF-α induce the generation of reactive oxygen and nitrogen species (RONS) in nonphagocytic cells. RONS promote DNA damage which accelerate or initiate tumorigenesis.[54] Also, cytokine polymorphism on gene expression has a great impact on various cancers.[60,61] Moreover, the epithelial mesenchymal transition (EMT) is a cellular reprogramming process during embryogenesis.[62,63] Epithelial cells acquire fibroblast characteristics and show morphological changes during EMT.[64,65] TGF-β promotes EMT progression by contributing a significant role in tumor development and embryogenesis in different EMT models. IL-6 and TNF-α synergistically mediate EMT progression via TGF-β signaling.[54] Both inflammatory cytokines induce nuclear factor-κB (NF-κB) activation, which controls the expression of a variety of transcription factors such as ZEB, Snail and Twist involved in EMT.[66,67]

Low TNF-α levels accelerate tumor growth and promote angiogenesis that generates new blood vessels. Angiogenesis is important in cancer development since the new blood vessel network provides oxygen and nutrients to cancer cells.[68,69]

Tumor cells secrete various angiogenic factors such as vascular endothelial growth factor (VEGF). VEGF is mainly expressed in response to growth factor and cytokines.[69] IL-6 is another angiogenic factor that promotes VEGF expression and induces angiogenesis by signaling the STAT3 pathway in cancer.[54,70] Besides, several inflammatory cytokines modulate metastatic cascade. For example, TGF-β might contribute a significant role in inducing metastasis. During metastasis, neoplastic cell spread from one organ to another.[54,71] Moreover, metastasis is closely associated with EMT that accelerates the migration of tumor cells.[72]

Cytokine-induced breast cancer

Breast cancer (BC) is an inflammation-linked disease affecting millions of people worldwide.[73] Cytokines are well known to regulate tumor microenvironment. Several cytokines including IL-1, IL-6, IL-11 and TGF-β contribute a significant role in the development of BC.[74] Actually, the IL-1 family of cytokines (IL-1α, IL-1β), the IL-1 receptors (IL-1RI and IL-1RII) and the receptor antagonist (IL-1Ra) have been observed to be expressed in human breast cancer cell lines.[74] IL-1 is involved in the development of tumor through the stimulation of angiogenesis and metastasis. It also controls the expression of other tumorigenic cytokines.[73] IL-1 is also known to stimulate expression of various endothelial adhesion molecules such as vascular adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1). ICAM-1 has a significant contribution in invasion of metastatic breast carcinoma cell lines.[75] IL-1β, a member of IL-1 family, has been observed to be expressed in breast cancer. At the cellular membrane, IL-1β through binding of IL-1 receptor I (IL-1RI) induces cellular changes.[75] IL-1β may be closely associated with induction of matrix metalloproteinase-9 (MMP-9), as reported by Wang et al.[76] in 2005. Increased expression of MMP-9 contributes a role in tumor invasion. IL-1β may induce angiogenesis by controlling expression of various angiogenic factors. It also promotes expression of hypoxia-inducible factor-1α, a transcription factor for VEGF in breast cancer cells.[75,76] Cytokine signaling is stimulated upon binding of certain cytokines to specific cognate receptors followed by initiation and induction of several intracellular kinases, including mitogen-activated protein kinase (MAPK), phosphatidyl ionositol-3-kinase (PI3/K)/Akt and Janus-activated kinase (JAK), with subsequent stimulation of transcription factors such as activator protein-1 (AP-1), NF-κB and STAT.[77] IL-6 activates the JAK/STAT signaling pathway by binding to its receptor and coreceptor glycoprotein 130 (gp 130), thus regulating the expression of certain genes involved in suppression of apoptosis and acceleration of proliferation.[78] IL-6 produces MCP-1 and various colony-stimulating factors (CSFs) by stimulating epithelial cells. Thus, serum circulating IL-6 induces breast cancer cell proliferation.[75] Besides, TGF-β is also a regulator of differentiation, proliferation, migration and apoptosis. It promotes tumor vascularity by controlling the expression of VEGF and MCP-1. VEGF enhances the invasion of breast cancer cells through the activation of PI3K/Akt and MAPK signaling.[79] Moreover, the expression of circulating TNF-α level has been observed in human breast carcinomas.[79] TNF-α proliferates breast cancer cells and accelerates estrogen-induced cell proliferation. Also, it stimulates mammary tumorigenesis.[75] This cytokine upregulates certain genes that are responsible for metastasis, proliferation and invasion. Besides, IL-19, IL-20 and IL-23 also induce breast tumorigenesis. IL-19 accelerates the proliferation of the Hs578T and MCF-7 breast cancer cell lines. IL-20 provides a tumor microenvironment.[79,80] Numerous studies have demonstrated the role of chemokines in cell proliferation, invasion and migration. Chemokines are categorized into four groups: CC, XC, CXC and CX3C. Proinflammatory cytokines usually produce chemokines. Chemokines act by attaching with specific receptors in a paracrine or an autocrine manner.[77] CC chemokine ligand-2 (CCL2) and CC chemokine ligand-5 (CCL5) have been studied broadly in breast carcinoma. Both chemokines have been detected in serum of patients with breast cancer. CCL2 contributes a crucial role in angiogenesis, while CCL5 promotes breast cancer cell migration and invasion.[75] Furthermore, increased expression of CXC chemokine ligand-12 (CXCL12) and its receptor CXC chemokine receptor 4 (CXCR4) in breast carcinoma plays a significant role in tumor angiogenesis.[75,81]

Cytokine-induced prostate cancer

Prostate cancer (PCa) is a common malignant tumor in men.[82] PCa has different mortality rate throughout the world. PCa mortality rate in Asia is lower than those in Europe or the United States.[83] Cytokines facilitate the development of prostate tumor.[84] IL-6 is extensively studied in PCa. It exerts its activity by attaching to its receptor and coreceptor. Circulating IL-6 activates the JAK, STAT3 and MAPK pathway, which stimulates the expression of androgen receptor-mediated gene.[85] The IL-6/JAK/STAT signaling pathway has an effect on tumor initiation and progression, as highlighted by numerous studies.[86] IL-6 accelerates cancer development by facilitating transformation of normal noncancer cells into cancer or tumor stem cells.[87] IL-6 induces proliferation in prostate tumor cells such as in LNCaP and MDA PCa 2b.[88,89] Besides, IL-1β is highly and IL-1α is rarely present in the tumor microenvironment. Both cytokines after binding to their receptors could potentiate IL-1 receptor-associated kinase (IRAK). IRAK is then attached to TNF receptor–associated factor (TRAF)-6. Finally, the IRAK/TRAF-6 complex induces the potentiation of NIK (NF-κB-inducing kinase).[90] Thus, IL-1 family of cytokines contributes a significant role in cancer development via NF-κB pathway. Furthermore, macrophage migration inhibitory factor (MIF) accelerates tumorigenesis by preventing the tumor inhibitor

gene p53. MIF promotes expression of a wide variety of inflammatory cytokines.[91] It also interacts with chemokine receptor CXCR2 and CXCR4 and recruits both T cells and monocytes. MIF is overexpressed in various carcinomas including PCa.[91,92] Moreover, PCa progression is also associated with TNF-α. This cytokine is mediated by two receptors, namely TNF-receptor I (TNFRI) and receptor II (TNFRII).[85] TNF-α recruits monocytes and neutrophils to inflammatory sites. It also potentiates vascular endothelial cells to secrete several adhesion molecules for monocytes and neutrophils.[91] Interestingly, TNF-α induces tumor necrosis and angiogenesis.[93] Circulating TNF-α has been found in PCa.[94] Besides, overexpression of TGF-β in tumors also promotes angiogenesis in prostate tumor.[95] CXCL2 is such a chemokine that induces angiogenesis and regulates macrophage infiltration within the tumor, thus facilitating PCa development.[96]

Cytokine-induced colorectal cancer

Colorectal adenocarcinoma or colorectal cancer (CRC) is one of the most frequent types of cancer worldwide. Colorectal carcinogenesis is an aggressive type of carcinoma.[97] Cytokines regulate cancer growth and also induce tumorigenesis, metastasis and invasion of tumors.[98] As a proinflammatory cytokine, IL-6 participates in carcinogenesis.[56] It acts as a growth factor for CRC cells.[99] The circulating levels of IL-6 have been observed to be highly elevated and correlated to tumorigenesis in patients with colon cancer.[99] IL-6/IL-6R complexes contribute in CRC development by inducing the activation of JAK/STAT3, PI3K/Akt and MAPK signaling pathways. In CRC cells, STAT3 is constitutively active.[100–102] TNF-α accelerates the growth of certain cancer cells and causes carcinogenesis.[103] This cytokine is an endogenous tumor promoter, as suggested by numerous preclinical studies. TNF-α has been observed to be expressed in CRC.[77] Another powerful cytokine is TGF-β. Its role in cancer is complex and varying by stage of tumorigenesis. It acts as a tumor inhibitor in early stages of tumorigenesis, inducing apoptosis and suppressing cell proliferation. Later, TGF-β induces metastasis and invasion by promoting EMT.[104] Moreover, MIF, an immune stimulatory cytokine, is overexpressed in CRC.[91] IFN-γ and IL-2 have been rarely detected to be expressed in CRC. Recently, few studies have revealed gene expression of IL-10, IL-8, IL-6, IL-7 and TGF-γ in numerous colon cancer cell lines.[97] An elevated expression of CXCL7 (a chemokine) and its receptor CXCR2 have been observed in patients with CRC, as reported by Uchiyama et al.[105] Furthermore, TNF-α triggers the production of reactive oxygen species (ROS) and nitric oxide (NO). Interestingly, two prominent inflammatory cytokines are TGF-β and IL-6, which together with TNF-α induce the generation of RONS in nonphagocytic cells. RONS, ROS and NO accelerate tumorigenesis by inducing DNA damage.[54,55] ROS and NO can initiate lipid peroxidation to produce other reactive molecules.[106] NO is an important mediator linking inflammation and cancer. During arginine metabolism, NO is produced by various isoforms of nitric oxide synthase (NOS).[107] During inflammation, inducible nitric oxide synthase (iNOS) in macrophages stimulate the production of NO (Figure 2). The levels of NO and iNOS have been detected to be increased in different carcinomas.[108,109] The enhanced expression of iNOS has been observed in colorectal carcinomas.[110]

Cytokine-induced epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is the fifth leading cause of malignancy-related death in women. It is a fatal gynecological malignancy throughout the world.[111,112] Different components stimulating inflammatory pathway such as cytokines, STAT3, NF-κB, iNOS, free radicals and VEGF have been observed to participate in the development of EOC.[113] Cytokines induce ovarian tumor development in vivo.[114] Circulating levels of IL-6, IL-7 and IL-10 have been detected to be enhanced in patients with ovarian cancer.[115] Also, IL-1β and TNF-α have been observed to accelerate EOC progression.[116,117] IL-6 triggers the development of EOC by inhibiting apoptosis, inducing cell proliferation and stimulating angiogenesis.[114] It is an important immune regulatory cytokine. Besides, IL-6 has a significant role in autocrine growth of ovarian tumor cells.[118] High serum levels of IL-6 have been observed in patients with advanced ovarian cancer.[119] Interestingly, IL-6 activates STAT3, an oncoprotein that is overexpressed in EOC tissue. Activated STAT3 in EOC contributes a significant role in the prognosis and invasion.[58,120] Like IL-6, IL-8 also modulates progression of ovarian cancer cells.[121] Moreover, numerous studies have shown increased levels of TNF-α in patients with ovarian cancer. This cytokine is crucial in accelerating tumor growth. TNF-α exerts its activity by binding to its receptors (TNF-Rs).[122] Besides, TGF-β is another cytokine that induces proliferation and differentiation of immune cells. It also prevents antitumor immune response. The expression of TGF-β is elevated in cancer cells.[123] Furthermore, MIF is overexpressed in ovarian cancer. It also promotes expression of other inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-8 and IL-1β in a feedback circuit.[58]

Cytokine-induced hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most frequent form of internal malignancy of the liver and the third most common cause of death from cancer throughout the world.[124,125] Numerous studies report that chronic infection with different types of hepatitis viruses is a risk factor for HCC growth.[126] Infectious agents induce carcinogenesis and are responsible for about 15% of human cancers. Inflammatory cytokines

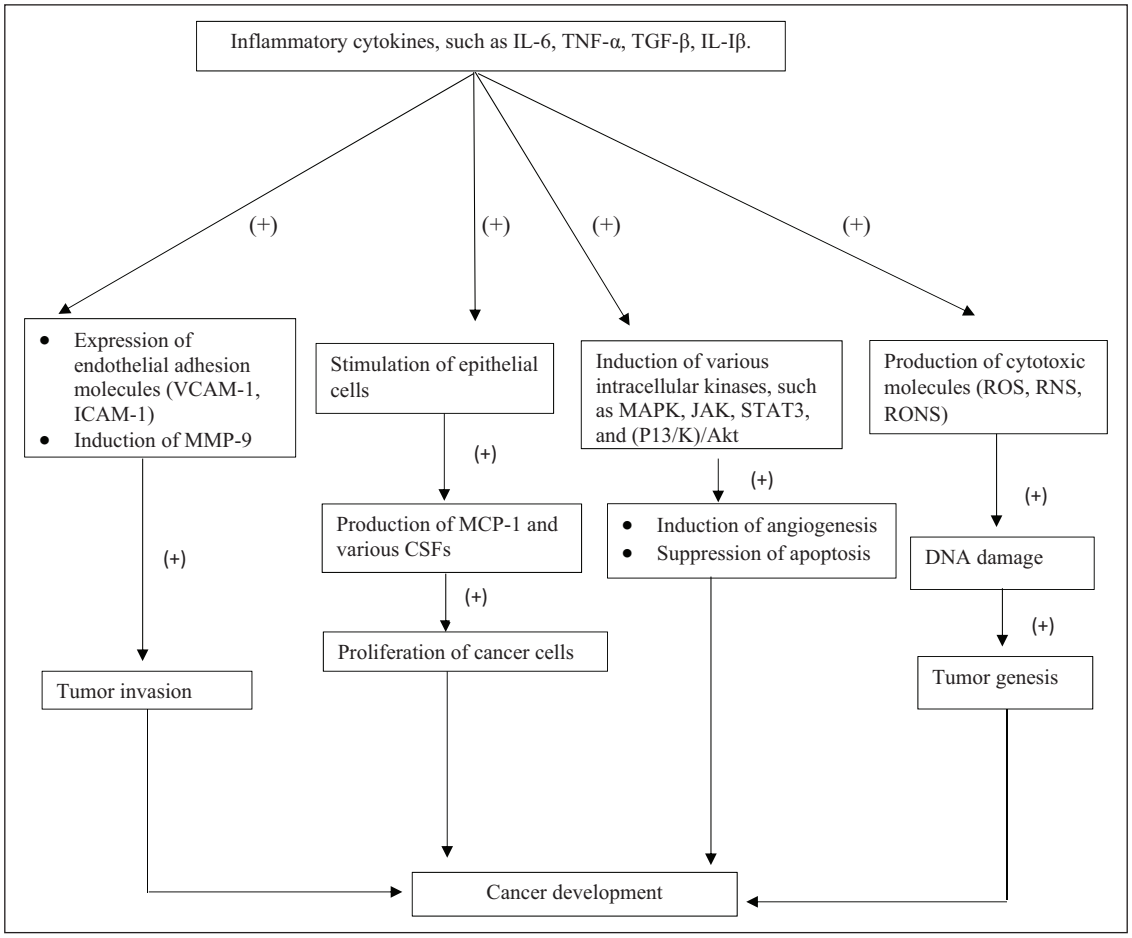

Figure 2. Cytokines in cancer development ("+" = increased).

contribute a significant role in HCC development.[127] TNF-α was shown to be elevated in patients with HCC.[128,129] Moreover, the circulating levels of TNF-αRs were higher in patients with HCC when compared with normal healthy subjects.[130] IFN-γ promotes TNF-α-mediated hepatic damage and also activates macrophages. In the liver, expression of IFN-γ causes chronic hepatitis. Recruitment of lymphomononuclear cells is responsible for this occurrence.[131,132] Raised serum levels of TGF-β1 were detected in HCC patients.[91] A member of the TGF-β family known as "Activin A" and its receptors are found in HCC patients and have been observed to accelerate VEGF transcription. Hence, TGF-β may enhance tumorigenesis.[133] Elevated levels of MIF were shown in hepatocytes from liver cirrhosis patients.[134] Increased levels of MIF associate with angiogenesis.[135] Increased expression of IL-1β was detected in HCC patients versus healthy subjects.[128] Numerous polymorphisms of IL-1β have been described. The IL-1β-511 genotype T/T and the IL-1β-511 genotype C/C were found to be highly expressed in HCC patients when compared with healthy individuals.[136,137] Serum IL-2, IL-10, IL-12 and IL-15 were higher in HCC.[127] In addition, elevated serum concentrations of IL-6 were found in HCC. IL-6 induces T-cell activation. Furthermore, it recruits neutrophils and enhances the proliferation and migration of T lymphocytes into the injured tissue.[91]

Cytokine-induced pancreatic cancer

Pancreatic cancer is another common cause of death from cancer in the Western world.[138,139] Inflammation contributes an important role in the development of pancreatic cancer. Several biological processes including inflammation and immunity are regulated by cytokines. Elevated expression of various cytokines has been detected in pancreatic cancer.[140] Increased levels of IL-6, IL-8, IL-10, IL-12, IL-18, TGF-β and MIF have been observed in patients with pancreatic cancer. In addition, IL-1β and TNF-α are also seen to be highly expressed in patients with pancreatic cancer versus normal healthy subjects.[140] IL-6 participates in tumorigenesis by inducing the activation of MAPKs, P13Ks and STATs signaling pathways.[141] It stimulates angiogenesis by regulating the secretion of VEGF in pancreatic tumor cells.[142] By promoting the production of VEGF, VEGF receptors and neuropilin (NRP-2), IL-8 also induces angiogenesis in pancreatic cancer.[143] Besides, TNF-α induces cancer cell proliferation by attaching to its receptor TNF-R2.[144] Additionally, it has

been observed that MIF also promotes pancreatic tumor cell proliferation.[145] Furthermore, it has been shown that expression of IL-1β can induce tumor cell invasiveness in pancreatic cancer.[145,146] It also contributes to metastasis.[147] Schmid et al.[148] showed that elevated levels of IL-1β enhance recruitment of macrophages in affected tissue.

Future directions of cytokines in cardiology and oncology

The possible role of inflammatory cytokines as diagnostic marker for cancer and CVD has been identified. Determining the serum levels of various cytokines can be associated with a tumorigenic process or poor prognosis.[54] Although progress has been made in understanding these cytokines' roles in the tumorigenic cycle, establishing a relationship between cytokine expression and disease progression, survival and therapy response remains a major challenge. A more detailed understanding of the body's inflammatory activation pathways may lead to the development of unique therapies that do not compromise host defense against pathogenic agents.[54,149] A variety of clinical trials in the field of therapy have been carried out to determine inhibitors of cytokine receptors or neutralizing antibodies that prevent the sustained exposure of the tumor progression and inflammation-promoting inflammatory mediators. Therapies explicitly directed against proinflammatory cytokines must be assessed in suitable prospective clinical trials in order to investigate their role in disease management.[54,150] However, further studies are required to evaluate trusted cut-off values of circulating cytokines in order to have a direct causal association with cancer and CVD. Thus, effective approaches to tackle cardiovascular disorders and multiple cancers can be identified both within and outside the laboratory.

Limitations of this review

This review article is not a meta-analysis either. The key actors and their mechanism of action in the immunopathogenesis of various inflammatory disorders should be established in further studies. Such studies are a prerequisite for developing new CVD and cancer treatment approaches targeting inflammatory and immunopathogenic pathways in these disorders.

Concluding remarks

Inflammation is widely considered to be an important contributing factor of the pathophysiology of CVDs including CHD, and the inflammatory cascade is particularly important in the atherosclerotic process. Many large-scale prospective studies demonstrate that various inflammatory cytokines strongly and independently predict adverse cardiovascular events, including MI, ischemic stroke and sudden cardiac death. Besides, cytokines have been shown to stimulate cancer stem cells (CSCs) in different tumor models. They have also been shown to increase tumor cell mobility. The mixture of cytokines that is produced in the tumor microenvironment has an important role in cancer pathogenesis. Different clinical and epidemiological data suggest that cytokines are associated with an increased risk of cancer.

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