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Review article

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A Survey on the Role of Interleukin-10 in Breast Cancer: A Narrative

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Abstract

Interleukin (IL)-10, a multifunctional immune-regulatory cytokine with both immunosuppressive and anti-angiogenic functions, is produced by immune cells including macrophages, T lymphocytes, and natural killer cells. Among other effects, IL-10 promotes tumor cell proliferation and metastasis via immunosuppression. Interleukin-10-mediated immunosuppression is aided by synthesis of tumor necrosis factor, IL-1, IL-12, and chemokines, and down regulation of the surface co-stimulatory molecules CD80 and CD86 on tumors. Interleukin-10 also promotes IL-6 expression and synthesis, which causes cell proliferation via B cell lymphoma-2 (Bcl-2) upregulation and changes the proliferation/apoptosis equivalence toward neoplastic cell proliferation. Moreover, IL-10 inhibits tumorigenesis via down-regulation of VEGF, IL-1b, TNF-α, IL-6, and MMP-9. Interleukin-10 also inhibits nuclear factor-κB (NF-κB) translocation. Interleukin-10 has been reported to have both tumor-promoting and -inhibiting properties. It seems that IL-10 agonists and antagonists may have therapeutic effects via different mechanisms. Moreover, IL-10 gene polymorphisms may determine breast cancer susceptibility.

Keywords: Breast cancer, Cytokine, IL-10

Introduction

Breast cancer is the most common cancer in women (1, 2), accounting for 25% of all female cancers worldwide (3). Despite new diagnostic and treatment options (3), 30% of women diagnosed with invasive breast cancer will develop metastatic disease (4); therefore, early detection is critical for patient survival. Immunoregulatory cytokines including interferons- (IFNs) -α, -β, and -γ; interleukins- (ILs) -2, -6, and -10, and tumor necrosis factor (TNF) -αare all associated with breast cancer (3, 5, 6, 7). Interleukin-10, which has an important coordinated role in breast carcinogenesis (3), is an anti-inflammatory cytokine that regulates the immune response (8) and inhibits the pro-inflammatory functions of antigen-presenting cells (APCs) through expression of antagonizing costimulatory molecules. Its low expression is associated with poor survival outcome (9). The aim of this study is to evaluate the mechanism and action of IL-10 in breast cancer patients.

Interleukin-10 (IL-10)

The IL-10 gene (*IL10*) contains five exons (10) located on chromosome 1 at q31-32 (11). The protein contains 160 amino acids, has a molecular weight of 18 kDa, and functions as a dimer (5). Human IL-10 is 73% homologous with murine IL-10 at the amino acid level (5) and is produced by

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immune cells including macrophages, T lymphocytes, and natural killer (NK) cells (12). It is a multifunctional immuno-regulatory cytokine (13) with both immunosuppressive (14, 15) and anti-angiogenic functions (14). It also plays major roles in the regulation of inflammatory responses, infection progression, autoimmunity, transplantation tolerance, and tumorigenesis (16, 17). Also known as cytokine synthesis inhibitory factor (CSIF), IL-10 suppresses expression of ILs-1α, -1β, -6, -8, -12, and -18, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in T cells and macrophages (5), IFN-γ in activated T helper (Th) cells and peripheral blood mononuclear cells (PBMCs), and induces mast cell proliferation. Interleukin-10 deficiency is associated with increased production of the pro-inflammatory cytokine IL-1, which promotes tumor growth in mice (8).

IL-10 and alpha-2-Macroglobulin (α2M)

Interleukin-10 has many functional partners including alpha-2-macroglobulin (α2M) (18), with which it can form a complex. Alpha-2-macroglobulin, a large homotetrameric glycoprotein (19) found in plasma and extracellular spaces, acts a protease inhibitor and can non-covalently bind (20) and transport cytokines, including IL-10. The formation of these complexes increases the concentrations of these cytokines in the blood (21, 22). Native α2M increases the half-life of bound cytokines in the plasma by protecting them from proteolysis (20) and facilitates their recruitment to inflammation sites, where they induce anti-inflammatory responses (22, 23). Disruption of these complexes promotes inflammation (21, 22) and favors cancer development.

IL-10 Polymorphism

Genetic polymorphism can play a role in initiation and progression of breast cancer (5). Genetic variations that affected IL-10 synthesis determined breast cancer susceptibility (11). Several single-nucleotide polymorphisms (SNPs) have been identified in the *IL10* promoter (10). Three functional *IL10* SNPs have been characterized; these are an adenine (A) to guanine (G) substitution at nucleotide -1082 (rs1800896), a thymine (T) to cytosine (C) substitution at nucleotide -819 (rs1800871), and an A to C substitution at nucleotide -592 (rs1800872). These polymorphisms led to different *IL10* expression levels and determined inter-individual differences in IL-10 (3). Moreover, factors including study population ethnicity, sample size, and subject inclusion and exclusion criteria affected findings (5). *IL10* polymorphisms and their associations with breast cancer are shown in Table 1.

Table 1. *IL10* polymorphisms associated with breast cancer

Study	Polymorphism	Population	Result	References
Giordani et al. (2003)	-1082	Italy	The -1082 polymorphism was associated with cancer risk	42
Abdolrahim-Zadeh et al. (2005)	-1082 -819 -592	Iran	No association was found between these polymorphisms and breast cancer	11
Langsenlehner et al. (2005)	-592	Austria	Association between The -592 polymorphism was associated with decreased breast cancer risk	25
Gerger et al. (2010)	-592	Austria	The -592 polymorphism was associated with breast cancer metastasis	15
Merendino et al. (1999)	-1082 -592	Brazil	No association was found between genotypes or haplotypes and sporadic breast cancer	26
Smith et al. (2004)	-1082	UK	No association was found between the -1082 A/G polymorphism and breast cancer susceptibility	27

IL-10 Induction and inhibition factors

Several factors influence IL-10 induction and inhibition. These agents are shown in Table 2.

Table 2. IL-10 inducing and inhibiting agents

Investigator	Agent	Effect	References
Pilette et al. (2007)	Immunoglobulin-A (Iga)	Inducing	28
McGeachyet al. (2007)	Transforming Growth Factor-*B* (TGF-*B)*	Inducing	29
McGeachyet al. (2007)	Interleukin-6 (IL-6)	Inducing	29
Awasthi A, et al. (2007)	Interleukin-27 (IL-27)	Inducing	30
Pang G et al. (1994)	Interleukin-1α (IL-1-A)	Weakly Inducing	31
Pang G et al. (1994)	Tumor Necrosis Factor-A (TNF-A)	Weakly Inducing	31
Scott et al. (1990)	Lipopolysaccharide (LPS)	Inducing	32
Brunsing et al. (2011)	G Protein-Coupled Estrogen Receptor (GPER) Agonist	Inducing	33
Brunsing et al. (2011)	Thalidomide	Inducing	33
Ji et al. (2005)	15-Deoxy-Delta12,14-Prostaglandin J2	Inhibiting	34
Kalechman et al. (2004)	AS101 (Ammonium Trichloro (Dioxoethylene-O,O′) Tellurate)	Inhibiting	35
Alas et al. (2001)	Rituximab	Inhibiting	36

IL-10 signaling pathways and chemotherapy

Interleukin-10 signals through a tetrameric trans-membrane receptor complex containing two IL-10RA (also known as IL-10R1) and two IL-10RB (also known as IL-10R2) proteins (8). Both receptors belong to the class II receptor family containing one each of intracellular, trans-membrane, and extracellular domains (8). These receptor complexes assemble consecutively; IL-10RA has greater affinity for IL-10 than IL-10RB. Interleukin-10 binding to the IL-10RA extracellular domain leads to Janus kinase-1 (JAK1) and tyrosine kinase-2 (TYK2) phosphorylation.

Janus kinase-1 phosphorylates signal transducer and activator of transcription-3 (STAT-3). Once phosphorylated, STAT-3 translocate to the nucleus and activates transcription of anti-apoptotic and cell-cycle-progression genes (8). Moreover, IL-10 expression is regulated through a balance of STAT-3 and suppressor of cytokine signaling-3 (SOCS3); STAT-3 silencing decreased IL-10 expression (5).Recent studies showed N-Myc downstream regulated gene 2 product (NDRG2) modulates SOCS3 and STAT-3 activities and inhibits IL-10 production (5).

The relatively large amount of IL-10 secreted by tumor-associated macrophages (TAMs) was found to be responsible for breast cancer drug resistance.

The mechanism of TAMs-modulated drug resistance may be associated with increased *BCL2* expression and up-regulation of STAT3 signaling in tumor cells; therefore, the suppression of TAMs-induced IL-10 by neutralizing antibody leads to decreased *BCL2* expression and STAT3 activation and the consequent enhanced sensitivity of breast cancer cells to drug treatment. It seems that TAMs cause drug resistance via the IL-10/STAT3/Bcl-2 signaling pathway, providing possible new targets for breast tumor therapy (37). Tumor-associated macrophages can mediate with many tumor therapies including chemotherapy, irradiation, and immunotherapy (38). Chemotherapy-induced macrophage infiltration suppresses IL-12 synthesis in dendritic cells (DCs), which in turn inhibits CD8+ T cell activity and limits chemotherapy efficacy (38). Macrophages express the highest IL-10 levels among tumor infiltrating leukocytes, including T regulatory cells, known to be a main source of IL-10 in murine tumor models. Therefore, it seems likely that the IL-10/IL-10R and IL-12/IL-12R pathways

may play major roles in the pathological response following breast cancer chemotherapy-induced TAM recruitment. Moreover, targeting of these pathways may reduce chemotherapy resistance and improve patient outcomes (38).

IL-10 and apoptosis

An association exists between IL-10 expression and apoptosis-related tumor markers. A relationship between IL-10 and Bcl-2 has also been observed in human breast and other cancer cells (39). The effect of IL-10 on cell survival caused increased IL-6 expression, which promotes cell proliferation by upregulating *BCL2* expression, therefore changing the proliferation/apoptosis balance toward neoplastic cell proliferation (40). On the other hand, high IL-6 expression and its receptors in breast tumors may promote cell proliferation (40). Fernandez et al. showed IL-10 expression is strongly associated with expression of Bcl-2-associated X protein (Bax), a member of the Bcl-2 family with pro-apoptotic effects (39). Another study found no association between IL-10 and the apoptotic markers in breast tumors, but also reported that the presence of IL-10 and high abundance of Bcl-2 family proteins in tumors may show the aggressiveness of breast tumors (39). Kim et al. proposed a model for the role of IL-10 in apoptosis of mammary epithelial cells; in this model IL-10 secreted through mammary epithelial cells recruit lymphocytes from blood vessels to the alveoli; then IL-10 stimulates lymphocytes to release the death factors Fas-L and TRAIL, which bind death factor receptors on epithelial cells. Then downstream signaling pathways activate epithelial cell apoptosis (41).

Relationship between IL-10 and breast cancer

The role of IL-10 in breast cancer is controversial. The results of various IL-10 studies in breast cancer are shown in Table 3.

Mechanism of IL-10 tumor act

The role of IL-10 in breast cancer is controversial. Interleukin -10 has both pro- and anti-tumor effects (50). IL-10 mRNA expression is seen in more than 50% of tumor samples (39). Also greater IL-10 protein concentrations are seen in serum of breast cancer patients than in that of healthy individuals (5, 39, 51) and this is associated with poor clinical outcomes (52). Interleukin-10 promoted proliferation and metastasis of tumor cells (53) and inhibited T-cell proliferation and function (39).

Therefore, it appears that IL-10 expression in metastatic cancer cells can down regulate the cell-mediated inflammatory response (5) and be a potential biomarker for prediction and prognosis of human cancers (50). Interleukin -10 also mediates immunosuppression by upregulating TNF, ILs -1 and -12, and chemokine expression (54) and downregulating expression of surface co-stimulatory molecules including CD80 and CD86 on tumor cells. It also prevents APCs from obtaining access to tumor antigens (54). It also appears that factors that contribute to IL-10 production may have potent roles in breast cancer development (11). Administration of IL-10 before anticancer

Table 3. Results of various studies on the role of IL-10 in breast cancer

Author	Result	Sample	References
Venetsanakos et al. (1997)	IL-10 mRNA detected in most breast tumors	Breast tumor tissue	42
Kozłowski et al. (2003)	Strong relationship between IL-10 expression and breast cancer	Serum breast cancer	43
Fernandez et al. (2006)	IL-10 is being a poor prognosticator for breast cancer	Breast tumor tissue	44
Chavey et al. (2007)	IL-10 protein expression was significantly greater in breast cancer tumors than in negative controls and inversely related to estrogen receptor- and progesterone receptor-status	Breast tumor tissue	45
Rao et al. (2008)	No significant difference in IL-10 expression was found between patients and controls	Serum of breast cancer	46
Li et al. (2014)	IL-10 expression is associated with disease-free survival.	Breast tumor tissue	47
Li, et al. (2014)	Low expression of IL-10 expression leads to poor survival outcome.	Breast tumor tissue	48
Venetsanakos. (1997)	IL-10 suppresses cellular immune responses	Breast tumor tissue	49

vaccination leads to tumor progression (55-58). Interleukin-10 stimulates metalloproteinase (TIMP) tissue inhibitors and inhibits expression of matrix metalloproteinase (MMP), thus affecting angiogenesis induction (10). Another study reported that IL-10 administration promoted proinflammatory effects through increased release of IFN-γ, IP-10, and other monokines induced by IFN-γ (59). Therefore, IL-10 antagonist administration may be an effective new cancer treatment (60).

Mechanism of IL-10 anti-tumor activity

Interleukin-10 expression is associated with anticancer immune responses in animal and human models. The anti-tumor activity of IL-10 is mediated via angiogenesis inhibition (11) and through down regulation of vascular endothelial growth factor(VEGF), ILs -1b and -6, TNF-α, and MMP-9 syntheses, all of which are needed for angiogenesis (54). It is also a potent stimulator of B-cell differentiation leading to immunoglobulin secretion. Interleukin-10 inhibits nuclear factor-κB (NF-κB) translocation as a mechanism to inhibit immediate-early pro-inflammatory responses (5). Therefore, IL-10 in the tumor site can prevent destruction by the host immune system (39) and suppress tumor growth and increase antitumor immunity via promotion of antitumor CTLs (55-58). The anti-tumor activity of IL-10 is also attributed to its effects on NK cell activation (10). Studies in animal models showed that IL-10 can activate NK cells and assist target cell destruction in a dose-dependent manner (59), while other research has indicated that the anti-tumor effect is due to CD8+ or CD4+ T-cell function (5). It seems that IL-10-mediated immune response inhibition at the tumor site has major implications for immunotherapy (39). Therefore, IL -10 administration may be considered as a new therapy for cancer patients (59).

IL-10 and the estrogen receptor

The role of the estrogen receptor in cytokine production and regulation is not known (61). Interleukin-10 has been found in both tumor cell cytoplasm and stroma. Moreover, cytokines, including IL-10, were over-expressed in estrogen receptor (ER) -negative breast carcinoma (62). Because IL-10 was expressed in ER-negative but not ER-positive tumors (5), and expression of the transcription factor activator protein (AP) -1 is greater in ER-negative than in ER-positive tumors, the increased AP-1 expression is related to increased IL-10 (5). Therefore, IL-10 can be a breast cancer prognosticator (9). Moreover, G1, a G protein-coupled estrogen receptor (GPER) agonist, and Thalidomide can induce IL-10 expression by acting on Th17 or hybrid T-cell populations (5), while another study reported that increasedIL-10 expression in tumor cell cytoplasm is associated with lower grade and positive estrogen receptor (9).

Conclusion

Interleukin-10 has been shown to exhibit both tumor-promoting and -inhibiting properties; therefore, it seems that IL-10 agonists and antagonists may have therapeutic effects in breast cancer via different mechanisms. Moreover, *IL10* polymorphisms may affect breast cancer susceptibility.
with lower grade and positive estrogen receptor (9).

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