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Review

The significant role of interleukin-6 and its signaling pathway in the immunopathogenesis and treatment of breast cancer

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ABSTRACT

Despite remarkable improvements in cancer treatment approaches, breast cancer is still the main cause of cancer-related death in women. Its principal cause is the resistance of the cancer cells against conventional anticancer therapeutics, mainly in advanced disease stages. It has been shown that chronic inflammation in the tumor microenvironment facilitates tumor growth and induces resistance toward chemo- and radiotherapy. Overexpression of interleukin-6 (IL-6) cytokine in the tumor microenvironment has been demonstrated in numerous tumors including breast cancer. Tumor cells and tumor-associated fibroblasts are the major sources of IL-6 secretion in the tumor microenvironment. Several studies have demonstrated the immunopathogenic function of IL-6 and its signaling in the tumor growth, metastasis, and therapeutic resistance in the breast cancer. Therefore, it seems that targeting IL-6 and/or its receptor in combination with other potent anticancer therapies may be a potent therapeutic approach for breast cancer therapy.

1. Introduction

Breast cancer, one of the most abundant malignant solid tumors, has been considered as the main cause of cancer-related death in women globally [1]. Despite the presence of extensive attempts and various therapeutic approaches, the way to reach a complete remission in breast cancer is yet complex [2]. Our previous approaches for modulation of tumor microenvironment with various immunotherapeutic methods had some hopeful outcomes [3–5]. However, it seems a long road remains to walk through breast cancer therapy. The relation of inflammation and various types of cancer has been suggested by several studies. As we recently showed [6], anti-inflammatory agents can attenuate tumor growth in the breast cancer-bearing mice implying the importance of inflammatory microenvironment in tumor growth. Malignant cells exhibit a high proliferation, which can be enhanced by inflammation. The inflammatory molecules in the tumor microenvironment are mainly secreted by tumor cells themselves and/or other stromal cells [7]. Interleukin-6 (IL-6) is a pro-inflammatory cytokine released by various cells in the tumor microenvironment including the cancerous cells. IL-6 plays a critical role in the expansion and differentiation of tumor cells [8,9]. Increased levels of IL-6 in the serum and tumor site has been demonstrated in several cancers including breast cancer [10]. While this increase is usually accompanied with poor prognosis and lower survival in breast cancer patients, downregulation of IL-6 is related to the better response to treatment [11,12]. IL-6 can affect all aspects of tumorigenesis process by regulating proliferation, apoptosis, metabolism, survival, angiogenesis, and metastasis [13]. IL-6 can also modulate a tumor therapeutic resistance such as multidrug resistance (MDR) [14].

While the obesity is considered as an important risk factor for breast cancer [15], it has been shown that the adipose tissue generates about the 30% of circulating IL-6. On the other hand, cancer-associated

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adipocytes trigger radio-resistance in breast cancer by secreting IL-6 [16]. Gyamfi and coworkers demonstrated that matured human adipocytes could intensify the aggressive behavior of breast cancer cells and induce an epithelial-mesenchymal transition (EMT)-phenotype through paracrine IL-6 [17]. These facts declare the importance of obesity/IL-6 axis for promoting cancer and therapeutic resistance [18].

Therefore, it seems that blocking IL-6 and/or its receptor can be considered as a potent therapeutic approach for cancers associated with high levels of IL-6 such as breast cancer. This review will try to clarify the role of IL-6 and its receptor in the immunopathogenesis and treatment of breast cancer.

2. IL-6/IL-6R

IL-6 (which is also known as IFN-β2, hepatocyte-stimulating factor, and hybridoma/plasmacytoma growth factor) was identified in 1986 for the first time as B cell stimulation factor which enhances the differentiation of effector B cells toward antibody-producing cells [19,20]. It is a small glycopeptide (185 amino acid, 25 kDa) [19], and secreted by the wide variety of immune and non-immune cells, including T and B cells, monocytes, endothelial cells, fibroblasts, keratinocytes, mesangial cells, and adipocytes. Interestingly, it has been shown that several tumor cells including breast cancer [21], colorectal cancer [22], lung cancer [23], prostate cancer [24], ovarian carcinoma [25], pancreatic cancer [26], and multiple myeloma [27] can also generate this cytokine. IL-6 can modulate several immune and physiological processes in the body, such as the generation of acute-phase proteins, inflammation, antigen-specific immune responses, hematopoiesis and cellular metabolism [28].

Several immune and non-immune cells including T cells, activated B cells, neutrophils, monocytes, and hepatocytes express the IL-6 receptor (IL-6R) [29]. IL-6 has two types of receptors including the transmembrane IL-6 receptor (mIL-6R) expressed on the cell surface and soluble IL-6 receptor (sIL-6R) present in the circulation [30]. The mIL-6R contains a short cytoplasmic domain that is not involved in ligation-derived signaling. The mIL-6R is also known as IL-6Rα, gp80 or CD126. There are two pathways for the generation of sIL-6R including the alternative splicing of mIL-6R mRNA (10%) and the spatial effect of proteinases ADAM10 and ADAM17 (90%) [30]. The sIL-6R lacks the cytoplasmic and transmembrane domains, but the essential domains involved in binding to IL-6 are present which mediate ligation with IL-6 with comparable affinity to mIL-6R.

The mIL-6R and sIL-6R cannot transduce intracellular signaling themselves, and require another transmembrane protein which is known as glycoprotein 130 (gp130, IL6ST, IL6Rβ or CD130). The gp130 can form a low-affinity complex with IL-6R and mediate intracellular cell signaling. It is expressed in various cells and participates in the development, growth, cell survival and tissue homeostasis [31]. The cytoplasmic domain of gp130 contains the critical area such as SHP-2 domain and YXXQ motif which is required to start intracellular signaling. Following ligation of gp130 to IL-6/IL-6R, gp130 forms a homodimerized structure and activates cytoplasmic tyrosine kinases leading to phosphorylation of different transcription factors. The soluble form of gp130 (sgp130) is mainly produced through alternative splicing. The sgp130 is present in blood circulation and its concentration has a direct effect on the inflammation and cancer. It has been demonstrated that sgp130 may form a complex with the IL-6/sIL-6R in the circulation and prevent trans-signaling [32,33].

3. IL-6 signaling pathways

There are various signaling pathways for IL-6 [34] (Fig. 1). Ligation of IL-6 with IL-6R activates Janus kinase (JAK) tyrosine kinases leading to phosphorylation of signal transducer and activator of transcription 3 (STAT3). Phosphorylation induces homodimerization and entrance of STAT3 into the nucleus [35]. Stimulation of IL-6/JAK/STAT3 pathway in cancer cells modulates the expression of several genes involved in the proliferation, survival, and transformation. The suppressors of cytokine signaling (SOCS) molecules and protein inhibitors of activated STAT (PIAS) proteins are the main modulators of the STAT3 pathway. Activated STAT3 usually enhances the expression of these inhibitors under physiological conditions.

Ras, which is another molecule induced following ligation of IL-6 to its receptor, can hyperphosphorylate and activate mitogen-activated protein kinases (MAPK). MAPK then activates various transcription factors involved in enhancing cell growth, increasing immunoglobulin synthesis, and generating acute phase protein [36].

The phosphoinositol-3 kinase (PI3K)–protein kinase B (PkB)/Akt is another signaling pathway which is induced by IL-6. Following phosphorylation by JAK, PI3K phosphorylates and converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 subsequently phosphorylates PkB/Akt serine/threonine kinase [37]. Afterward, Akt modulates the expression of several genes involved in the cell survival [38].

4. IL-6/IL-6R in breast cancer

Local and systemic overexpression of IL-6 has been reported in several cancer types such as breast cancer [39]. Upregulation of IL-6 serum levels is generally associated with poor prognosis and low survival rate in patients with breast cancer [11] (Fig. 2). On the other hand, it has been shown that STAT3 is highly active in more than 50% of breast cancers and this is an important issue, because we know IL-6 is its primary activator [40]. Several cell types such as cancer cells, tumor-associated macrophages (TAMs), helper T (Th) cells, myeloid-derived suppressor cells (MDSCs) and fibroblasts are considered as the primary sources of IL-6 in the tumor microenvironment [41,42]. Thus, it seems we can suppose a new tumor promoting mechanism for these cells in addition to their conventional previously described tumor promoting mechanisms [43]. Cancerous cells usually use IL-6 as a growth factor in an autocrine manner, and paracrine release of IL-6 by other cells has less importance in survival and progression [44]. Nevertheless, both autocrine and paracrine release of IL-6 affects tumor progression via IL-6 trans-signaling [9,45].

The responsiveness of breast cancer cells to IL-6 intimately depends on the expression of estrogen and progesterone receptors (ER and PR). Hormone-sensitive cells exhibit a higher response to IL-6 than hormone insensitive cells, which is associated with the intrinsic generation of higher IL-6 in these cells [46,47]. While the ER-expressing breast cancer cells mostly secrete the sIL-6R, ER-negative cells mainly express the mIL-6R [48]. It has also been shown that IL-6 suppresses ER-negative cells under normal condition in an autocrine manner [49].

IL-6 also increases estrogen levels in circulation and tumor site by activating estrogen-generating enzymes including aromatase, estrone sulfatase, and 17 β-hydroxysteroid dehydrogenase [50]. Estrogen sulfate remains in circulation more than estrogen, so that it is considered as an estrogen reservoir. On the other hand, it is demonstrated that the estrone sulfatase is overexpressed in malignant breast tissues. Accordingly, IL-6 is a crucial modulator of converting estrone to estradiol in MCF-7 ER-positive cells [51], which may imply the cause of high concentration of estradiol in malignant breast tissue.

The IL-6 polymorphisms have also been linked with breast cancer risk. Several studies have performed on the IL-6 promoter single nucleotide polymorphism (SNP) 174 G > C (rs1800795), where IL-6 was upregulated in the samples with the expression of 174 G allele and downregulated in the samples with 174C allele [52]. Another study implied that GG SNP at IL-6 (rs1800795) could enhance metastasis incidence of primary breast cancer [53]. It has also been shown that IL6 rs1800797 AG or AA genotypes are related to a lower disease-free survival [54]. A cohort investigation of 634 primary breast cancer patients in Sweden indicated that regardless of ER-status, chemotherapy-treated patients with C-genotype show a higher risk of early events