



INTERLEUKIN-18 AND BREAST CANCER: A REVIEW



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Abstract:

Interleukin 18 (IL-18) is a pleiotropic cytokine involved in the regulation of innate and acquired immune response. IL-18 possesses strong immunomodulatory biological activity, exerts anti-infection, antiparasite and antitumor effects by inducing interferon- γ , promotes perforin- and FasL-mediated cytotoxicity and directly or indirectly inhibits and destroys malignant tumors via multiple channels. Thus, IL-18 inhibits or prevents the growth of breast cancer, bladder cancer and neuroblastoma. Breast Cancer is the leading cancer diagnosed in women aged 20 - 45 with risk factors including breast density, age and family history. The systemic levels of IL-18 shows promising correlations with disease stage and progression. Here, we review the role of IL-18 in the immune response against breast cancer. A literature search was conducted in Pubmed for to articles published in the English language using combinations of the following terms: IL-18, cytokines, breast cancer and interleukins. Focused searches using keywords relevant to the role of IL-18 in breast cancer immunology.

Keywords: IL-18, cytokines, breast cancer and interleukins.

Introduction:

Breast Cancer (BC) is the most common malignancy, which accounted for ~11.6% of all neoplasms worldwide in 2018 [1] and it accounts for ~15% of new cancer cases in women, seriously threatening their health and lives [2]. Despite great progress in surgery, radiotherapy, chemotherapy and endocrine therapy, the prognosis of advanced and metastatic BC remains poor [3]. With the advancement of molecular biology, cell biology and immunology research, biological immunotherapy has become a new therapeutic method for solid tumors, thus altering the treatment mode for a variety of cancer types, such as lung cancer, cancer of the neck and head, renal cancer and malignant melanoma [4]. However, for BC, the clinical benefits of immunotherapy remain unsatisfactory, except in a small number of patients with triple-negative BC [5]. Exploring the immunological mechanism of BC may provide a new theoretical basis and clinical strategy for the treatment of BC.

Interleukin-18 (IL-18):

It is a multifunctional cytokine that was first reported in 1995 [6]. IL-18 possesses strong immunomodulatory biological activity, exerts anti-infection, antiparasite and antitumor effects by inducing interferon- γ [7], promotes perforin- and FasL-mediated cytotoxicity, and directly or indirectly inhibits and destroys malignant tumors via multiple channels [8]. Thus, IL-18 inhibits or prevents the growth of BC, bladder cancer and neuroblastoma [9, 10].

IL-18, a member of the IL-1 family, was originally observed as an inducer of interferon-gamma (IFN- γ) production [11]. It is produced by numerous immune and non-immune cells, which modulate both innate and adaptive immune responses [12, 13]. Evidence has shown that IL-18 can exert both anti-cancerous and pro cancerous activities. On the one hand, IL-18 plays pleiotropic functions in activating natural killer cell cytotoxic effect and enhancing Th1 immune response mainly by stimulating the expression of IFN- γ and tumor

necrosis factor- α (TNF- α), which result in the elimination of tumor cells in vivo [14-17]. On the other hand, recent evidence suggests a tumor stimulating activity of this multi-functional cytokine under some conditions [18]. Higher expression levels of IL-18 have been observed in various cancer cells [18-20]. It also has been shown that IL-18 has an important role in tumor progression. Evidence has suggested an increased level of IL-18 in the blood of metastatic patients compared to patients without metastasis and healthy controls [21].

The human IL-18 gene is composed of six exons and five introns located on chromosome 11q22.2–q22.3. Several single nucleotide polymorphisms (SNPs) have been identified in the IL-18 gene. A number of SNPs in the promoter region of IL-18 gene have been associated with differential levels of gene transcription and protein production. The G to C substitution at position -137 abolishes a histone 4 transcription factor-1-binding site and the C to A substitution at position -607 disrupts a cyclic AMP (cAMP) protein-binding site. The functional significance of these two SNPs has been shown by several researchers and these two SNPs were attributed to the IL-18 higher transcription and protein production [22].

IL-18 and BC:

Numerous studies have investigated the association between -607C/A polymorphism of IL-18 gene and cancer risk [23], but the results are conflicting rather than conclusive. From 2010 to 2013, studies were conducted with the aim to investigate the association between -607C/A polymorphism in IL-18 gene and cancer risk, demonstrating that it was associated with an increased overall cancer risk. However these studies have some limitations and demerits such as relatively small numbers of articles, including irrelevant studies and not including all eligible studies; and from then on, a number of new case-control studies have been conducted [24-28].

Adipocytes secrete leptin that promotes BC cell migration and invasion by enhancing the expression and secretion of IL-18 through tumor-associated macrophages (TAMs), which are linked to tumor progression and metastasis [29,30]. Moreover, IL-18 gene polymorphisms are associated with increased risk of BC [31,32]. However, multiple studies show that IL-18 plays a positive role in BC therapy. IL-18 overexpressing human mesenchymal stem cells derived from the human umbilical cord (HUMSCs) suppress the proliferation, migration and invasion of BC cells [33,34]. This contradictory role of IL-18 suggests that the context and cell types that generate IL-18 critically modulate cancer progression.

It is also observed that when HUMSCs strain transfected with IL-18 gene and examined for its effects on the proliferation of BC cell (MCF-7), the IL-18-HUMSCs effectively inhibited the proliferation of BC cells in vitro [35].

Study which investigated the presence and expression levels of the IL-18 in the primary BC tissue in relation to the unchanged breast tissue in same patients and the breast tissue in patients with benign breast disease, as well as the correlation between the IL-18 expression levels and pathohistological factors, including the correlation between IL-18 expression and the estrogens and progesterone receptor status was done it was found that IL-18 was present in the BC tumour, in the surrounding unchanged tissue of the same patients and in the breast tissue of patients with benign breast tumour and other benign breast disease. The expression was significantly higher in BC tumour tissue as compared to its expression in surrounding unchanged tissue of the same patients whereas its expression was not significantly higher in BC tumours compared to its expression in breast tissue of the patients with benign breast diseases. There was also no significant correlation between IL-18 expression and the lymph node status and between IL-18 expression and the pathohistological factors which suggests the possible involvement of IL-18 in complex mechanisms of breast carcinogenesis [36]. IL-18 which plays an important role in the T-cell-helper type 1 response and also acts as an angiogenesis and tumor suppressor irrespective of its biological activity this could also be represented as a marker for metastatic BC[37]. IL-18 combined with other cytokines, such as IL-12 and -15, can regulate the activity of multiple types of immune cells to exert antitumor effects. IL-10 is highly expressed in BC tissues and its expression

correlates positively with that of IL-18. Both IL-18 and -10 correlate positively with lymph node metastasis in BC, suggesting a possible synergistic effect between them that promotes the development, infiltration and migration of BC. Combined detection of the expression of IL-18 and -10 may provide new indicators for the early diagnosis and prognosis of BC [38] and it is also found that IL-18 rs1946518 and rs187238 polymorphisms may confer susceptibility to BC for East Asians from China [39].

From the above review we can assess that the role of IL-18 is conflicting in case of BC. More studies from different ethnic backgrounds are required to accurately assess the role of IL-18 in BC.

Abbreviations:

IL-18	: Interleukin 18
BC	: Breast Cancer
TNF- α	: Tumor necrosis factor- α
SNPs	: Single nucleotide polymorphisms
cAMP	: Cyclic AMP
TAMs	: Tumor-associated macrophages
hUMSCs	: Human umbilical cord stem cells

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