Interleukin-6 in Breast Cancer: Mechanisms and Research Progress

Abstract: Interleukin-6 (IL-6), a pleiotropic proinflammatory cytokine, plays a pivotal role in the initiation, progression, and therapeutic resistance of breast cancer. Emerging evidence demonstrates that IL-6 drives tumor cell proliferation, epithelial-mesenchymal transition (EMT), and remodeling of the metastatic tumor microenvironment (TME) through activation of signaling pathways such as JAK/STAT3. At the clinical-translational level, elevated IL-6 levels are strongly associated with increased chemoresistance, diminished targeted therapy responsiveness, and adverse prognosis in breast cancer patients. Intervention strategies targeting the IL-6 pathway have shown promising efficacy in preclinical models, including tumor growth suppression and reversal of therapeutic resistance, yet their clinical applicability requires validation through large-scale clinical trials. Future research should focus on integrating multi-omics data to develop prognostic stratification models that optimize precision treatment strategies. This study provides a multidimensional exploration of IL-6's functional landscape in breast cancer, aiming to advance innovative molecular perspectives for precision diagnostics and therapeutics, while establishing theoretical foundations and directional guidance for translational medicine research targeting IL-6 signaling.

Keywords: Interleukin-6 (IL-6), Breast Cancer, Tumor Microenvironment, Treatment, Review

Breast cancer is the leading cause of cancer-related mortality among women worldwide [1-2], with both its incidence and mortality rates showing an increasing trend globally. Interleukin-6 (IL-6) is a multifunctional cytokine that plays important roles in immune responses, inflammatory reactions, and cell proliferation [3]. In recent years, studies have found that the abnormal expression of IL-6 and its receptor in breast cancer patients is associated with low survival rates, promotes tumor growth and invasion, and mediates metastatic progression, thereby identifying the IL-6 signaling axis as a potential therapeutic target [4]. Currently, research on the mechanisms of IL-6 in tumorigenesis has made certain progress, and the development of IL-6-targeted inhibitors has attracted significant attention. Blocking IL-6 or its receptor is considered a potentially effective treatment for cancers with high levels of IL-6, such as breast cancer. Various targeted inhibition strategies have been proposed

and have entered preclinical or clinical research stages. However, how to precisely and effectively block IL-6 and its signaling pathway to achieve anti-tumor effects remains a key issue that needs to be resolved. The author summarizes the clinical research progress of IL-6 in breast cancer, with the expectation of bringing better therapeutic outcomes for breast cancer patients and improving their survival rates and quality of life.

1. IL-6 and Its Signaling Pathway

1.1 Multidimensional Roles of IL-6 in the Body

IL-6 is a pro-inflammatory, multifunctional cytokine secreted by malignant cells, stromal cells, and immune cells within the tumor microenvironment (TME). Its biological functions are extensively involved in physiological processes such as immune regulation, metabolic homeostasis, and tissue repair. IL-6 is also closely associated with various pathological conditions, including chronic inflammation, hematopoiesis, cell metabolism, cardiovascular diseases, and malignant tumors [5]. In the field of oncology, IL-6 has emerged as a key mediator driving cancer development and progression by promoting cell proliferation, inhibiting apoptosis, inducing epithelial-mesenchymal transition (EMT), and remodeling the immunosuppressive microenvironment [6]. Studies have shown that abnormal overexpression of IL-6 is significantly correlated with the invasion, metastasis, and therapeutic resistance of various solid tumors, including breast cancer and lung cancer. Elevated serum levels of IL-6 can serve as an independent prognostic indicator of poor outcomes in breast cancer patients [7].

1.2 Molecular Mechanisms of the IL-6 Signaling Pathway

The biological effects of IL-6 are dependent on the formation of a hexameric complex with the transmembrane receptor IL-6R and the co-receptor glycoprotein 130 (gp130) [8]. This complex triggers the phosphorylation of JAK kinases, which subsequently activates the downstream signal transducer and activator of transcription 3 (STAT3) [9,10]. Phosphorylated STAT3 regulates the transcription of anti-apoptotic genes (e.g., Bcl-2, Mcl-1), proliferative genes (e.g., CyclinD1, c-Myc), and pro-inflammatory factors, thereby forming a positive feedback loop that continuously

drives tumor development [11]. IL-6 derived from adipocytes promotes breast cancer metastasis by activating the JAK/STAT3 and PI3K/AKT signaling pathways [12]. IL-6 activates STAT3-mediated signaling through the cGAS-STING pathway and the non-canonical NF-κB pathway, triggering chromosomal instability (CIN)-associated pro-tumorigenic effects. This mechanism plays a central regulatory role in the resistance of triple-negative breast cancer (TNBC) [13]. Cancer-associated fibroblasts (CAFs) induce trastuzumab resistance in HER2-positive breast cancer patients by activating multiple pathways, including JAK/STAT3 and PI3K/AKT [14].

1.3 The Central Regulatory Role of IL-6 in Breast Cancer

As a central regulator in the chemokine network, IL-6 recruits various immune cells through direct or indirect pathways to construct an immunosuppressive microenvironment. IL-6, in combination with TGF-β, induces the differentiation of naïve T cells into regulatory T cells (Tregs), which expand and suppress the function of $CD8^+$ cytotoxic T lymphocytes (CTLs), thereby establishing an immunosuppressive microenvironment [15]. Tumor-associated macrophages (TAMs) secrete IL-6 and CCL2 to form a positive feedback loop, further amplifying IL-6 secretion, promoting angiogenesis and extracellular matrix degradation, and creating a pro-tumorigenic inflammatory cycle [16]. IL-6, in synergy with IL-1β and TNF-α, activates the NF-κB pathway, amplifying the inflammatory response and inducing epithelial-mesenchymal transition (EMT), thereby enhancing metastatic potential.

As a context-dependent pleiotropic cytokine, the source and concentration of IL-6 can influence the dynamic balance of downstream signaling pathways, resulting in its dual role in promoting and inhibiting cancer in breast cancer. Acute release of IL-6 from skeletal muscles during exercise may contribute to cancer prevention through biological effects, including increased insulin sensitivity, induction of an anti-inflammatory environment, and reduced DNA damage [17]. In breast cancer, physical activity intensity is negatively correlated with IL-6 expression levels in older breast cancer survivors [18]. Studies have confirmed that exercise can reduce IL-6 levels by decreasing the amount and activity of adipose tissue, thereby inhibiting

inflammatory responses and tumor progression [19]. However, high levels of IL-6 detected in the early stages of invasive breast cancer may be associated with better prognosis [20]. Therefore, the role of IL-6 in modulating the tumor microenvironment and altering cancer cell motility and metastatic potential requires further investigation.

2. Current Clinical Applications of IL-6 in Breast Cancer

2.1 Anti-IL-6R Antibody Therapy

Targeting IL-6 and its receptor has become a focal point in the treatment of breast cancer. Due to the heterogeneity of breast cancer, different subtypes exhibit varying responses to IL-6-targeted therapies. Anti-IL-6R antibodies represent the most extensively studied IL-6-targeted approach. These antibodies block the binding of IL-6 to its receptor, thereby inhibiting the activation of the IL-6 signaling pathway. To date, no IL-6/JAK/STAT3 pathway inhibitors have been approved for the treatment of breast cancer. Tocilizumab, an anti-IL-6R antibody, is a clinically used drug that has been widely investigated in various cancers, including breast cancer. By blocking IL-6 signaling, tocilizumab selectively impairs the growth of triple-negative breast cancer (TNBC) cells with chromosomal instability (CIN) in culture [21], inhibits the ability of cancer-associated fibroblasts (CAFs) to promote epithelial-mesenchymal transition (EMT) [22], and reverses CAF-induced breast cancer cell growth and radioresistance [23].

Resistance to conventional chemotherapy and targeted therapies is a major bottleneck in the treatment of breast cancer. Targeting the IL-6/STAT3 signaling pathway with tocilizumab has been shown to successfully reverse tamoxifen resistance both in vitro and in vivo [24]. IL-6 collaborates with the STAT3 and p16INK4a pathways to promote the transformation of breast fibroblasts into CAFs and induce a cancer stem cell-like phenotype, thereby enhancing chemoresistance [18]. Tocilizumab has also been found to enhance the pro-apoptotic effects of cisplatin in humanized breast tumors [25]. In a study, patients with TNBC treated with tocilizumab in combination with chemotherapy experienced delayed tumor progression compared to those receiving docetaxel monotherapy [26]. Tocilizumab, either alone or in combination with HER2 inhibitors, inhibits the

IL-6-JAK2-STAT3-S100A8/9 axis and reduces the tumorigenicity of HR–/HER2+ breast cancer [27]. Recently, a Phase I clinical trial (NCT03135171) investigated the combination of tocilizumab with trastuzumab and pertuzumab in patients with metastatic trastuzumab-resistant HER2+ breast cancer. Combination therapy with anti-IL-6R and PD-L1 immunotherapy has been shown to more effectively reduce the stemness of TNBC cells and M2 macrophage activity compared to monotherapy [28]. Preliminary results from clinical trials combining tocilizumab with chemotherapy or immunotherapy suggest that this approach is effective for some patients with breast cancer. Overall, modulating the IL-6/IL-6Rα interaction has shown promising results across all breast cancer subtypes mediated by IL-6/JAK/STAT3 signaling.

2.2 Pathway Targeted Therapy

Given the central role of the IL-6/STAT3 pathway in breast cancer, in addition to directly inhibiting IL-6 and its receptor, researchers are also exploring other key components of the IL-6 pathway, such as JAK kinases and STAT3. Ruxolitinib, a potent JAK2 inhibitor, has been shown to attenuate STAT3 phosphorylation. Clinical studies have demonstrated [29] that ruxolitinib can inhibit the proliferation and tumor growth of tamoxifen-resistant breast cancer cells. The STAT3 pathway inhibitor S31-201 can suppress IL-6 expression and STAT3 activation in TNBC cells, and ruxolitinib alone can effectively inhibit JAK/STAT3 signaling [30]. Moreover, the combination of ruxolitinib and exemestane has proven effective in treating patients with aromatase inhibitor (AI) resistance and high systemic inflammation [31]. Ruxolitinib and calcitriol have exhibited synergistic anticancer effects in HER2-positive and triple-negative breast cancer subtypes [32]. Inhibitors targeting the IL-6-STAT3/AKT-PD-L1 axis can improve chemoresistance [33].

Considering the complex role of IL-6 in the development and progression of breast cancer, exploring the combination of IL-6-targeted therapies with other treatment modalities, such as chemotherapy, targeted therapy, and immunotherapy, holds significant clinical importance. There is a substantial body of clinical research outcomes in this area.

2.3 IL-6 Gene Therapy

Gene-editing technologies, such as CRISPR/Cas9, have been employed to knock out IL-6 and its related genes, thereby inhibiting the growth and spread of breast cancer cells. In colorectal cancer cell lines, IL-6 gene knockout has been shown to increase sensitivity to the chemotherapeutic drug cisplatin, a process that may be associated with the suppression of the STAT3 signaling pathway [34]. The MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes the progression of triple-negative breast cancer (TNBC) [35]. Knockdown of MCT-1 induces the expression of the tumor-suppressor gene miR-34a, thereby enhancing its antitumor activity in cancer cells. Knockout of MnSOD inhibits the invasion of TNBC cells, the activity of breast cancer stem cells (BCSCs), the production of mitochondrial reactive oxygen species (mROS), and IL-6 secretion promoted by MCT-1 [36]. This approach has demonstrated promising results in laboratory studies, but further clinical trials are needed to verify its safety and efficacy.

Conclusion and Outlook

As a pleiotropic cytokine, IL-6 regulates both anti-inflammatory and pro-inflammatory responses and plays a crucial role in the development, progression, and treatment resistance of breast cancer [37]. Breast cancer cells can hijack the IL-6/JAK/STAT3 signaling pathway to evade normal immune responses and further promote tumor growth by activating surrounding microenvironmental cells. The IL-6/STAT3 axis also plays an indispensable role in immune resistance [38] and hormone resistance [31]. Multiple therapeutic targets exist within the IL-6 pathway, including direct inhibition of IL-6, IL-6R, gp130 receptor, JAK, or STAT3 [39]. Although research on IL-6 in breast cancer has made some progress, there are still limitations in current studies. Current research aims to explore the potential role of IL-6 in the metastatic process in vitro [40] and to examine IL-6 expression in breast cancer tissues to determine their correlation with clinicopathological parameters and prognostic significance. Specifically, most studies have only confirmed the association between IL-6 levels and the malignant features of breast cancer [41, 42], but have not been able to distinguish whether it is a driver or a result of disease progression. Therefore, there is an urgent need for more clinical experiments and

research to verify the causal relationship between IL-6 and breast cancer. In addition, existing studies often focus excessively on the direct effects of IL-6 on breast cancer [43], while neglecting the complex interaction networks involved within breast cancer. This limitation in research methods, combined with insufficient interdisciplinary integration and limited cross-collaboration between tumor biology, immunology, and traditional Chinese medicine research fields, has collectively restricted our in-depth exploration of the mechanisms of action. Therefore, exploring the interactions between IL-6 and other biomarkers and fully understanding its role in breast cancer will require further experimental validation.

In summary, although research on IL-6 has made progress in promoting breast cancer progression, interactions with other signaling pathways, single or combined targeted therapies, and applications in clinical trials, we must clearly recognize that there is still a gap between current research achievements and practical clinical applications. Therefore, it is necessary to conduct more research on the role of IL-6 inhibitors in breast cancer. Future research should be committed to exploring more precise immunotherapy targets, expanding the application scope of targeted therapies for breast cancer, and providing a solid theoretical basis for the development of more targeted treatment strategies.

References

[1] Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263.

[2] Bray F, Laversanne M, Weiderpass E, et al. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer. 2021 Aug 15;127(16):3029-3030.

[3] Kang S, Narazaki M, Metwally H, et al. Historical overview of the interleukin-6 family cytokine. J Exp Med. 2020 May 4;217(5):e20190347.

[4] Masjedi A, Hashemi V, Hojjat-Farsangi M, et al. The significant role of interleukin-6 and its signaling pathway in the immunopathogenesis and treatment of breast cancer. Biomed Pharmacother. 2018 Dec;108:1415-1424.

[5] Mohamed AH, Ahmed AT, Al Abdulmonem W, et al., Interleukin-6 serves as a critical factor in various cancer progression and therapy. Med Oncol. 2024 Jun 20;41(7):182.

[6] Tang H, Bai Y, Shen W, Zhao J. Research progress on interleukin-6 in lung cancer. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2018 Dec 25;47(6):659-664. Chinese.
[7] Song M, Tang Y, Cao K, et al., Unveiling the role of interleukin-6 in pancreatic cancer occurrence and progression. Front Endocrinol (Lausanne). 2024 May 17;15:1408312.
[8] Huang B, Lang X, Li X. The role of IL-6/JAK2/STAT3 signaling pathway in cancers. Front Oncol. 2022 Dec 16;12:1023177.
[9] Kang S, Narazaki M, Metwally H, et al., Historical overview of the interleukin-6 family cytokine. J Exp Med. 2020 May 4;217(5):e20190347.
[10] Kampan NC, Xiang SD, McNally OM, et al., Immunotherapeutic Interleukin-6 or Interleukin-6 receptor blockade in cancer: challenges and opportunities. Curr Med Chem. 2017.
[11] Manore SG, Doheny DL, Wong GL, et al. IL-6/JAK/STAT3 Signaling in Breast Cancer Metastasis: Biology and Treatment. Front Oncol. 2022 Mar 15;12:866014.
[12] He JY, Wei XH, Li SJ, et al. Adipocyte-derived IL-6 and leptin promote breast Cancer metastasis via upregulation of Lysyl Hydroxylase-2 expression. Cell Commun Signal. 2018 Dec 18;16(1):100.
[13] Hong C, Schubert M, Tijhuis AE, et al. cGAS-STING drives the IL-6-dependent survival of chromosomally instable cancers. Nature. 2022 Jul;607(7918):366-373.
[14] Mao Y, Zhang Y, Qu Q, et al. Cancer-associated fibroblasts induce trastuzumab resistance in HER2 positive breast cancer cells. Mol Biosyst. 2015 Apr;11(4):1029-40.
[15] Huseni MA, Wang L, Klementowicz JE,et al. CD8+ T cell-intrinsic IL-6 signaling promotes resistance to anti-PD-L1 immunotherapy. Cell Rep Med. 2023 Jan 17;4(1):100878.
[16] Zhou B, Mo Z, Lai G, et al. Targeting tumor exosomal circular RNA cSERPINE2 suppresses breast cancer progression by modulating MALT1-NF-γB-IL-6 axis of tumor-associated macrophages. J Exp Clin Cancer Res. 2023 Feb 17;42(1):48.
[17] Orange ST, Leslie J, et al. The exercise IL-6 enigma in cancer. Trends Endocrinol Metab. 2023;34(11):749-763.
[18] Artese AL, Zhou X, Tometich DB, et al. Physical activity and cognition: longitudinal findings from the Thinking and Living with Cancer Study. J Natl Cancer Inst. 2024 Dec 1;116(12):2009-2021.
[19] Tan L, Mei J, Tang R, et al. Can exercise as a complementary technique manage inflammatory markers in women with breast cancer who are overweight and obese? A systematic review and meta-analysis. Complement Ther Med. 2025 Mar;88:103119.
[20] Ahmad N, Ammar A, Storr SJ, et al. IL-6 and IL-10 are associated with good prognosis in early stage invasive breast cancer patients. Cancer Immunol Immunother. 2018 Apr;67(4):537-549.
[21] Hong, C., Schubert, et al. cGAS–STING drives the IL-6-dependent survival of chromosomally instable cancers. Nature 607, 366–373 (2022).

[22] Al-Jomah N, Al-Mohanna FH, Aboussekhra A. Tocilizumab suppresses the pro-carcinogenic effects of breast cancer-associated fibroblasts through inhibition of the STAT3/AUF1 pathway. Carcinogenesis. 2021 Dec 31;42(12):1439-1448.
[23] Guo Z, Zhang H, Fu Y, et al. Cancer-associated fibroblasts induce growth and radioresistance of breast cancer cells through paracrine IL-6. Cell Death Discov. 2023 Jan 13;9(1):6.
[24] Tsoi H, Man EPS, Chau KM, et al. Targeting the IL-6/STAT3 Signalling Cascade to Reverse Tamoxifen Resistance in Estrogen Receptor Positive Breast Cancer. Cancers (Basel). 2021 Mar 25;13(7):1511.
[25] Alraouji NN, Al-Mohanna FH, Ghebeh H, et al. Tocilizumab potentiates cisplatin cytotoxicity and targets cancer stem cells in triple-negative breast cancer. Mol Carcinog. 2020 Sep;59(9):1041-1051.
[26] Chung AW, Kozielski AJ, Qian W, et al. Tocilizumab overcomes chemotherapy resistance in mesenchymal stem-like breast cancer by negating autocrine IL-1A induction of IL-6. NPJ Breast Cancer. 2022 Mar 8;8(1):30.
[27] Rodriguez-Barrueco R, Yu J, Saucedo-Cuevas LP, et al. Inhibition of the autocrine IL-6-JAK2-STAT3 -calprotectin axis as targeted therapy for HR-/HER2+ breast cancers. Genes Dev. 2015 Aug 1;29(15):1631-48.
[28] Haq ATA, Yang PP, Jin C, et al. Immunotherapeutic IL-6R and targeting the MCT-1/IL-6/CXCL7/PD-L1 circuit prevent relapse and metastasis of triple-negative breast cancer. Theranostics. 2024 Mar 3;14(5):2167-2189.
[29] Kim JW, Gautam J, Kim JE, et al. Inhibition of tumor growth and angiogenesis of tamoxifen-resistant breast cancer cells by ruxolitinib, a selective JAK2 inhibitor. Oncol Lett. 2019 Apr;17(4):3981-3989.
[30] Liu H, Yan R, Xiao Z, et al. Targeting DCLK1 attenuates tumor stemness and evokes antitumor immunity in triple-negative breast cancer by inhibiting IL-6/STAT3 signaling. Breast Cancer Res. 2023 Apr 17;25(1):43.
[31] Makhlin I, McAndrew NP, Wileyto EP, et al. Ruxolitinib and exemestane for estrogen receptor positive, aromatase inhibitor resistant advanced breast cancer. NPJ Breast Cancer. 2022 Nov 11;8(1):122.
[32] Schneider J, Jeon YW, Suh YJ, et al. Effects of Ruxolitinib and Calcitriol Combination Treatment on Various Molecular Subtypes of Breast Cancer. Int J Mol Sci. 2022 Feb 25;23(5):2535.
[33] Chuangchot N, Jamjuntra P, Yangngam S, et al. Enhancement of PD-L1-attenuated CAR-T cell function through breast cancer-associated fibroblasts-derived IL-6 signaling via STAT3/AKT pathways. Breast Cancer Res. 2023 Jul 21;25(1):86.
[34] 马燕,叶子瑜,梁艳芳,等.CRISPR/Cas9介导的IL-6基因敲除对结肠癌SW1116细胞化疗敏感性的影响[J].重庆医学,2018,47(32):4093-4097+4101.
[35] Weng, YS., Tseng, et al. MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes EMT progression, cancer stemness and M2 macrophage polarization in triple-negative breast cancer. Mol Cancer 18, 42 (2019).
[36] Al Haq AT, Tseng HY, Chen LM, et al. Targeting prooxidant MnSOD effect

inhibits triple-negative breast cancer (TNBC) progression and M2 macrophage functions under the oncogenic stress. Cell Death Dis. 2022 Jan 11;13(1):49.
[37] Habanjar O, Bingula R, Decombat C, et al. Crosstalk of Inflammatory Cytokines within the Breast Tumor Microenvironment. Int J Mol Sci. 2023 Feb 16;24(4):4002.
[38] Neo SY, Tong L, Chong J, et al. Tumor-associated NK cells drive MDSC-mediated tumor immune tolerance through the IL-6/STAT3 axis. Sci Transl Med. 2024 May 15;16(747):eadi2952.
[39] Cui Y, Cui S, Lu W, et al. CRP, IL-1α, IL-1β, and IL-6 levels and the risk of breast cancer: a two-sample Mendelian randomization study. Sci Rep. 2024 Jan 23;14(1):1982.
[40] Avalle L, Raggi L, Monteleone E, et al. STAT3 induces breast cancer growth via ANGPTL4, MMP13 and STC1 secretion by cancer associated fibroblasts. Oncogene. 2022 Mar;41(10):1456-1467.
[41] Zhou X, Zhao J, Yan T, et al. ANXA9 facilitates S100A4 and promotes breast cancer progression through modulating STAT3 pathway. Cell Death Dis. 2024 Apr 12;15(4):260.
[42] Ma Y, Zhu Y, Shang L, et al. LncRNA XIST regulates breast cancer stem cells by activating proinflammatory IL-6/STAT3 signaling. Oncogene. 2023 May;42(18):1419-1437.
[43] Zhang M, Ma N, Wang R. Mendelian Randomization Study on Causal Association of IL-6With Breast Cancer. Clin Breast Cancer. 2023 Jun;23(4):e182-e188.