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Interleukin-17 Signalling in Breast Cancer: Molecular Mechanisms and Therapeutic Prospects

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ABSTRACT

Background: Breast cancer remains the most commonly diagnosed malignancy among women and a leading cause of cancer-related mortality worldwide. Increasing evidence highlights the importance of immune-mediated inflammation as a driver of breast carcinogenesis, tumor progression, and therapeutic resistance. Among inflammatory cytokines, the interleukin-17 (IL-17) family has emerged as a central mediator linking innate and adaptive immune responses to the breast tumor microenvironment. IL-17 ligands, produced by Th17 cells, γδ T cells, neutrophils, macrophages, and stromal populations, engage IL-17 receptor complexes on tumor and immune cells to activate downstream NF-κB, MAPK, and STAT signaling pathways. These molecular events shape key tumor-promoting processes, including enhanced proliferation, epithelial–mesenchymal transition, angiogenesis, lymphangiogenesis, and recruitment of immunosuppressive myeloid cells. Nonetheless, accumulating data also reveal that IL-17 may exert antitumor functions in specific contexts through activation of cytotoxic lymphocytes, promotion of innate immune surveillance, and induction of apoptotic pathways within breast cancer cells.

This review provides an updated and integrated analysis of the IL-17 signaling axis in breast cancer, beginning with the structural and biochemical properties of IL-17 ligands and receptors, followed by an examination of their intracellular signaling mechanisms. We explore the diverse cellular sources of IL-17 within the tumor microenvironment, the regulatory networks governing IL-17 expression, and the clinical associations between IL-17 levels and breast cancer phenotypes. The dual tumor-promoting and tumor-restraining actions of IL-17 are discussed in detail, emphasizing how these context-dependent effects arise from the interplay between cytokine milieu, receptor expression patterns, molecular subtype, and immune composition of the tumor niche. Finally, we evaluate current and emerging therapeutic strategies aimed at modulating the IL-17 pathway, including monoclonal antibodies targeting IL-17 or IL-17R and combination approaches integrating IL-17 blockade with immune checkpoint inhibitors or targeted therapies.

A deeper mechanistic understanding of IL-17 biology in breast cancer will be essential for translating this knowledge into precision immunomodulatory therapies. Defining patient subsets most likely to benefit from IL-17-directed interventions represents a critical next step in optimizing clinical applications of this pathway.

Keywords: *Interleukin-17, Breast Cancer, Molecular Mechanisms*

1.Introduction

Breast cancer is the most frequently diagnosed malignancy among women and represents a major global burden, with incidence and mortality continuing to rise despite advances in screening and systemic therapy [1]. The disease encompasses a heterogeneous group of tumors with distinct histopathological features, molecular signatures, and therapeutic vulnerabilities. These include the major intrinsic subtypes—luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)—each characterized by unique biological behaviors and clinical outcomes [2]. Accumulating

10.48047/jocaaa.2024.33.06.158

evidence positions chronic inflammation as a fundamental contributor to breast carcinogenesis, acting through sustained cytokine signaling, oxidative stress, and remodeling of the tumor microenvironment (TME). In this context, immune-derived mediators increasingly appear as critical determinants of tumor progression, therapeutic resistance, and metastatic potential [3].

Among inflammatory cytokines, the interleukin-17 (IL-17) family has emerged as a key regulator at the interface of innate and adaptive immunity. Initially characterized for its role in host defense and autoimmune disorders, IL-17 signaling is now recognized as a potent modulator of tumor biology, particularly within epithelial malignancies such as breast cancer [4]. The IL-17 axis comprises six ligands and five receptor subunits that orchestrate a range of downstream molecular cascades, including NF-κB, MAPK, and STAT pathways, which collectively regulate cell survival, proliferation, angiogenesis, lymphangiogenesis, and recruitment of myeloid-derived suppressor cells (MDSCs) [4,5]. These processes are tightly integrated into the inflammatory circuitry of the breast TME, positioning IL-17 family cytokines as both biomarkers of disease behavior and potential modulators of therapeutic response [6].

Despite growing insights, the functional consequences of IL-17 signaling in breast cancer remain incompletely understood. Notably, IL-17 exhibits a dual, context-dependent role: while numerous studies demonstrate its tumor-promoting effects through enhancement of immunosuppressive inflammation, metastatic potential, and chemoresistance, other reports highlight antitumor activities involving activation of cytotoxic lymphocytes and apoptosis pathways in mammary epithelium [4,7]. The factors underlying these opposing outcomes—such as cytokine milieu, stromal composition, receptor expression, and molecular subtype—remain inadequately defined. This represents a critical research gap limiting effective translational application of IL-17-directed interventions [8].

2.Aim of the Review:

This review provides a comprehensive and mechanistically grounded analysis of IL-17 signaling in breast cancer. We synthesize current knowledge of IL-17 family biology, ligand–receptor interactions, downstream signaling mechanisms, and their functional consequences within the breast TME. We further examine clinical correlations between IL-17 expression and disease features and evaluate therapeutic strategies targeting the IL-17 axis. By integrating molecular biochemistry with translational oncology, the objective is to clarify IL-17's role as both a driver and potential suppressor of breast cancer and to identify opportunities for clinical intervention.

3. Biology of the IL-17 Cytokine Family

3.1 IL-17 Family Ligands

The interleukin-17 (IL-17) family comprises six cytokines—IL-17A, IL-17B, IL-17C, IL-17D, IL-17E/IL-25, and IL-17F—which share conserved structural characteristics yet exhibit diverse biological functions. IL-17A, the prototypic and most extensively studied member, is encoded on chromosome

10.48047/jocaaa.2024.33.06.158

6p12 and consists of 155 amino acids, forming homodimers or IL-17A/F heterodimers with closely related IL-17F [9]. While Th17 cells constitute the principal source of IL-17A, several innate and adaptive immune cells—including γδ T cells, NK cells, NKT cells, dendritic cells, macrophages, CD8+ T cells, and neutrophils—also contribute to IL-17 production, thereby broadening its immunological influence within peripheral tissues, including the breast tumor microenvironment [10]. IL-17F shares ~50% sequence homology with IL-17A and displays overlapping but generally weaker bioactivity, whereas IL-17A/F heterodimers exhibit intermediate potency, highlighting a fine-tuned gradation of signaling intensity [11]. Beyond these canonical Th17-associated members, IL-17B, IL-17C, IL-17D, and IL-17E participate in inflammatory and neoplastic pathways, with IL-17B/IL-17RB signaling implicated in tumor cell survival and aggressiveness in various cancers, including breast malignancies [12]. IL-17E/IL-25, conversely, is expressed by epithelial, endothelial, and immune cells and elicits potent type-2 immune responses, underscoring functional heterogeneity within the IL-17 cytokine family [13].

3.2 IL-17 Receptors and Structural Features

IL-17 cytokines exert their biological actions through five receptor subunits—IL-17RA, IL-17RB, IL-17RC, IL-17RD (SEF), and IL-17RE—which form heterodimeric complexes with specific ligand affinities. These receptors are broadly expressed in keratinocytes, fibroblasts, epithelial cells, endothelial cells, and diverse leukocyte subsets, enabling widespread responsiveness to IL-17 signals in tissues such as the mammary gland [14]. A hallmark of IL-17 receptors is the presence of the intracellular SEFIR (similar expression to fibroblast growth factor genes/IL-17R) domain, a structural motif essential for recruiting the adaptor protein Act1, which is indispensable for downstream signaling. In addition to SEFIR, IL-17RA possesses an extended regulatory region known as the SEFIR-extension (SEFEX), which forms a composite structural unit with SEFIR and enhances signaling competence, as demonstrated in mutational analyses and crystallographic studies [15]. Structural elucidations further reveal that IL-17RA adopts similar conformational changes on binding IL-17A or IL-17F, with conserved amino acid residues mediating ligand–receptor interactions across the IL-17 family [16]. Distinct receptor combinations confer ligand specificity—for example, IL-17A/F signals through IL-17RA–RC, IL-17B through IL-17RB, IL-17C through IL-17RA–RE, and IL-17E through IL-17RA–RB—while IL-17D's receptor remains undefined, representing a gap in cytokine biology with potential relevance to cancer [13,16].

3.3 IL-17 Signal Transduction

IL-17 receptor engagement initiates a unique signaling pathway fundamentally dependent on recruitment of the adaptor protein Act1 (CIKS), which binds IL-17RA via SEFIR–SEFIR domain interactions. Act1 contains E3 ubiquitin ligase activity enabling Lys63-linked ubiquitination of TRAF6, which subsequently activates canonical NF-κB and MAPK cascades, including ERK, JNK,

10.48047/jocaaa.2024.33.06.158

and p38 [17]. These transcriptional regulators induce expression of pro-inflammatory mediators, chemokines, and matrix-remodeling enzymes that collectively shape the inflammatory milieu characteristic of IL-17-responsive tissues. In addition to Act1–TRAF6 signaling, IL-17 stimulates C/EBP activation and stabilizes target mRNAs through recruitment of RNA-binding proteins, thereby amplifying cytokine responses even in the absence of strong transcriptional activation [18]. IL-17A/F signaling in breast cancer cells has been shown to increase NF-κB activity, ERK1/2 phosphorylation, and chemoresistance, underscoring the relevance of this pathway beyond classical immune responses [19]. Noncanonical IL-17 signaling also intersects with STAT3, PI3K/AKT, and AP-1, providing mechanistic links to proliferation, epithelial–mesenchymal transition, and metastasis observed in breast tumors. Collectively, IL-17 signal transduction represents a multifaceted network integrating inflammatory cues with oncogenic pathways, thereby contributing to tumor microenvironmental remodeling and disease progression [17–19].

4. IL-17 in the Breast Tumor Microenvironment

4.1 Cellular Sources of IL-17 in Breast Tumors

Within the breast tumor microenvironment (TME), IL-17 originates from multiple immune and stromal populations that cooperate to establish a chronic inflammatory state conducive to tumor progression. Th17 cells, characterized by their production of IL-17A and IL-17F, represent the primary adaptive immune source of IL-17 and accumulate as tumor-infiltrating lymphocytes (TILs) under the influence of IL-6, IL-1β, TGF-β, and other tumor-derived factors [20]. These Th17 cells exhibit a memory-like phenotype ($CD45RA^{-}CD45RO^{+}$) and express receptors such as CXCR4, CCR6, and CD161, which facilitate their homing to tumor tissues. In addition to Th17 cells, innate-like lymphocytes—including γδ T cells, natural killer (NK) and NKT cells—substantially contribute IL-17 in response to inflammatory cues, with γδ T cells representing potent and rapid producers of IL-17 in breast cancer models [21]. Neutrophils and macrophages within the TME also produce IL-17A and IL-17F under specific stimulatory conditions, further amplifying inflammatory loops that enhance myeloid cell recruitment. Stromal components such as cancer-associated fibroblasts (CAFs) can indirectly modulate IL-17 production or respond robustly to IL-17, contributing to extracellular matrix remodeling and tumor invasion. Collectively, these cellular sources create a multilayered IL-17–rich microenvironment with profound implications for tumor behavior [20–22].

4.2 IL-17 Expression Patterns and Clinical Associations in Breast Cancer

Elevated IL-17 expression has been observed in both tumor tissue and peripheral circulation of breast cancer patients, with significant correlations to adverse clinical and pathological features. Studies demonstrate that high IL-17A expression is strongly associated with larger tumor size, lymph node positivity, and increased recurrence risk; for instance, one cohort reported that 75% of patients with high IL-17A levels had tumors >5 cm and 92% exhibited nodal involvement, while low IL-17A

10.48047/jocaaa.2024.33.06.158

expression was linked to early-stage disease and absence of recurrence [23]. IL-17-producing cells are particularly abundant in aggressive subtypes such as triple-negative breast cancer (TNBC) and HER2-amplified tumors, reflecting the strong inflammatory phenotype of these cancers and their reliance on cytokine-driven signaling pathways [24]. Furthermore, serum IL-17 concentrations often rise in association with tumor burden and can fluctuate with treatment, suggesting potential utility as a biomarker for disease activity or therapeutic response. In early invasive breast cancer, higher densities of IL-17-positive TILs correlate with immunosuppressive microenvironmental features and poorer overall prognosis, although some studies describe context-dependent protective roles, indicating that IL-17's prognostic significance may vary by molecular subtype, immune contexture, and cytokine milieu [25]. Ultimately, the consistent association of IL-17 with clinicopathologic aggressiveness supports its mechanistic involvement in tumor progression and highlights its relevance as a biomarker and therapeutic target within breast cancer biology [23–25].

5. Tumor-Promoting Functions of IL-17 in Breast Cancer

5.1 Direct Pro-Tumorigenic Effects on Breast Cancer Cells

IL-17 exerts potent tumor-promoting activity by directly stimulating breast cancer cells through IL-17RA/RC receptor complexes, triggering downstream activation of NF-κB, MAPKs, and STAT transcriptional programs [26]. Activation of these cascades enhances tumor cell proliferation, survival, and resistance to apoptosis by upregulating anti-apoptotic proteins and pro-survival kinases, while also promoting epithelial–mesenchymal transition (EMT) and motility. IL-17 has been shown to promote chemoresistance by inducing ERK1/2 activation and inflammatory gene expression in breast cancer cell lines, thereby reducing responsiveness to cytotoxic agents [27]. Moreover, IL-17 can augment HER family receptor signaling, particularly HER1/EGFR, which synergistically amplifies proliferative and invasive behaviors in aggressive tumor subtypes. These molecular interactions underscore IL-17's role as a biochemical driver of malignant cell remodeling and highlight the convergence of inflammatory and oncogenic pathways within the breast tumor niche [26–28].

5.2 Promotion of Angiogenesis and Lymphangiogenesis

IL-17 significantly contributes to neovascularization by inducing the secretion of vascular endothelial growth factor (VEGF) family members, including VEGF-A and VEGF-C, which stimulate endothelial proliferation and enhance vascular permeability [29]. In breast cancer models, IL-17 promotes lymphangiogenesis through upregulation of VEGF-C in both tumor and stromal compartments, facilitating expansion of lymphatic endothelial networks that support metastatic dissemination. Increased IL-17-producing cell infiltration has been correlated with accelerated lymphatic vessel sprouting, higher lymph node metastasis, and poorer survival outcomes, particularly in aggressive subtypes [30]. Additionally, IL-17-mediated activation of NF-κB and STAT3 pathways reinforces pro-

10.48047/jocaaa.2024.33.06.158

angiogenic gene expression while fostering cross-talk with hypoxia-inducible factors, further enhancing vascular remodeling under hypoxic TME conditions. These findings integrate IL-17 into the broader framework of angiogenic and lymphangiogenic signaling, supporting a mechanistic basis for its association with metastatic progression in breast cancer [29–30].

5.3 Immune Evasion and Establishment of a Protumor Inflammatory Microenvironment

A hallmark of IL-17-driven tumor promotion is its capacity to remodel the immune landscape into an immunosuppressive environment that favors tumor expansion. IL-17 induces systemic and intratumoral granulocyte colony-stimulating factor (G-CSF) production, leading to recruitment and activation of neutrophils and myeloid-derived suppressor cells (MDSC-like populations), which inhibit CD8+ T-cell cytotoxicity and facilitate immune escape [31]. In breast cancer, IL-17-producing γδ T cells and neutrophils act cooperatively to enhance metastatic potential by suppressing antitumor immunity through ROS production, T-cell exclusion, and secretion of immunosuppressive cytokines. IL-17 also stimulates CAFs to produce chemokines and matrix metalloproteinases, thereby enhancing extracellular matrix degradation, tumor invasion, and metastatic fitness [32]. These alterations collectively shift the TME toward chronic inflammation characterized by immune dysregulation, stromal activation, and diminished effector lymphocyte function. This protumor immunological reprogramming represents a central mechanism by which IL-17 accelerates breast cancer progression andmetastasis[31–32].

6. Tumor-Protective and Context-Dependent Roles of IL-17 in Breast Cancer

6.1 Direct Antitumor Effects of IL-17 on Breast Cancer Cells

Although IL-17 is widely recognized for its tumor-promoting functions, evidence indicates that IL-17 can also exert direct antitumor effects under specific biological contexts. Non-malignant mammary epithelial cells have been shown to secrete IL-17, which binds IL-17R on breast cancer cells and induces caspase-mediated apoptosis, suggesting that IL-17 may participate in intrinsic tumor-suppressive surveillance mechanisms [33]. This apoptotic response appears to involve receptor-mediated activation of pro-death signaling cascades rather than inflammatory proliferative pathways. Variability in receptor subunit expression, particularly the balance between IL-17RA and IL-17RC, may determine the strength and nature of signaling outputs, influencing whether IL-17 stimulation favors cell death or survival. In early tumorigenesis, IL-17-induced apoptosis may function as a mechanism to eliminate emerging malignant clones before the establishment of an immunosuppressive microenvironment. These observations underscore the complexity of IL-17 biology and highlight the importance of cellular context in determining its functional consequences [33–34].

6.2 IL-17 Enhancement of Antitumor Immunity

IL-17 also contributes indirectly to tumor suppression by modulating innate and adaptive immune responses that oppose cancer progression. IL-17 can promote recruitment and activation of cytotoxic

10.48047/jocaaa.2024.33.06.158

immune populations, including NK cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), thereby enhancing antitumor effector functions [34]. Through induction of chemokines such as CXCL9 and CXCL10 in specific inflammatory environments, IL-17 may facilitate lymphocyte trafficking to tumor sites and strengthen antitumor immune surveillance. In certain settings, IL-17-induced inflammation synergizes with IL-6/STAT3 and IL-12/IFN-γ pathways to potentiate Th1 and CTL responses, thereby shifting the immune landscape toward tumor rejection. Furthermore, IL-17 signaling may modulate antigen-presenting cell function, enhancing dendritic cell maturation and promoting effective T-cell priming. These protective mechanisms are particularly evident in early-stage disease or in tumors that remain immunologically "hot," where effector immune cells have not yet been functionally excluded by suppressive myeloid populations. Thus, IL-17's capacity to reinforce anti-tumor immunity represents a biologically significant counterbalance to its protumor roles [34–35].

6.3 Determinants of IL-17's Dualistic Behavior in Breast Cancer

The dichotomous actions of IL-17—tumor-promoting in some contexts and tumor-suppressing in others—reflect intricate interplay between cytokine milieu, receptor expression, tumor subtype, and the evolving microenvironment. IL-17's effects are strongly shaped by the cellular composition of the TME: in neutrophil- or MDSC-dominant environments, IL-17 reinforces immunosuppression and metastasis, whereas in lymphocyte-rich microenvironments it can potentiate cytotoxic immunity [35]. Breast cancer molecular subtype further influences IL-17 signaling outcomes, with TNBC and HER2-enriched tumors exhibiting heightened sensitivity to IL-17–driven inflammatory pathways, while luminal tumors may display more balanced or even protective responses. Crosstalk between IL-17 and oncogenic pathways—such as HER1, HIF-1α, or STAT3—can favor protumor phenotypes, whereas integration with apoptotic or immune-stimulatory pathways may yield antitumor effects. Additionally, temporal dynamics matter: IL-17 may be protective during early tumor evolution but becomes tumor-promoting as chronic inflammation, stromal activation, and immune dysregulation progress. Understanding these determinants is essential for designing precision therapies that modulate IL-17 signaling in a subtype- and context-specific manner [35–36].

7. IL-17 Crosstalk with Key Oncogenic Pathways in Breast Cancer

7.1 IL-17 Interaction with ER, HER2, and EGFR/HER1 Signaling

IL-17 signaling intersects with several oncogenic pathways in breast cancer, most notably the estrogen receptor (ER), HER2, and EGFR/HER1 axes. In ER-negative and HER2-enriched tumors, IL-17 can potentiate tumor cell proliferation by enhancing MAPK and NF-κB activity, thereby amplifying downstream transcriptional programs that promote growth and resistance to apoptosis [37]. Evidence from breast cancer cell models demonstrates that IL-17A stimulation increases phosphorylation of ERK1/2 and augments EGFR/HER1 signaling, which synergistically promotes invasion and survival, particularly in highly inflammatory subtypes such as TNBC [38]. HER2-overexpressing tumors show

10.48047/jocaaa.2024.33.06.158

increased IL-17B/IL-17RB signaling, which correlates with aggressive behavior and therapeutic resistance; inhibition of IL-17RB reduces tumorigenicity in HER2-amplified models, underscoring the pathological integration of cytokine-driven and receptor tyrosine kinase pathways [39]. Crosstalk between IL-17 and ER signaling is less direct but may involve modulation of cytokine-responsive transcription factors that alter ER pathway sensitivity, especially in endocrine-resistant disease. Together, these findings reveal IL-17 as a biochemical amplifier of key receptor-mediated oncogenic cascades in breast cancer [37–39].

7.2 Integration of IL-17 Signaling with NF-κB, STAT3, and the Inflammatory Circuitry

IL-17 plays a central role in coordinating inflammatory signaling through its convergent activation of canonical NF-κB and STAT3 pathways, which are frequently dysregulated in breast cancer. NF-κB activation downstream of the Act1–TRAF6 axis results in upregulation of chemokines, cytokines, and matrix-remodeling enzymes that promote tumor growth and immune evasion [40]. IL-17 also acts in synergy with IL-6 and other inflammatory mediators to activate STAT3, a transcription factor known to drive proliferation, EMT, stemness, and metastasis in aggressive breast cancer phenotypes. This IL-17–STAT3–NF-κB network creates a positive feedback loop that sustains chronic inflammation and recruits suppressive immune subsets, including neutrophils and myeloid-derived suppressor cells (MDSCs) [41]. As a result, these signaling interactions not only reshape the tumor microenvironment but also promote therapy resistance by enhancing DNA repair, survival pathways, and anti-apoptotic programs. The integration of IL-17 with major inflammatory regulators positions the cytokine as a central orchestrator of tumor-promoting inflammation [40–41].

7.3 IL-17, Metabolic Reprogramming, and Hypoxia-Associated Pathways

IL-17 also interfaces with metabolic pathways essential for breast cancer growth, including glycolysis and hypoxia responses. IL-17-mediated activation of NF-κB and STAT3 enhances expression of glutamine and glucose transporters, including GLUT1 and GLUT3, which support the Warburg metabolic phenotype that characterizes many breast cancer subtypes [42]. Through promotion of sustained inflammatory signaling, IL-17 indirectly stabilizes HIF-1α, enhancing transcription of glycolytic enzymes and facilitating adaptation to hypoxic tumor niches [43]. These metabolic alterations confer proliferative advantages, resistance to apoptosis, and increased invasive potential. Furthermore, IL-17-driven neutrophil infiltration contributes to hypoxic remodeling through reactive oxygen species (ROS) production and extracellular matrix degradation, processes known to accelerate angiogenesis and metastatic dissemination. Because metabolic reprogramming is tightly associated with therapeutic resistance—particularly to chemotherapy and radiotherapy—the IL-17–metabolism axis represents an important mechanistic link between inflammation and treatment failure [42–43].

7.4 Crosstalk Between IL-17 and Non-Coding RNAs in Breast Cancer

10.48047/jocaaa.2024.33.06.158

Emerging evidence indicates that IL-17 signaling interacts with regulatory non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs), which modulate inflammatory and oncogenic processes. LncRNA NEAT1, frequently overexpressed in breast cancer, enhances IL-6/STAT3 signaling and supports tumor growth, metastasis, and chemoresistance, forming feedback circuits that can potentiate IL-17–driven inflammation [44]. NEAT1 can also regulate the transcription of IL-17-responsive genes by stabilizing paraspeckle structures that modulate RNA processing and stress responses, contributing to breast cancer metabolic adaptation and survival. Additional ncRNAs, such as miR-124, have been shown to interact with STAT3 signaling, further linking IL-17-associated inflammatory pathways to the post-transcriptional regulatory landscape [45]. These interactions highlight how IL-17 does not act as a stand-alone cytokine but is embedded within multilayered regulatory networks that include ncRNA-mediated modulation of oncogenic programs. Understanding these networks offers opportunities to develop combined IL-17 and ncRNA-targeted therapies for difficult-to-treat breast cancer subtypes [44–45].

8. Clinical Evidence: IL-17 as a Biomarker in Breast Cancer

8.1 Serum IL-17 Levels and Clinical Outcomes

Clinical studies evaluating circulating IL-17 concentrations consistently demonstrate that elevated serum IL-17 is associated with more advanced disease and adverse prognostic indicators in breast cancer. Patients presenting with high serum IL-17 frequently exhibit larger tumors, higher stage at diagnosis, and increased likelihood of lymph node involvement [46]. These elevated levels often correlate with intensified systemic inflammation and a more immunosuppressive profile, characterized by increased neutrophil counts and reduced cytotoxic T-cell activity. Furthermore, IL-17 levels may fluctuate in response to treatment: some studies observed a significant decline in serum IL-17 following chemotherapy, suggesting that IL-17 could serve as a dynamic biomarker of therapeutic response or tumor burden. However, heterogeneity in assay methods and timing of sampling currently limits the establishment of universal clinical cutoffs. Despite these limitations, the cumulative evidence supports circulating IL-17 as a potentially valuable serological marker for disease monitoring and prognostication in breast cancer [46–47].

8.2 Tumor-Infiltrating IL-17–Producing Cells as Prognostic Indicators

Assessments of IL-17 expression within breast tumor tissues reveal that IL-17–producing tumor-infiltrating lymphocytes (TILs) hold strong prognostic relevance. Immunohistochemical analyses have shown that patients with high densities of IL-17A-positive cells are more likely to present with aggressive disease features, including high tumor grade, increased proliferation indices, and greater metastatic risk [48]. These IL-17–rich microenvironments often reflect extensive recruitment of γδ T cells and Th17 cells, along with enrichment of neutrophils and myeloid-derived suppressor cells

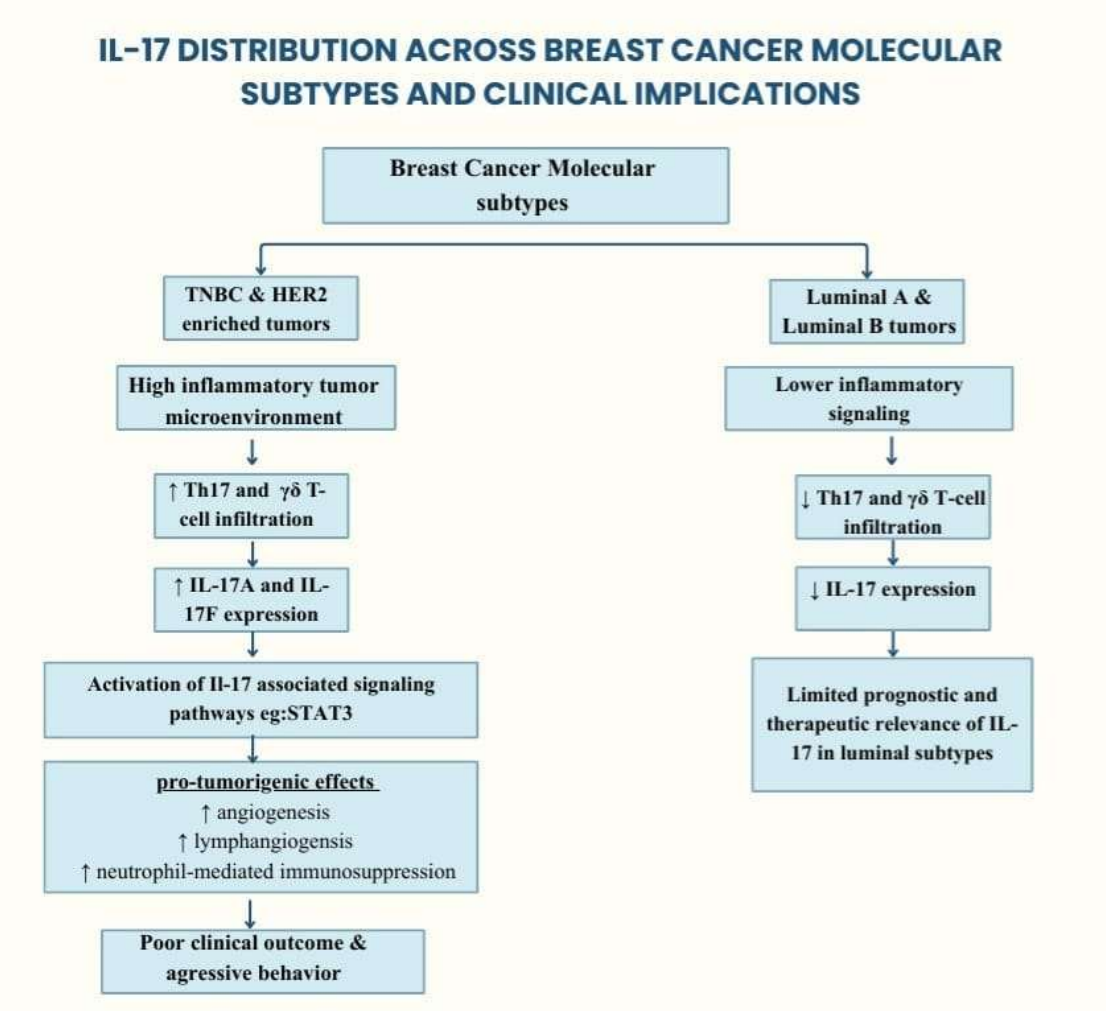
10.48047/jocaaa.2024.33.06.158

(MDSCs), which collectively reinforce immune evasion and promote tumor progression. In early invasive breast cancer, increased IL-17 expression correlates with poorer relapse-free survival, suggesting that IL-17 could serve as a tissue-based prognostic biomarker for early-stage disease. Importantly, some heterogeneity exists between subtypes: TNBC and HER2-positive tumors tend to exhibit higher IL-17 expression, whereas luminal tumors more frequently display lower densities of IL-17–producing cells. This subtype dependence underscores the need for biomarker stratification when integrating IL-17 into clinical decision-making frameworks [48–49].

8.3 IL-17 Expression Across Molecular Subtypes and Implications for Targeted Therapies

The distribution of IL-17 varies significantly across molecular subtypes of breast cancer, contributing to its prognostic and therapeutic significance. Studies show that TNBC and HER2-enriched tumors, which are characterized by high inflammatory signatures, tend to express elevated IL-17A and IL-17F, reflecting the enhanced presence of Th17 and γδ T-cell populations [49]. High IL-17 expression in these subtypes correlates with increased angiogenesis, lymphangiogenesis, and neutrophil-mediated immunosuppression, all of which contribute to poor clinical outcomes. In contrast, luminal A and luminal B tumors frequently exhibit lower IL-17 expression and may demonstrate weaker associations with IL-17-driven inflammatory pathways. These subtype-specific patterns suggest that IL-17–based therapeutic strategies may be particularly relevant for TNBC and HER2-positive disease, where IL-17 intersects with signaling networks such as STAT3, EGFR/HER1, and HER2. Incorporating IL-17 profiling into molecular diagnostics may allow identification of patients most likely to benefit from IL-17-targeted interventions or combination immunotherapies **(Figure 1)** [49–50].

10.48047/jocaaa.2024.33.06.158



(Figure 1). Schematic illustrating subtype-specific IL-17 expression in breast cancer, with elevated IL-17 signaling in TNBC and HER2-enriched tumors and limited IL-17-mediated relevance in luminal subtypes

9. IL-17 as a Therapeutic Target in Breast Cancer

9.1 Direct Targeting of the IL-17/IL-17R Axis

Therapeutic blockade of IL-17 signaling has gained considerable attention due to the cytokine's central role in breast cancer–associated inflammation, tumor progression, and immunosuppression. Biological agents targeting IL-17A or IL-17RA—originally developed for autoimmune disorders such as psoriasis—demonstrate promising antitumor effects in preclinical breast cancer models [51]. Secukinumab, a fully human monoclonal antibody against IL-17A, significantly reduces tumor growth in murine ER-negative and triple-negative breast cancer (TNBC) models by decreasing regulatory T-cell infiltration, reducing PD-L1 expression, and enhancing CD4+ and CD8+ T-cell responses within the tumor microenvironment. These findings support repurposing IL-17 inhibitors for breast cancer

10.48047/jocaaa.2024.33.06.158

treatment, especially in subtypes characterized by high IL-17 expression and inflammatory activity [52].

9.2 Combination Therapies Involving IL-17 Blockade

Given the complex and interconnected role of IL-17 in tumor immunity, combination therapeutic strategies may offer superior benefits compared to monotherapy. One of the most compelling combinations involves co-inhibition of IL-17A and PD-1/PD-L1 pathways. IL-17A enhances PD-L1 expression on tumor cells, promoting immune escape; therefore, simultaneous blockade of IL-17A and immune checkpoint inhibitors augments antitumor immunity more effectively than either agent alone [51,53]. In ER-negative murine models, dual treatment with secukinumab and pembrolizumab led to marked tumor regression and restored immune competence. IL-17 inhibition may also synergize with HER2-targeted therapies by reversing IL-17B-mediated resistance mechanisms, particularly in trastuzumab-resistant HER2-positive cells [52]. Furthermore, preclinical evidence suggests that IL-17 blockade increases sensitivity to chemotherapy and radiotherapy by reducing inflammatory signaling, improving DNA damage responses, and mitigating neutrophil-driven immunosuppression that limits treatment efficacy. Such combination regimens could be especially advantageous in TNBC, where targeted therapy options remain limited [53].

9.3 Challenges, Safety Considerations, and Translational Barriers

Despite promising therapeutic potential, several challenges complicate the translation of IL-17–targeted therapy into clinical practice. IL-17 plays a nonredundant role in mucocutaneous immunity, particularly in defense against fungal and extracellular bacterial pathogens; thus, IL-17 blockade increases the risk of infections, which must be carefully managed in cancer patients who may already be immunocompromised [54]. Another major barrier lies in the context-dependent and sometimes contradictory effects of IL-17 in breast cancer. Because IL-17 can stimulate either protumor inflammation or antitumor immunity depending on tumor subtype, cytokine milieu, and immune landscape, indiscriminate inhibition may not benefit all patients and could even be detrimental in specific contexts. Biomarker-driven patient selection—potentially involving IL-17 cytokine levels, IL-17R expression patterns, immune infiltration profiles, and molecular subtype—will be essential for optimizing therapeutic outcomes [55]. Furthermore, a lack of clinical trials directly evaluating IL-17 inhibitors in breast cancer highlights the need for robust translational studies to define dosing schedules, safety profiles, and effective combinations. Overcoming these barriers is critical for integrating IL-17 blockade into precision immunotherapy strategies for breast cancer.

10.48047/jocaaa.2024.33.06.158

Conclusion

Interleukin-17 (IL-17) has emerged as a central immunological and biochemical modulator in breast cancer, exerting profound effects across tumor initiation, progression, metastasis, and therapeutic responsiveness. Its signaling pathways—mediated primarily through IL-17A/F and their receptor complexes—integrate inflammatory cues with oncogenic networks such as NF-κB, MAPKs, STAT3, and metabolic reprogramming pathways. This integration shapes key hallmarks of breast cancer, including enhanced proliferation, epithelial–mesenchymal transition, angiogenesis, lymphangiogenesis, and immune evasion. The robust capacity of IL-17 to recruit and activate neutrophils, γδ T cells, and myeloid-derived suppressor cells further contributes to the establishment of an immunosuppressive tumor microenvironment that favors metastasis and therapeutic resistance.

At the same time, IL-17 exhibits a striking context dependency, capable of mediating antitumor responses under specific biological conditions. These include direct induction of caspase-mediated apoptosis in breast cancer cells and facilitation of cytotoxic lymphocyte recruitment and activation. The balance between these opposing functions is influenced by a complex interaction of cytokine milieu, tumor subtype, receptor expression patterns, stromal composition, and disease stage. This duality underscores the need for a nuanced understanding of IL-17 biology when considering therapeutic modulation of the pathway.

The translational interest in IL-17 as a therapeutic target continues to grow, driven by encouraging preclinical data demonstrating that IL-17 blockade—alone or in combination with immune checkpoint inhibitors or HER2-targeted agents—can enhance antitumor immunity and overcome key mechanisms of resistance. Nonetheless, several challenges impede clinical implementation, including the essential role of IL-17 in host defense, its complex bidirectional functions in tumor biology, and the lack of validated biomarkers to identify patients most likely to benefit from IL-17–directed therapies.

Overall, IL-17 represents both an opportunity and a challenge in breast cancer management: a powerful driver of protumor inflammation that can also serve as a therapeutic fulcrum if precisely targeted. Future progress will depend on integrating mechanistic insights, molecular subtype stratification, and immune profiling into clinical trial design, ultimately enabling precision immunomodulatory strategies that leverage the IL-17 axis to improve outcomes for patients with breast cancer.

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