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REVIEW

The role of IL-1, IL-6 and TNF-α in breast cancer development and progression

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Keywords
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Abstract

Background: Breast cancer (BC) is the most diagnosed cancer among women worldwide and the second-most cause of women's deaths. The interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) are critical for BC pathogenesis. They participate in BC development and progression by regulating several pathways. The findings of this review paper can potentially guide the development of targeted therapies that can improve the prognosis and treatment outcomes for BC patients. **Objective:** To make a comprehensive and up-to-date review of the original papers on the role of IL-1, IL-6, and TNF-α in BC development and progression. **Method:** This literature review is an iterative and objective analysis of the English original papers published in the last five years, which linked IL-1, IL-6, TNF-α, and BC. **Result:** IL-1, IL-6, and TNF-α significantly affect angiogenesis, proliferation, apoptosis, survival, and metastatic in BC by regulating the PI3K-PKB/Akt, JNK, IL-6/JAK/STAT3, Ras/Raf, AKT, MAPK, and NF-κB pathways. They also modulate the TME by promoting the production of extracellular matrix components and stimulating the recruitment of immune cells. **Conclusion:** Inhibiting IL-1, IL-6, and TNF-α and their downstream signalling intermediates could be promising strategies for suppressing BC development and progression. Further in-depth research is necessary to develop novel targeted therapies and improve patient outcomes.

Introduction

Breast cancer (BC) is a worldwide health thrilling disease. It is the most frequently diagnosed cancer among women and the second-most prevalent reason for women's deaths (Rahmani *et al*., 2020; Wang *et al*., 2020; Perez-Tejada *et al*., 2021; Wilkinson & Gathani, 2022). Numerous studies have shown that proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), are crucial in BC development and progression (Zielińska *et al*., 2018). They can alter cancer cells' behaviour or microenvironment by activating particular signalling pathways (Zielińska *et al*., 2018; Tzang *et al*., 2020). They regulate the duration and intensity of the inflammatory and immune responses (Gelfo *et al*., 2020; Zhao *et al*., 2021).

Despite improvements in cancer therapy, more than 410,000 women die each year (Zan *et al*., 2019). Metastasis and resistance to existing treatments are the leading causes of patient death (Zan *et al*., 2019). Therefore, this review paper is a comprehensive and up-to-date review of the original papers in the last five years on the roles of IL-1, IL-6, and TNF-α in BC development and progression. Thus, the findings of this review paper have the potential to guide the development of targeted therapies that can improve the prognosis and treatment outcomes for breast cancer patients.

Method

This paper followed the ENTREQ guidelines (Appendix A) as an iterative and objective analysis of the original English papers published in the last five years, which linked IL-1, IL-6, TNF-α, and breast cancer. Search was conducted on PubMed and Scopus databases using the following query on PubMed: ("*proinflammatory cytokines*"[Title] OR "*pro-inflammatory cytokines*"[Title] OR "*IL-1*"[Title] OR "*interleukin-1*"[Title] OR "*IL-6*"[Title] OR "*interleukin-6*"[Title] OR "*TNF-α*"[Title] OR "*TNF-alpha*"[Title] OR "*tumour* necrosis factor alpha*"[Title]) AND ("breast cancer"[Title]) AND (2018/1/1:2022/12/31[pdat]). The query was adjusted for the Scopus search. The title, abstract and full text were screened by two reviewers to check for their relevancy in making the necessary assessments to obtain the results.

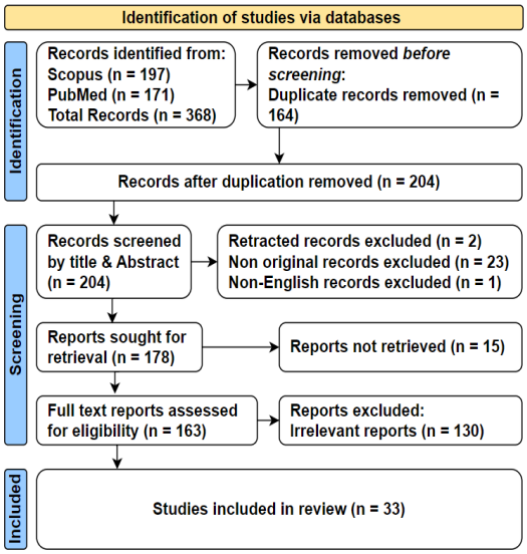

Figure 1: A PRISMA diagram for the review selection process

Results

After searching the electronic databases, (368) articles were identified. After importing the records to EndNote software version 20.5, duplicates (164) were removed, resulting in a total of 204 records. Exactly 178 records remained after the "*Title and Abstract*" screening. Finally, full-text screening and application of the inclusion and exclusion criteria resulted in the 31 studies included in this review. Figure 1 illustrates A PRISMA diagram for the selection process.

Discussion

Proinflammatory cytokines and BC

Several types of tumours exhibit excessive production of specific cytokines, which are crucial in BC development and progression (Table I) (Fasoulakis *et al*., 2018; Zimta *et al*., 2019). These cytokines can function in an autocrine manner, stimulating the programming changes in MAPK, STAT3, RAS gene, metabolism re-adjusted, RAF gene, and NF-κB. These pathways may activate angiogenesis-promoting mechanisms, such as the Epithelial-mesenchymal transition (EMT), proliferation, anti-apoptosis, and migration (Briukhovetska *et al*., 2021). Cytokines modify the activity of tumour cells or the tumour microenvironment (TME) via particular pathways. Studies have indicated that cancer TME and metastatic sites contain IL-6, IL-1, and TNF-α (Tzang *et al*., 2020), which activate the JAK/STAT3 (Zhao *et al*., 2021) and NF-κB pathways, resulting in BC cell proliferation and anti-apoptosis (Fasoulakis *et al*., 2018; Zimta *et al*., 2019; Malla & Kiran, 2022).

Table I: The impact of Proinflammatory cytokines in BC development and progression

Cytokine	Source	Impact on immunity	Impact on BC
IL-1	MP, DC	Induces the release of other proinflammatory intermediaries and stimulates Th17.	Provides a tacky prognosis, and enhances cancer cell expansion, transition and invasiveness.
IL-6	T cells, MP	Activates JAK/STAT3 pathway, prevents infection, boosts tissue infiltration and promotes the inflammatory response.	Provides tacky prognosis and elevates statuses in progressive phases of BC
TNF-α	NK, NEUT, Mastocyte, Eos	Promotes inflammatory response and has a controlling role in immune response	Inflammatory initiation, enhances BC cell apoptosis, increases BC cell transition and Stimulates NF-κB.

MP: Macrophages, DC: Dendritic cells, T cells: T lymphocyte and thymocyte, NK; Natural killer cells, NEUT: Neutrophils, Eos: Eosinophil.

The role of IL-1 in BC

The IL-1 family consists of cytokines inducers, including the IL-1α, IL-1β, IL-33 and IL-1RA, which is a cytokines inhibitor (Fasoulakis *et al*., 2018; Rébé & Ghiringhelli, 2020; Diep *et al*., 2022). The main produced IL-1 agonist, which is prevalent in the TME, is IL-1β. Myeloid cells create IL-1β in the TME infiltrating, whereas epithelial tumour cells produce IL-1α (Kaplanov *et al*., 2019). Current research indicates that IL-1 is present in its primordial form in all tumour cells originating from epithelial cells, which will be readily available following the cells' death through necrosis or processing in its active state by inflammasome activation, resulting in tumour formation (Gelfo *et al*., 2020). IL-1β is the main form of IL-1 associated with breast cancer (Nisar *et al*., 2021), where it promotes metastasis and progression. Moreover, IL-1β is required to create IL-22, a cytokine that promotes cancer and reduces the anti-tumour effects of some chemotherapy (Kaplanov *et al*., 2019).

According to Rébé & Ghiringhelli (2020), BC samples isolated from patients express the IL-1 beta protein (Rebe & Ghiringhelli, 2020). Moreover, IL-1β is elevated during the onset and growth of BC, and polymorphisms of IL-1β and IL-1βR are associated with the initiation of BC. A hypothesis suggests that IL-1 stimulates IL-6 secretion via the activation of NF-κB. This results in increasing the severity of luminal BC. A different experiment used a fibroblast FGFR1-induced mouse mammary cancer model to describe another mechanism. It linked early-stage mammary tumours to COX-2 expression mediated by IL-1β (Rébé & Ghiringhelli 2020). Research showed that animals lacking the IL-1 gene occupied smaller tumours and reduced cancer growth compared to those who have the gene. Also, animals treated with anti-IL-1 antibodies had a reduction in tumour growth. This indicates that suppressing IL-1 in TME could inhibit BC growth (Gomes *et al*., 2019; Kaplanov *et al*., 2019).

The role of IL-6 in BC

The IL-6 is receiving considerable attention with the most robust understanding of its central function pathologically and physiologically. Many solid tumours, including BC, exhibit high concentrations of IL-6 (Chen *et al*., 2022). It has some biological effects, including promoting malignant cell proliferation in human myeloma and mouse plasmacytoma (Chonov *et al*., 2019).

The conventional IL-6/JAK/STAT3 pathways increase the multiplication and suppress the apoptosis of BC cells by activating the bcl-2, Bax, c-myc, and cyclin D-1 transcription (Ma *et al*., 2020). When IL-6 binds to IL-6R, it homodimerises gp130, which stimulates JAK (Chen *et al*., 2022; Huang *et al*., 2022; To *et al*., 2022); this phosphorylates STAT3 (Masjedi *et al*., 2018). The binding of stimulated STAT3 to other STAT proteins to create homodimers or heterodimers facilitates the transcription of many different gene pathways which promote BC development and progression (Chen *et al*., 2022; Huang *et al*., 2022; To *et al*., 2022).

Studies of the impact of IL-6 on BC cell lines conducted *in vitro* provided mixed findings (Taher *et al*., 2018). In some cases, IL-6 promotes tumour growth, while in others, it has a suppression effect. These mixed findings align with the significant levels of IL-6 found in the supernatants of MCF-7/Adriamycin multidrug-resistant BC cells but not in those of the original sensitive cells (Taher *et al*., 2018). Furthermore, introducing exogenous IL-6 to MCF-7 cells increased their doxorubicin resistance by eight to ten-fold (Taher *et al*., 2018). In contrast, the altered MCF-7 cells expressing IL-6 exhibited much higher resistance to various medications, with a 70-fold increase (Taher *et al*., 2018). The possible differences in IL-6 production patterns could be because multidrug-resistant BC cells have a different genetic makeup from non-multidrug-resistant BC cells. This means that they may have different levels of expression of genes that are involved in the production and regulation of IL-6. Another possibility is that multidrug-resistant BC cells are exposed to different environmental factors unlike the non-multidrug-resistant BC cells (Martínez-Pérez *et al*., 2021).

Moreover, the up-regulation of IL-6 has been documented at the systemic and local levels in BC (Masjedi *et al*., 2018). The augmentation of IL-6 in the blood is linked with unfavourable prognosis and reduced survival rates among BC patients. High levels of IL-6 can affect all aspects of the tumourigenesis process by regulating proliferation, apoptosis, metabolism, survival, angiogenesis and metastasis. In contrast, the down-regulation of IL-6 is related to a better response to treatment. (Masjedi *et al*., 2018). In addition, IL-6 activates the STAT3 pathway, promoting proliferation, anti-apoptosis, tumour cell growth and metastasis of breast cancer cells by up-regulating cyclin D-1, Bax, bcl-2 and c-myc (Ma *et al*., 2020). Extant research indicated that STAT3 exhibits significant activity in over 50% of BC cases (Masjedi *et al*., 2018).

The role of TNF-α in BC

TNF-α is a significant intermediary between inflammation and immunity response to malignancies (Liu *et al*., 2020). It has several functions that modulate various physiological processes, including inflammation and cancer development (Zhao *et al*., 2021; Rahimian *et al*., 2022) TNF-α is rarely found in healthy women's serum but in large amounts in BC patients. About 97%

of the 93 BC samples reported by Lee *et al*. were TNF-α positive. Exactly 61% of them were thought to be high-grade TNF-α (Lee *et al*., 2022).

The cell-based responses to TNF-α are initiated by activating TNFR1 and TNFR2 (Meškytė *et al*., 2023; Martinez-Reza *et al*., 2019). The TNFR1 induces either necroptosis or cell apoptosis according to the cell's biological setting, conditions, and environment. Conversely, the interaction between TNF-α and TNFR2 is believed to primarily facilitate the development of cancer cells (Martinez-Reza *et al*., 2019). *In vitro* studies showed that TNF-α enhances BC cell migration by controlling several genes linked to invasion, proliferation, and metastasis (Méndez-García *et al*., 2019).

Macrophages improve the invasiveness of MCF-7 in co-culture research. In accordance with the results of the microarray investigation, TNF-α stimulated macrophages, which promoted the expression of thirty-nine genes involving MMP-9 and MMP-13, which also elevated Type III EMT; CD44, which is a marker of BC, with CXCR-4 and its ligand CXCL-12, which are linked with cancer migration (Méndez-García *et al*., 2019). Thus, macrophages promote the invasiveness of MCF-7.

Invasive carcinomas were discovered to have higher amounts of TNF-α than benign tissues (Liu *et al*., 2020), and the proportion of cells expressing TNF-α levels rose as tumour levels elevated. Moreover, research revealed that TNF-α was widely distributed in malignant BC biopsies and was secreted by tumour-associated macrophage hotspots with cancer cells and endothelial cells as the targets (Cruceriu *et al*., 2020). Also, TNF-α stimulates the NF-κB pathway cascade by attaching to its receptors. Then, this activates IKK, IBα phosphorylated, ubiquitinated, and degraded, which results in p65, RelB, or p50 translocation to the nucleus. TNF-α can potentially activate many signalling pathways besides the classical NF-κB pathway. These pathways, including the AKT, MAPK, and JNK, are crucial in BC development and progression (Liu *et al*., 2020). The role of proinflammatory cytokines in BC development and progression is illustrated in Figure 2. binding of IL-1 to its receptor, IL-1R, on the surface of BC cells leads to the activation of MYD88, which activates a multitude of molecules, such as TRAF6, TAB1, TAK1, IKK, and IkB which finally activate NF-κB pathway (Rébé & Ghiringhelli, 2020).

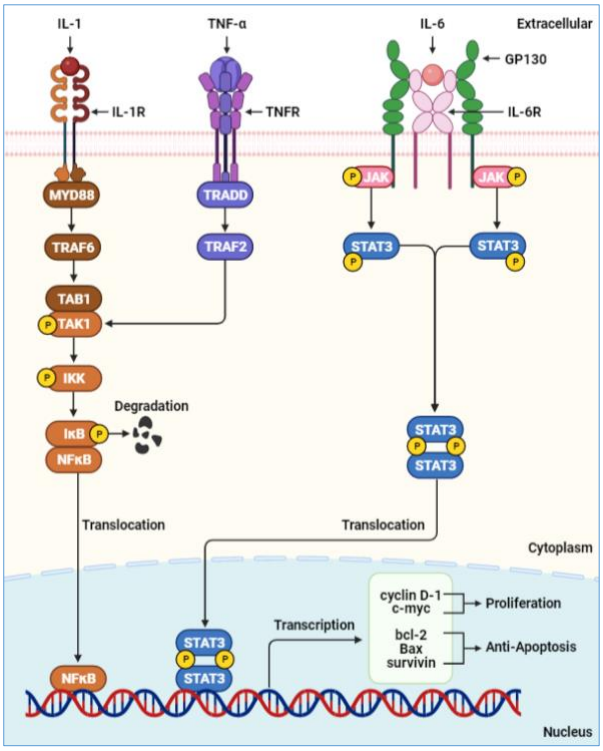

Figure 2: The role of proinflammatory in BC

Furthermore, when TNF-α binds to TNFR, it activates the TRADD protein, which recruits downstream signalling proteins, such as TRAF2, which can also activate several downstream signalling pathways, including TAB1, TAK1, IKK, and IkB. These signals' activation can potentially translocate NF-κB into the nucleus (Liu *et al*., 2020; Zhang *et al*., 2021).

In addition, IL-6 binds to its receptor (IL-6R) on the surface of breast cancer cells and induces a conformational change that allows GP130 to dimerise and become phosphorylated by JAK proteins (Chen *et al*., 2022; Huang *et al*., 2022; To *et al*., 2022). Phosphorylated GP130 recruits the STAT3 pathway (Masjedi *et al*., 2018; Chen *et al*., 2022).

The activation of NF-κB and STAT3 promotes the transcription of genes such as cyclin D-1, c-myc, bcl-2, Bax, and survivin, which are involved in tumour growth, survival, proliferation, anti-apoptosis, angiogenesis and metastasis (Hashimoto *et al*., 2022).

Conclusion

BC is a multifactorial disease that entails the dysregulation of multiple pathways involving IL-1, IL-6, and TNF-α. These cytokines significantly affect BC development by regulating PI3K-PKB/Akt, JNK, IL-6/JAK/STAT3, Ras/Raf, AKT, MAPK, and NF-κB

pathways. They also modulate the TME by promoting extracellular matrix component production and immune cell recruitment. These pathways promote the hallmarks of cancer such as proliferation, survival, angiogenesis, invasion, and metastasis. Inhibiting these proinflammatory cytokines and their downstream signalling intermediates could be promising strategies for suppressing BC development and progression. Comprehending the role of proinflammatory cytokines on BC pathogenesis is critical for developing more effective therapies. In-depth research is necessary to understand this relation to develop novel targeted strategies and improve patient outcomes by targeting IL-1, IL-6, and TNF-α signalling pathways.

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Conflict of interest

The authors declare that there is no conflict of interest regarding this study.

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Authors contributions

JK: Supervision, Methodology, Reviewing. AA: Screening, Data Curation, Writing-manuscript, Editing. MR &TW: Reviewing, Editing. JA: Screening and Reviewing. The authors have approved the final manuscript and are responsible for the content and similarity index.

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Appendix A: Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ Checklist (Tong *et al*., 2012)[†]

Item no.	Guide and description	Report on page
1. Aim	State the research question the synthesis addresses	1
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	2
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	2
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	2
5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	2
6. Electronic search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	2
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	2
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	2
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	2
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings)	2
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	2
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	2
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	2
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software)	2
15. Software	State the computer software used, if any	None
16. Number of reviewers	Identify who was involved in coding and analysis	2
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	2
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	2
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	2
20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	*2*
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	2

† Reference: Tong A, Flemming K, McInnes E, Oliver SA, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Medical Research Methodology 2012, 12:181.