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Overcoming Chemoresistance in Triple-negative Breast Cancer: New Strategies

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Abstract

Triple-negative breast cancer (TNBC) remains a formidable challenge in oncology due to its aggressive nature, limited treatment options, and high propensity for chemoresistance, underscoring the urgent need for innovative therapeutic strategies. This review synthesizes current research to address the molecular mechanisms driving chemoresistance and explores emerging approaches to overcome this critical barrier in TNBC management. The review highlights key insights, including the roles of cancer stem cells (CSCs), dysregulated signaling pathways (e.g., PI3K/AKT, Wnt/β-catenin), and epigenetic modifications in fostering resistance. It examines advances in miRNA-based therapies, targeted inhibition of resistance-associated proteins (e.g., mixed lineage kinase 4 (MLK4), dual serine/threonine and tyrosine protein kinase (DSTYK)), and the potential of nanotechnology for precision drug delivery. Additionally, the discussion covers combination therapies, metabolic reprogramming, and immune modulation as promising strategies. The integration of these approaches aims to disrupt resistance mechanisms and improve therapeutic efficacy in TNBC. Future research should prioritize biomarker-driven patient stratification, clinical validation of preclinical findings, and the development of multi-targeted regimens to address TNBC heterogeneity. Exploring the tumor microenvironment (TME) and leveraging multi-omics data will further refine personalized treatment paradigms. These efforts are essential to translate scientific discoveries into effective therapies and improve outcomes for TNBC patients.

Keywords: Cancer stem cells, Chemoresistance, Combination therapies, Epigenetic modifications, Signaling pathways, Targeted therapy, Triple-negative breast cancer

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Introduction

TNBC is a particularly aggressive subtype of breast cancer characterized by the absence of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 [1-5]. This subtype accounts for approximately 15% to 20% of all breast cancer cases and is associated with a high rate of metastasis and poor prognosis due to its inherent chemoresistance [6]. Overcoming chemoresistance in TNBC remains a formidable challenge due to its aggressive nature and limited therapeutic options. Recent research efforts have focused on elucidating molecular mechanisms underlying resistance and developing targeted strategies to enhance chemosensitivity. The collective findings from various studies highlight promising avenues, including molecular targeting, combination therapies, nanotechnology-based delivery systems, and drug repurposing, which collectively contribute to advancing treatment paradigms for TNBC [7-9].

One of the pivotal approaches involves targeting specific molecular pathways that confer resistance. Haritha et al. [10] identified thymidylate synthase as a critical target, demonstrating that pharmacological inhibition of thymidylate synthase enhances the chemosensitivity of TNBC cells to 5-fluorouracil. Their preclinical studies confirmed the safety of this combinatorial approach, advocating for clinical validation, especially given the paucity of effective options for TNBC patients. Similarly, Rodriguez et al. [11] explored substance P receptor antagonism in combination with cisplatin, revealing that this strategy not only potentiates cisplatin efficacy but also offers protective effects against oxidative stress and apoptosis in neuronal and TNBC cell lines. These findings underscore the potential of receptor antagonists as adjuncts to conventional chemotherapy.

Further insights into resistance mechanisms have been gained through the investigation of specific signaling pathways and gene regulators. Jiang et al. [12] elucidated the role of the TBX15/miR-152/KIF2C pathway in doxorubicin resistance, demonstrating that modulation of this axis influences PKM2 ubiquitination and, consequently, drug sensitivity. Similarly, Mehlich et al. [13] identified MLK4 as a promoter of DNA damage response and chemoresistance, with MLK4 inhibition sensitizing TNBC cells to DNA-damaging agents. These studies highlight the importance of targeting intracellular signaling and repair pathways to overcome resistance.

CSCs have also been recognized as key contributors to chemoresistance and metastasis. He et al. [14] provided a comprehensive overview of the molecular landscape of breast CSCs (BCSCs), emphasizing the need to develop therapies that target these subpopulations to prevent relapse and dissemination. The identification of specific biomarkers and signaling pathways in BCSCs offers promising targets for future therapies aimed at eradicating resistant cell populations. In addition to molecular targeting, modulation of the TME and immune landscape has gained attention. Wu et al. [15] reviewed plant-derived natural products that modulate immune responses and tumor metabolism, suggesting their potential in reprogramming the TME to favor anti-tumor activity. Such agents could complement existing therapies by enhancing immune-mediated tumor clearance.

Innovative drug delivery systems have also been developed to improve therapeutic efficacy and reduce toxicity. Date et al. [16] designed dual-action cisplatin(IV) prodrugs conjugated with bioactive moieties, which demonstrated superior tumor reduction in TNBC models compared to cisplatin alone. Similarly, Cho et al. [17] developed albumin-binding peptide-drug conjugates exploiting PTEN-loss pathways, facilitating targeted delivery and bystander killing effects in metastatic TNBC. These nanotechnology-based approaches aim to enhance drug accumulation within tumors and target multiple cellular pathways simultaneously. Drug repurposing strategies have emerged as a rapid means to identify effective agents against resistant TNBC. Sari et al. [18] identified proteasome inhibitors, such as bortezomib and carfilzomib, through high-throughput screening, which suppressed TNBC organoid growth by impairing translation and cell cycle progression. Likewise, López-Tejada et al. [19] focused on transcriptomic signature-based drug repurposing, identifying compounds that mimic the effects of TGF-β pathway inhibition, which is implicated in tumor progression and resistance.

Targeting specific resistance-associated genes has also shown promise. Ogbu et al. [20] demonstrated that knockout of DSTYK via CRISPR/Cas9 induces apoptosis in chemoresistant cells, suggesting that DSTYK could serve as a therapeutic target. Similarly, Wang et al. [21] linked high CENPF expression to poor prognosis and chemoresistance, indicating that CENPF suppression might restore chemosensitivity. Furthermore, Zhou et al. [22] uncovered the role of METTL3/IGF2BP3-mediated m6A modification of HYOU1 in conferring doxorubicin resistance, providing a novel epigenetic target for overcoming resistance. The role of BCSCs in chemoresistance has been further elucidated by He et al. [14], who emphasized the importance of targeting BCSC-specific pathways and biomarkers. Strategies such as differentiation therapy, as explored by Wu et al. [23], involve transforming resistant stem-like cells into more differentiated, chemosensitive states, thereby indirectly eradicating the resistant subpopulation.

Finally, the integration of multi-targeted approaches appears promising. Cheng et al. [24] identified protein kinase C as a therapeutic target to restore Aurora kinase B expression, thereby overcoming paclitaxel resistance. Similarly, dual metabolic inhibition of glutaminase and xCT by Choi et al. [25] successfully sensitized resistant TNBC cells, highlighting the potential of metabolic reprogramming in overcoming chemoresistance. Overall, the multifaceted nature of chemoresistance in TNBC necessitates a combination of targeted molecular therapies, innovative drug delivery systems, and drug repurpose strategies. The studies reviewed demonstrate that targeting specific pathways such as thymidylate synthase, MLK4, DSTYK, and epigenetic modifications, alongside approaches that eliminate CSCs and modulate the TME, hold significant promise. The development of nanotechnology-based delivery systems and the repurposing of existing drugs further expand the arsenal against resistant TNBC. Collectively, these strategies pave the way for more effective, personalized treatments aimed at overcoming chemoresistance and improving patient outcomes in TNBC.

Understanding Chemoresistance in TNBC

TNBC remains one of the most aggressive and therapeutically challenging subtypes of breast cancer, primarily due to its propensity for developing chemoresistance [26-30]. Recent studies have focused on elucidating the molecular mechanisms underlying this resistance, with the aim of identifying novel therapeutic targets and improving patient outcomes (Table 1). Chemoresistance in TNBC arises from a complex interplay of various biological mechanisms. These include alterations in drug efflux, changes in apoptosis pathways, and the presence of CSCs [6, 31]. TME also plays a significant role, with inflammatory mediators such as IL-6 contributing to resistance by activating pathways that promote cell survival [32]. Furthermore, the high heterogeneity of TNBC complicates treatment, as different tumor cells may respond variably to chemotherapy [6]. Recent studies have identified specific miRNAs that correlate with chemoresistance in TNBC. For instance, Ouyang et al. [33] identified 11 deregulated miRNAs, with several being associated with chemoresistance. This suggests that targeting these miRNAs could be a potential strategy to enhance chemosensitivity in TNBC patients.

A significant body of research emphasizes the role of CSCs in mediating chemoresistance in TNBC. Shadbad et al. [34] highlights the prognostic significance of CSC phenotypes, particularly the

Table 1: Understanding chemoresistance in TNBC.

Category	Key mechanisms/factors	Therapeutic implications
CSCs	CD44+/CD24−/low phenotype; self-renewal pathways (Notch, Wnt, and Hedgehog) sustain resistance.	Target CSC markers or signaling pathways; differentiation therapies to reduce stemness.
TME	Hypoxia, IL-6 signaling, CAF-mediated ECM remodeling promotes survival and drug evasion.	Inhibit IL-6/HIF-1α; target CAFs or ECM components (e.g., LOX inhibitors).
DNA repair mechanisms	Enhanced homologous recombination (e.g., RAD51); MLK4-mediated DNA damage response.	PARP inhibitors for BRCA-mutated TNBC; MLK4 inhibition to sensitize cells.
Epigenetic modifications	m6A RNA methylation (METTL3/IGF2BP3), H3K27me3, and DNA methylation silence tumor suppressors.	Epigenetic drugs (DNMT/HDAC inhibitors) to re-sensitize cells.
Drug efflux pumps	Overexpression of ABC transporters (e.g., ABCB1/P-gp) reduces intracellular drug accumulation.	Nanocarriers to bypass pumps; target upstream regulators (e.g., USP51).
Metabolic reprogramming	Lipid metabolism (PLIN4), oxidative phosphorylation, and glutaminase dependency fuel resistance.	Metabolic inhibitors (e.g., glutaminase/xCT blockers) combined with chemotherapy.
Noncoding RNAs	miRNAs (e.g., miR-152) and lncRNAs regulate apoptosis and drug-efflux pathways.	RNA-based therapies (e.g., antagomiRs) to restore chemosensitivity.
Heterogeneity	Intratumoral diversity leads to variable treatment responses; subclones evade therapy.	Single-cell profiling guide personalized combinations.

CD44+CD24−/low phenotype, which is associated with tumor aggressiveness and poor prognosis. Understanding the phenotypic heterogeneity of CSCs can facilitate the development of targeted therapies aimed at eradicating these resistant cell populations. Similarly, He et al. [14] delve into the molecular landscape of BCSCs, exploring signaling pathways that sustain their self-renewal and resistance capabilities [7]. Their review underscores the importance of identifying specific biomarkers to target BCSCs, thereby potentially overcoming chemoresistance and metastasis.

Intratumoral heterogeneity further complicates the treatment landscape of TNBC. Thankamony et al. [35] investigates phenotypic heterogeneity within TNBC tumors, revealing that distinct tumor cell populations exhibit different proliferative and metastatic potentials. Such heterogeneity contributes to variable responses to chemotherapy, as different subpopulations may harbor unique resistance mechanisms. This underscores the necessity for personalized treatment strategies that account for tumor heterogeneity. Molecular mechanisms at gene and pathway levels have also been extensively studied. For instance, BIRC5 (survivin) has been identified as a prognostic biomarker linked to chemoresistance. Adinew et al. [36] demonstrate that BIRC5 expression correlates with resistance to chemotherapy, suggesting its potential as a therapeutic target. Similarly, the enzyme paraoxonase-2 is upregulated in TNBC and contributes to tumor progression and chemoresistance, as shown by Campagna et al. [37]. These findings highlight the importance of metabolic and survival pathways in mediating resistance.

The DNA damage response pathway is another critical area of focus. Ward [38] investigates the role of RAD51, a key protein in homologous recombination repair, in TNBC. Gene editing approaches reveal that alterations in RAD51 can influence the tumor's response to DNA-damaging agents, suggesting that targeting DDR components may sensitize tumors to chemotherapy. Complementing this, Foutadakis et al. [39] employ single-cell transcriptomics to identify novel chemoresistance-associated genes, emphasizing the heterogeneity of resistance mechanisms at the cellular level. Targeting specific signaling pathways involved in chemoresistance has gained traction. For example, Kong et al. [40] demonstrates that PRMT5 enhances autophagy via ULK1 methylation, conferring resistance to nanoparticle albumin-bound paclitaxel (nab-paclitaxel). Autophagy, a cellular survival mechanism, appears to be a common resistance pathway, and its modulation could improve chemotherapeutic efficacy. Similarly, the USP51-GRP78-ABCB1 axis, elucidated by Ou et al. [41], promotes doxorubicin resistance by decreasing drug accumulation within cells. These molecular insights suggest that disrupting such pathways may restore chemosensitivity.

Other studies focus on the role of pro-survival proteins and signaling cascades. Paul et al. [42] reveal that thrombin-induced activation of PAR1 stabilizes MCL1, a pro-survival protein, thereby promoting multidrug resistance. Additionally, Long et al. [43] identify UGCG as a promoter of chemoresistance through activation of NF-κB and Wnt/β-catenin pathways, which are known to support tumor progression and resistance. These findings underscore the complexity of resistance mechanisms involving both survival signaling and metabolic reprogramming. Emerging therapeutic strategies aim to overcome chemoresistance by targeting these molecular pathways. Chadar et al. [44] review nanotechnology-based delivery systems, such as siRNA nanocarriers, designed to enhance gene silencing and reduce side effects. Such advanced delivery methods could improve the targeting of resistant tumor cell populations. Similarly, Zhang et al. [45] highlights the role of peroxisome proliferator-activated receptor signaling in TNBC heterogeneity, suggesting that modulation of this pathway might sensitize tumors to therapy.

Noncoding RNAs, particularly long noncoding RNAs, have emerged as key regulators of chemoresistance. Thakur et al. [46] and Xia et al. [47] review the mechanisms by which noncoding RNAs influence tumor progression and drug response, proposing that targeting these molecules could reverse resistance. The regulatory functions of ncRNAs in gene expression and signaling pathways make them promising candidates for novel therapeutic interventions.

In summary, the multifaceted nature of chemoresistance in TNBC involves a complex interplay of CSC phenotypes, tumor heterogeneity, DNA repair mechanisms, survival signaling pathways, and noncoding RNA regulation. The integration of molecular insights from gene editing, transcriptomics, and pathway analysis provides a comprehensive understanding of resistance mechanisms. Future therapeutic approaches are likely to benefit from targeting these pathways, employing nanotechnology for efficient delivery, and considering tumor heterogeneity to develop personalized treatment regimens. Continued research into these areas holds promise for overcoming chemoresistance and improving prognosis for TNBC patients.

Novel Therapeutic Strategies

Overcoming chemoresistance in TNBC is a critical challenge in oncology. Recent research has explored various novel therapeutic strategies targeting different molecular mechanisms underlying this resistance. Several studies have focused on identifying key modulators of chemoresistance. For example, Lian et al. [48] identified truncated HDAC9 as a key modulator of paclitaxel resistance in TNBC using an integrated genome-wide screen. This finding suggests that targeting HDAC9 could be a promising therapeutic strategy to overcome paclitaxel resistance. Similarly, research has highlighted the role of FZD5 in TNBC proliferation, DNA damage repair, and stemness [49], indicating that inhibiting FZD5 could potentially reduce tumor growth and enhance chemosensitivity.

Newer therapeutic approaches are being developed targeting novel mechanisms. Meng et al. [50] demonstrated that targeting CRL4 suppresses chemoresistant ovarian cancer growth by inducing mitophagy, highlighting the potential of targeting mitochondrial dynamics. Carotenuto et al. [51] investigated a combination therapy using β-carotene and 5-fluorouracil via polymeric nanoparticles to overcome uL3-mediated chemoresistance in colorectal cancer. Cheng et al. [24] proposed targeting protein kinase C to overcome paclitaxel resistance in TNBC by restoring Aurora Kinase B expression. Wei et al. [52] demonstrated that HuR inhibition overcomes CFLIP-mediated doxorubicin resistance, offering a novel therapeutic strategy by combining HuR inhibition with doxorubicin. Cortesi et al. [53] highlighted TROP2 as a potential drug target in breast cancer, suggesting that targeting this transmembrane glycoprotein might be beneficial. De Francesco et al. [54] emphasized the importance of integrating advanced biological insights and emerging drug modalities for more effective and durable treatments. Ghavami et al. [55] discussed the interplay between autophagy and epigenetics in gastrointestinal cancers, and how modulating epigenetics might influence autophagy to overcome chemoresistance. These findings indicate that multiple avenues are actively being investigated to overcome chemoresistance in TNBC. The combination of novel drug targets, synergistic drug combinations, and improved drug delivery systems holds great promise

for improving treatment outcomes for patients with TNBC.

Targeting miRNAs

The role of miRNAs in regulating chemoresistance has garnered attention as a potential therapeutic target. Wang et al. [31] highlighted the importance of miRNAs in influencing chemotherapy responses across various cancers, including breast cancer. By modulating the expression of specific miRNAs, it may be possible to reverse chemoresistance and improve treatment efficacy.

- Dysregulation of miRNAs: miRNAs are frequently dysregulated in TNBC, contributing to tumor progression and chemoresistance. For instance, miR-214-3p, miR-4758-3p, and miR-200c-3p are upregulated in chemoresistant TNBC tissues, while miR-142-5p and miR-146-5p are downregulated, affecting key pathways involved in drug resistance [56].

- Target genes and pathways: miRNAs regulate genes associated with drug resistance, such as RAC1, MYC, and CCND1 for upregulated miRNAs, and IL-6, SOCS1, and PDGFRA for downregulated miRNAs. These genes are involved in pathways that influence cell survival and proliferation [56].

- miRNA modulation: Modulating miRNA levels can alter chemoresistance. For example, increasing miR-200 and miR-205 levels can inhibit epithelial-to-mesenchymal transition and enhance chemosensitivity [57].

- miRNA-loaded nanoparticles: Chitosan nanoparticles co-loaded with 5-fluorouracil and miRNAs like miR-1275 and Let-7i have shown potential in reducing chemoresistance in TNBC cells by targeting pathways such as JAK/STAT and PI3K/Akt/mTOR [58].

- Exosomal miRNAs: Exosomes carrying miRNAs can mediate epigenetic changes in recipient cells, offering a novel delivery system for miRNA-based therapies. These exosomal miRNAs can serve as biomarkers for diagnosis and prognosis, as well as therapeutic agents [59].

- Predictive biomarkers: miRNAs such as miR-3133 and miR-655-3p have been identified as potential predictive biomarkers for drug response, correlating with progression-free survival and overall survival in TNBC patients [60].

- Resistance to multiple drugs: miRNAs like miR-29a and miR-181b confer resistance to multiple chemotherapeutic agents, suggesting that targeting these miRNAs could enhance the efficacy of existing treatments [61].

Inhibition of signaling pathways

Targeting key signaling pathways involved in chemoresistance is another promising strategy. For example, the IL-6/HIF-1α signaling pathway has been implicated in TNBC chemoresistance, with studies showing that inhibiting this pathway can sensitize TNBC cells to chemotherapy [32]. Similarly, the role of specific signaling pathways in chemoresistance is also being extensively investigated. The MLK4 has been identified as a regulator of the DNA damage response, and its inhibition has been shown to enhance sensitivity to chemotherapeutic agents. Mehlich et al. [13] demonstrated that MLK4 promotes TNBC chemoresistance by regulating the pro-survival response to DNA-damaging therapies. Knocking down or inhibiting MLK4 sensitized TNBC cells to chemotherapeutic agents, indicating a potential therapeutic target.

Additionally, Chen et al. [62] discovered a novel mechanism for reversing doxorubicin-induced chemoresistance by TXNIP via promoting reactive oxygen-mediated DNA damage in TNBC. These studies emphasize the importance of understanding the specific signaling pathways involved in chemoresistance to develop targeted therapies. Another area of focus involves targeting cancer stemness, which is often linked to chemoresistance. Li et al. [63] highlighted the role of nicotine-regulated ILF2 in facilitating nuclear mRNA export to promote cancer stemness in esophageal cancer, suggesting that targeting ILF2 could be a therapeutic strategy against nicotine-induced chemoresistance. While not specific to TNBC, this study emphasizes the general importance of addressing cancer stemness in overcoming chemoresistance.

Furthermore, research explores the impact of other cellular processes on chemoresistance. Hussein et al. [64] reviewed the role of endolysosomal trafficking in multi-drug resistance, suggesting that targeting endolysosomal pathways could be a novel therapeutic strategy. Pan et al. [65] identified METTL3's role in inhibiting mesenchymal stem cell adipogenesis and promoting chemoresistance in acute myeloid leukemia. Although not in TNBC, this study highlights the broader implications of targeting metabolic processes in overcoming chemoresistance. Similarly, Yang et al. [66] reviewed the role of altered lipid metabolism in chemoresistance, suggesting that targeting lipid metabolism in combination with traditional chemotherapeutic drugs holds promise. Chen et al. [67] showed that Oligo-Fucoidan supplementation enhances the effect of Olaparib on preventing metastasis and recurrence of TNBC by impacting macrophage polarity, stemness properties, and glucose metabolism.

Exploiting BCSCs

BCSCs are known to contribute to chemoresistance in TNBC. Targeting BCSCs through specific markers such as CD44 and ALDH1 has emerged as a potential therapeutic approach [14]. By selectively targeting these cells, it may be possible to reduce tumor recurrence and improve overall treatment outcomes.

- Self-renewal and differentiation: BCSCs have the ability to self-renew and differentiate, which allows them to survive chemotherapy and repopulate the tumor, leading to relapse and metastasis [68, 69].

- Signaling pathways: Key signaling pathways such as Wnt/β-catenin, Hedgehog, and JAK/STAT are involved in maintaining BCSC properties and contribute to chemoresistance [69, 70].

- TME: The TME, including immune cells and cytokines, supports BCSC survival and chemoresistance by providing a niche that protects BCSCs from chemotherapeutic agents [71].

- Molecular targets: Surface markers like CD44 and CD133 and signaling pathways such as Notch and IL-6/JAK/STAT3, are potential targets for therapies aimed at eradicating BCSCs [72, 73].

- Nanocarrier-based drug delivery: Nanoparticle-based therapies can deliver drugs specifically to BCSCs, minimizing systemic toxicity and enhancing treatment efficacy [74].

- Combination therapies: Combining conventional chemotherapeutics with BCSC-targeting agents, such as dasatinib, has shown promise in reducing BCSC populations and enhancing sensitivity to chemotherapy [75].

- Heterogeneity of BCSCs: The heterogeneity within BCSC populations poses a challenge for developing universal targeting

strategies. Personalized approaches may be necessary to effectively target BCSCs in different patients [69].

- Clinical translation: While preclinical studies have shown promise, translating these findings into effective clinical therapies requires further research and clinical trials to validate the safety and efficacy of BCSC-targeting strategies [73, 75].

Combination therapies

Combination therapies that integrate traditional chemotherapeutics with novel agents are being explored to overcome chemoresistance. For instance, the use of proteasome inhibitors has shown promise in counteracting inflammation-driven chemoresistance in TNBC organoids [18]. Additionally, dual-action cisplatin(IV) prodrugs have been developed to enhance therapeutic efficacy while minimizing systemic toxicity [16].

Other studies have investigated the efficacy of drug combinations to overcome chemoresistance. Sinha et al. [76] demonstrated the anti-cancerous effect of a sulforaphane-cisplatin combination against TNBC metastasis and cisplatin resistance, suggesting that targeting the sirtuins-mediated epithelial-to-mesenchymal transition signaling axis might be beneficial. Furthermore, Eskiler and Ozturk [77] found a synergistic effect between the PI3K inhibitor LY294002 and the PARP inhibitor Talazoparib in inhibiting the proliferation of BRCA1 mutant TNBC cells. This synergistic effect was attributed to increased apoptosis, G0/G1 arrest, oxidative stress, and DNA damage. This research suggests that combining targeted therapies can effectively overcome chemoresistance. Another approach involves enhancing the efficacy of existing chemotherapeutic agents. Rodriguez et al. [11] explored the potential of substance P receptor antagonism in combination with cisplatin to enhance its efficacy and reduce toxicity in TNBC. Date et al. [16] developed cisplatin(IV) conjugates with distinct bioactive moieties, demonstrating enhanced *in vitro* and *in vivo* activity against TNBC, highlighting the potential of multi-target approaches.

Nanotechnology and targeted drug delivery

Nanotechnology offers innovative solutions for targeted drug delivery at TNBC. By utilizing nanocarriers, researchers aim to deliver chemotherapeutic agents specifically to tumor cells, thereby enhancing efficacy and reducing off-target effects [72]. This approach has the potential to improve the therapeutic index of existing chemotherapeutics.

- Nanocarriers such as polymeric micelles, liposomes, and dendrimers are employed to enhance drug bioavailability, prolong circulation time, and facilitate targeted drug accumulation at tumor sites [78, 79].

- Biodegradable polymeric nanoparticles are designed to encapsulate chemotherapeutic agents, ensuring controlled release and targeted delivery to TNBC cells, thereby reducing off-target effects [80].

- The use of targeting ligands, such as the A6 peptide, enhances the specificity of nanoparticles for TNBC cells, improving drug delivery efficiency and reducing systemic toxicity [81].

- Nanoparticles can be engineered to co-deliver chemotherapeutic agents and microRNA therapies, which regulate pathways involved in drug resistance, thereby enhancing treatment effectiveness [82].

- For instance, poly(lactic-co-glycolic acid)–polyethylene glycol nanoparticles loaded with doxorubicin and anti-miR-21 have shown significant efficacy in reducing drug resistance and tumor size in TNBC models [81].

- Advanced nanomedicines, including DNA origami and CRISPR/Cas9 systems, are being explored for their potential to knockdown specific genes and control angiogenesis and metastasis in TNBC [83].

- Despite the promising results, the clinical translation of nanotechnology-based therapies for TNBC faces challenges such as scalability, regulatory approval, and long-term safety [84].

- Further optimization of nanoparticle formulations and comprehensive clinical studies are necessary to establish their efficacy and safety in humans [80].

- The development of theranostic nanoparticles, which combine therapeutic and diagnostic functions, represents a novel approach to simultaneously treat and monitor TNBC, potentially leading to more personalized treatment strategies [85].

The exploration of novel therapeutic strategies for overcoming chemoresistance in TNBC has unveiled promising approaches, including targeting miRNAs, inhibiting key signaling pathways, exploiting CSCs, and leveraging nanotechnology for precise drug delivery. Combination therapies and advanced delivery systems further enhance treatment efficacy while minimizing toxicity. These multifaceted strategies highlight the potential for personalized and targeted interventions to improve outcomes for TNBC patients.

Clinical Studies

Overcoming chemoresistance in TNBC is a critical challenge due to the aggressive nature of the disease and the lack of targeted therapies. Recent studies have explored various strategies to address this issue, focusing on molecular targets and pathways that contribute to chemoresistance. These studies highlight the potential of novel inhibitors, combination therapies, and targeting specific proteins and pathways to enhance chemosensitivity in TNBC.

A study by Cetin et al. [86] identified novel bi-thiazole lysyl oxidase (LOX) inhibitors as a strategy to overcome chemotherapy resistance in TNBC. Bi-thiazole derivatives were identified as novel and potent LOX inhibitors through a robust screening platform combined with cell-based and recombinant protein assays. Structure-activity relationship analysis led to two lead compounds: (i) 6403, compound was found to be a relatively LOX-specific inhibitor and (ii) 6415, compound demonstrated activity as a more LOX/LOXL2 dual inhibitor. Both 6403 and 6415 effectively reduced collagen crosslinking. They led to chemosensitization in TNBC cell lines when grown in 3D cultures. Chemosensitization was also observed in chemoresistant TNBC patient-derived xenograft organoids. Re-analysis of single-cell RNA sequencing data from TNBC patients showed that LOX+ cells were enriched specifically in treatment-refractory patients after chemotherapy. A significant correlation was identified between LOX and gene sets related to reactive oxygen species and DNA repair in chemotherapy-treated TNBC patients. LOX inhibition enhanced chemotherapy penetration, leading to elevated reactive oxygen species levels and increased DNA damage in cells. This process resulted in the inhibition of the FAK/Akt survival signaling pathway. The efficacy of compound 6403 was tested in a chemoresistant TNBC patient-derived xenograft model. Combining doxorubicin with the LOX inhibitor (6403) successfully overcame doxorubicin resistance without causing significant changes in body weight. Advanced techniques like

MALDI-MSI and MP-SHG experiments confirmed efficient reduction of collagen content and crosslinking, respectively, in patient-derived xenograft tumors upon LOX inhibition. In summary, the study's results indicate that novel bi-thiazole LOX inhibitors can block collagen crosslinking and enhance chemotherapy's effectiveness by potentiating the reactive oxygen species DNA damage axis, thereby overcoming chemoresistance in TNBC.

A study by Connell et al. [87] observed significant differences in gene transcription and protein expression between doxorubicin-resistant (MDA-MB-231/ADR) and sensitive (MDA-MB-231/S) TNBC cell lines. Specifically, SCD1 was found to be significantly upregulated at both mRNA and protein levels in the resistant cell line. Metabolomic analyses revealed distinct lipid metabolic profiles differentiating the MDA-MB-231/ADR and MDA-MB-231/S cell lines. Treatment with Erastin, a ferroptosis inducer, in MDA-MB-231/ADR cells led to an increase in PD-L1 expression. Erastin treatment also resulted in changes in the expression levels of SCD1, p53, and TNFAIP3, molecules known to be associated with poor prognosis and therapy resistance. The research elucidated that TRIM28 modulates the stability of PD-L1 through SUMOylation. Furthermore, TRIM28 facilitates the ubiquitination and degradation of p53 via a TRIM28-MDM2 dependent pathway, thereby influencing immune surveillance and therapeutic response. In TNBC patients treated with anthracycline-based chemotherapy, those categorized as having progressive disease/stable disease exhibited higher expressions of SCD1 and TNFAIP3, but lower TRIM28 expression, compared to patients with partial response/complete response. Similar expression patterns were also observed in serum extracellular vesicles from these patients. These findings collectively highlight the potential of targeting the SCD1-TRIM28-PD-L1 axis to overcome chemoresistance in TNBC, suggesting a promising therapeutic strategy involving SCD1 inhibition combined with ferroptosis inducers to enhance PD-L1 blockade efficacy.

A study by Lin et al. [88] investigated the role of ubiquitin-specific protease 7 (USP7) in the chemoresistance of TNBC, particularly focusing on its interaction with ATP-binding cassette B1 (ABCB1). USP7 was identified as a specific promoter of chemo-drug tolerance in TNBC cells. Overexpression of USP7 increased resistance to doxorubicin and paclitaxel treatments in MDA-MB-231 and MDA-MB-468 cells (Figure 1). This was evidenced by higher cell viability and growth rates in USP7-expressing cells compared to controls under increasing drug doses. USP7 specifically represses doxorubicin- or paclitaxel-induced apoptosis in TNBC cells. USP7 expression levels were consistently higher in TNBC cell lines compared to normal breast cell lines. Knockdown of USP7 effectively increased the chemosensitivity of chemoresistant TNBC cells. This led to lower cell viability and proliferative activity in MDA-MB-231-DoxR and MDA-MB-231-PtxR cells under serial doses of doxorubicin and paclitaxel. Suppression of USP7 significantly induced apoptosis in chemoresistant TNBC cells, as indicated by increased levels of cleaved PARP, caspase 3, and caspase 7, and depolarization of mitochondrial membrane potential. This also led to decreased levels of anti-apoptotic proteins (Bcl2, Bcl-xL) and increased levels of pro-apoptotic proteins (BAX, Bim). USP7 suppression repressed the migration and invasive activities of chemoresistant TNBC cells, and an USP7 inhibitor (GNE-6776) effectively suppressed metastasis. This was associated with changes in epithelial-mesenchymal transition markers, specifically increased E-cadherin and plakoglobin, and decreased vimentin and N-cadherin. In orthotopic mouse models, USP7-silencing TNBC cells exhibited significantly reduced tumorigenesis and lung metastasis compared to control groups. USP7 was found to upregulate ABCB1 expression in a dose-dependent manner. ABCB1 expression was significantly downregulated in USP7-silencing cells but rescued upon re-expression of USP7. USP7 directly interacted with ABCB1 and regulated its stability. USP7 acts as a specific deubiquitinating enzyme for ABCB1, removing K48-linked polyubiquitin chains and thus stabilizing the ABCB1 protein. Knockdown of USP7 increased the K48-linked polyubiquitin chain of ABCB1. ABCB1 expression was observed to be higher in TNBC cell lines compared to ER-positive breast cancer cell lines, and also higher in doxorubicin- and paclitaxel-resistant TNBC

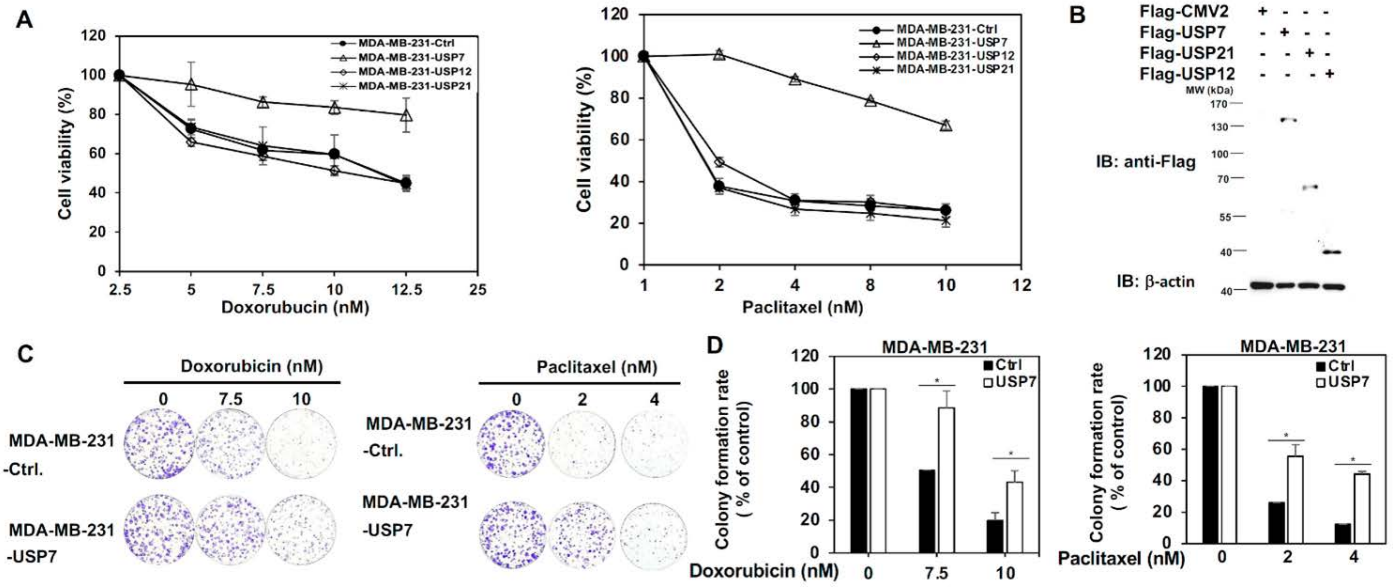

Figure 1: Role of USP7 in acquired chemoresistance of TNBC. **(A)** Assessment of MDA-MB-231 cell viability following transient overexpression of USP7, USP12, or USP21 under increasing concentrations of doxorubicin (left) or paclitaxel (right), measured via 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. **(B)** Western blot analysis of USP7, USP12, and USP21 protein expression levels in MDA-MB-231 cells after transient transfection. **(C)** Evaluation of the proliferative capacity of USP7-overexpressing MDA-MB-231 cells exposed to doxorubicin (left) or paclitaxel (right) using colony formation assays. **(D)** Quantification of colony formation in doxorubicin- (left) or paclitaxel- (right) treated MDA-MB-231 cells overexpressing USP7 [88].

cells than in parental cells. Re-expression of ABCB1 in USP7-silencing cells promoted chemoresistance. In summary, the study demonstrates that USP7 promotes chemoresistance in TNBC by stabilizing the ABCB1 protein through its deubiquitinating activity. This suggests that targeting USP7 could be a promising strategy to overcome drug resistance in TNBC.

A study by Alemi et al. [89] investigated the effectiveness of combination therapy involving heme-targeting agents (HeSP2 and (Cyclopamine tartrate) CycT) and chemotherapeutic drugs (cisplatin and etoposide) for treating TNBC. *In vitro* experiments demonstrated that both HeSP2 and CycT effectively inhibited cell proliferation and colony formation in TNBC cell lines. This effect was observed both when these agents were used alone and in combination with chemotherapeutic drugs. The experiments were conducted using three different TNBC cell lines: 4T1-Fluc-Neo, EMT6_Fluc_Puro, and MDA-MBA-231. The combination therapy significantly reduced cell proliferation and inhibited colony formation in TNBC cells. This suggests that combining HeSP2 and CycT with chemotherapy enhances their therapeutic efficacy. HeSP2 and CycT are agents that reduce hypoxia and oxidative phosphorylation. Due to these properties, they may also help delay the emergence of drug resistance in cancer cells treated with chemotherapy. The results indicate that the combination of HeSP2 and CycT with chemotherapy drugs could serve as a promising therapeutic strategy to diminish the tumorigenic function in TNBC and overcome resistance to chemotherapy. In summary, the study's results highlight that combining HeSP2 and CycT with conventional chemotherapeutic agents like cisplatin and etoposide is an effective strategy to combat TNBC by inhibiting cell growth, reducing colony formation, and potentially mitigating drug resistance.

A study by Tian et al. [75] reported dasatinib's role in TNBC treatment. Dasatinib, a Src kinase family inhibitor, was identified as a potent suppressor of BCSC numbers and effectively blocked the self-renewal ability of chemotherapy-resistant breast cancer cells. It was observed that dasatinib prevented paclitaxel-induced BCSC enrichment and Src activation in both parental and paclitaxel-resistant TNBC cells. Dasatinib induced an epithelial differentiation in paclitaxel-resistant mesenchymal cells, leading to increased sensitivity to paclitaxel. The combined treatment of dasatinib and paclitaxel significantly reduced the proportion of BCSCs and their self-renewal capacity. This combination also synergistically decreased the cell viability of paclitaxel-resistant cells. Preclinical studies using xenograft mouse models of breast cancer further demonstrated that the dasatinib/paclitaxel combination treatment was effective in inhibiting tumor growth (Figure 2). In summary, the research highlights dasatinib as a promising anti-BCSC agent that can be effectively combined with paclitaxel to overcome chemotherapy resistance in TNBC, primarily by targeting BCSCs and enhancing drug sensitivity.

While these strategies show promise, it is important to consider the complexity and heterogeneity of TNBC, which may require personalized approaches to treatment. Additionally, the development of resistance mechanisms can vary among patients, necessitating ongoing research to identify and validate new targets and combination therapies. The integration of these novel strategies into clinical practice could potentially transform the management of TNBC and improve patient outcomes.

Limitations of Literature

While current research has significantly advanced our understanding of chemoresistance in TNBC, several methodological and conceptual limitations constrain the interpretation and clinical translation of these findings. Key challenges include small sample sizes, reliance on preclinical models that may not fully replicate human tumor complexity, and a lack of longitudinal data tracking resistance evolution over time. Addressing these limitations will be crucial for developing more reliable, clinically actionable strategies to overcome chemoresistance in TNBC.

- Small sample sizes: Several studies rely on limited patient cohorts or small sample sizes, which restricts the generalizability and external validity of findings. This limitation may lead to overestimation of effects and reduce confidence in the reproducibility of results across diverse populations [90-92].

- Lack of longitudinal data: Many investigations lack longitudinal follow-up, impeding the understanding of temporal dynamics in chemoresistance development and tumor evolution. This methodological constraint limits insights into resistance mechanisms over time and treatment courses [93-95].

- *In vitro* model limitations: Predominant use of *in vitro* cell line models may not fully recapitulate the TME, and heterogeneity seen in patients, thus limiting external validity. Such models may fail to capture complex interactions influencing chemoresistance *in vivo* [96].

- Heterogeneity of TNBC subtypes: The high molecular and phenotypic heterogeneity within TNBC subtypes complicates the identification of universal mechanisms of chemoresistance, reducing the applicability of findings to all TNBC cases and challenging the development of broadly effective therapies [97].

- Limited clinical validation: Many mechanistic insights and therapeutic targets identified lack robust clinical validation, which undermines translational potential and external validity. Without clinical trials, the efficacy and safety of proposed interventions remain uncertain [98].

- Focus on single pathways: Several studies concentrate on isolated molecular pathways or targets, neglecting the multifactorial and interconnected nature of chemoresistance. This narrow focus may oversimplify resistance mechanisms and limit comprehensive therapeutic strategies [13].

- Insufficient biomarker development: There is a paucity of validated predictive biomarkers for chemoresistance, hindering patient stratification and personalized treatment approaches. This limitation affects the clinical utility and external validity of research findings [99].

- Overreliance on preclinical models: Heavy dependence on patient-derived xenografts and animal models may not fully capture human tumor complexity and immune interactions, limiting the extrapolation of results to clinical settings and affecting external validity [94].

- Epigenetic mechanism complexity: The intricate and dynamic nature of epigenetic modifications poses challenges in fully elucidating their roles in chemoresistance, leading to incomplete mechanistic understanding and potential methodological constraints in targeting these pathways [95].

- Variability in chemoresistance definitions: Inconsistent criteria and models for defining and measuring chemoresistance across studies reduce comparability and may introduce bias, affecting the validity and synthesis of findings [100].

Despite valuable insights into TNBC chemoresistance, current

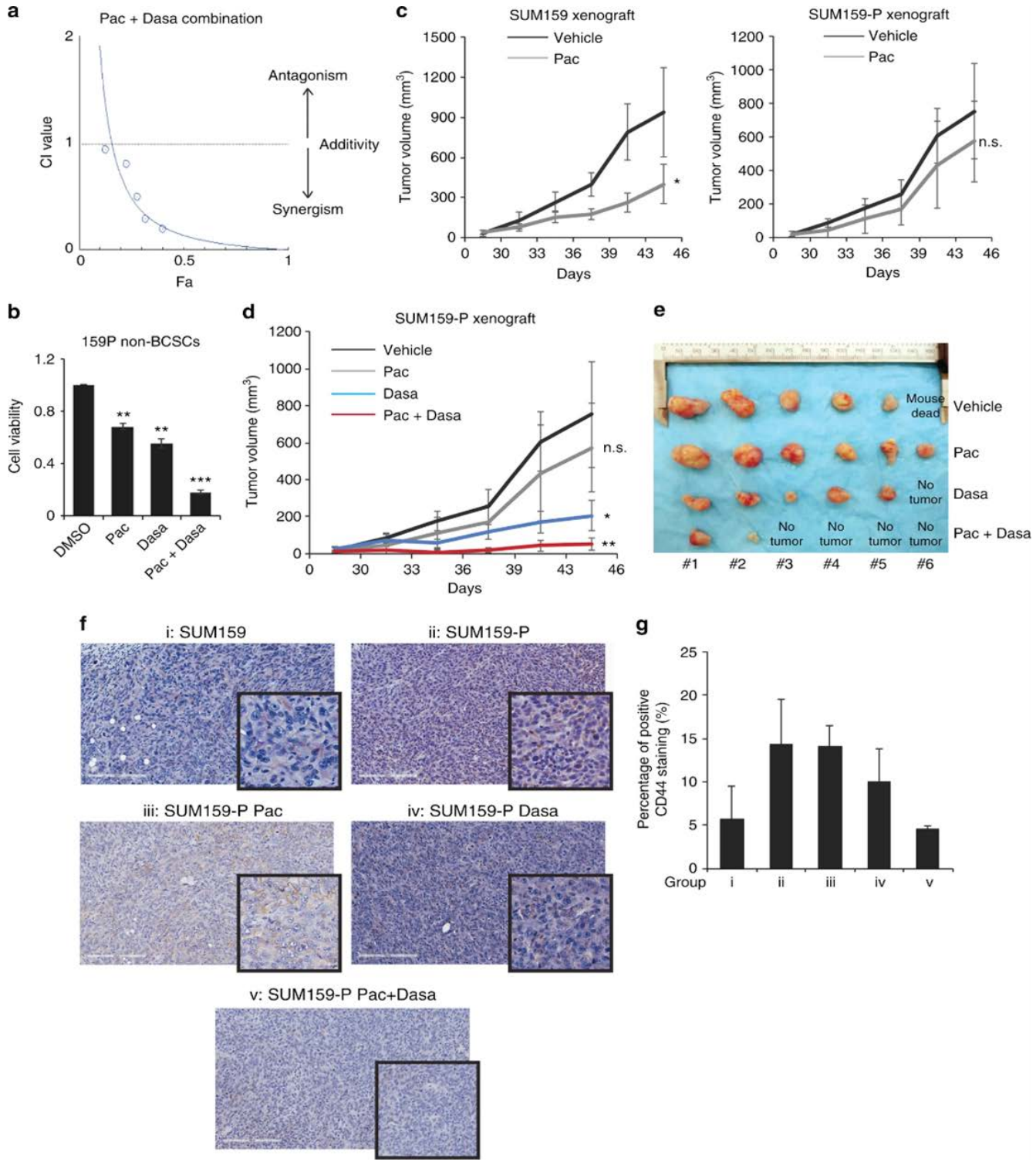

Figure 2: Combination of dasatinib and paclitaxel effectively targets breast cancer cells. **(a)** The combination index and fraction affected (Fa, representing the proportion of inhibited cell viability) were analyzed in SUM159-P cells treated with varying doses of paclitaxel and dasatinib, using a ratio based on their respective IC_{50} values. **(b)** Non-BCSCs expressing CD24 and CD44 were isolated from SUM159-P cells and assessed for viability using the PrestoBlue assay following treatment with the specified drugs. **(c–e)** SUM159 and SUM159-P cells were implanted in mice, which were then randomly divided into groups (n = 6 per group). Treatment was administered as outlined in the Methods section. **(c)** Tumor growth in SUM159 and SUM159-P-derived xenografts were evaluated with and without paclitaxel treatment. Tumor volume was calculated using the formula: volume (mm^3) = (length (mm))^2 × (width (mm)) × 0.5. **(d)** Growth curves of SUM159-P-derived tumors were compared across treatment groups: vehicle control, paclitaxel alone, dasatinib alone, and the combination of paclitaxel and dasatinib. **(e)** Representative images of SUM159-P-derived tumors from each treatment group. **(f, g)** CD44 expression was analyzed in tumor xenografts from different treatment groups: **(i)** SUM159 xenograft (control), **(ii)** SUM159-P xenograft treated with vehicle, **(iii)** SUM159-P xenograft treated with paclitaxel alone, **(iv)** SUM159-P xenograft treated with dasatinib alone, and **(v)** SUM159-P xenograft treated with paclitaxel + dasatinib. The intensity of CD44 staining and the percentage of stained areas were quantified. The total percentage of membrane and cytoplasmic CD44 staining was determined for each tumor sample. **(f)** Representative immunohistochemistry images (20× magnification) of CD44 in breast cancer samples (scale bar = 200 μm). **(g)** The average percentage of CD44-positive tumor cells was calculated for each treatment group [75].

Table 2: Research gaps and future research directions.

Gap area	Description	Future research directions	Justification	Research priority
Targeting metabolic vulnerabilities in chemoresistant TNBC	Metabolic reprogramming, including lipid metabolism and oxidative phosphorylation, is implicated in chemoresistance, but therapeutic targeting remains underexplored.	Investigate inhibitors targeting lipid droplet-associated proteins like PLIN4 and oxidative phosphorylation pathways in preclinical and clinical TNBC models; develop biomarkers for metabolic vulnerabilities.	Metabolic adaptations sustain chemoresistant phenotypes and represent actionable targets, as shown by PLIN4 dependence and oxidative phosphorylation inhibitor efficacy [101].	High
CSCs heterogeneity and plasticity	CSC subpopulations with distinct epithelial and mesenchymal phenotypes contribute to chemoresistance, but their dynamic regulation and therapeutic targeting are insufficiently characterized.	Employ single-cell multi-omics and lineage tracing to define CSC heterogeneity; develop combination therapies targeting both epithelial and mesenchymal CSCs; assess microenvironmental influences.	CSC plasticity underlies resistance and relapse; targeting diverse CSC states is critical for durable responses [68].	High
Epigenetic regulation and chemoresistance	The role of epigenetic modifications such as H3K27me3, DNA methylation, and histone deacetylation in chemoresistance are recognized, yet mechanisms and therapeutic windows need clarification.	Conduct longitudinal epigenomic profiling during chemotherapy; evaluate timing and combination of epigenetic inhibitors (e.g., DNMT, HDAC, EZH2 inhibitors) with chemotherapy; identify predictive epigenetic biomarkers.	Epigenetic priming and plasticity contribute to drug tolerance; epigenetic therapies can sensitize resistant cells but require precise application [95].	High
Signaling pathway crosstalk and resistance mechanisms	Complex interactions among PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, and NF-κB pathways drive chemoresistance, but compensatory feedback and pathway rewiring limit monotherapies.	Develop multi-targeted combination therapies addressing pathway crosstalk; use systems biology to model resistance networks; validate biomarkers for patient stratification.	Redundant and adaptive signaling networks promote resistance; combination targeting improves efficacy [26].	High
Role of TME and extracellular matrix remodeling	Extracellular matrix stiffness, collagen cross-linking, and cancer-associated fibroblasts activation support CSC maintenance and chemoresistance yet targeting stromal components is not fully integrated into therapy.	Investigate inhibitors of LOX, FAK/Src, and Hedgehog signaling in cancer-associated fibroblasts; assess stromal biomarkers predictive of response; design clinical trials combining stromal targeting with chemotherapy.	Stromal remodeling fosters CSC niches and drug resistance; targeting cancer-associated fibroblasts improves chemotherapy response [92].	Medium
Overcoming drug efflux-mediated resistance	ABC transporters like ABCB1/Pgp contribute to chemoresistance, but clinical translation of inhibitors or antibody therapies remains limited.	Develop novel strategies to inhibit ABC transporters via targeting regulatory proteins (e.g., USP7, USP51) or immunotherapy; evaluate combination with standard chemotherapy in TNBC models.	Direct inhibition of transporters has failed clinically; targeting upstream regulators offers alternative approaches [41, 88].	Medium
Therapeutic targeting of CSC-associated signaling	Pathways such as Notch, Hedgehog, and Wnt sustain CSCs and resistance, but clinical translation of inhibitors is incomplete.	Advance clinical trials of pathway inhibitors combined with chemotherapy; identify biomarkers for CSC pathway activation; explore resistance mechanisms to these inhibitors.	CSC signaling pathways are validated resistance drivers; combinatorial targeting may prevent relapses [72, 90].	Medium
RNA-binding proteins and noncoding RNAs in resistance	Post-transcriptional regulation by HuR and noncoding RNAs (miRNAs, lncRNAs, circRNAs) modulate chemoresistance, but mechanistic insights and therapeutic targeting are nascent.	Elucidate RNA regulatory networks in chemoresistance; develop small molecule inhibitors of HuR and RNA-based therapeutics; validate miRNA/lncRNA biomarkers.	RNA regulators influence multiple resistance pathways; targeting them may overcome resistance [102].	Medium
Mechanisms of therapy-induced senescence and survival	Therapy-induced senescence and autophagy promote survival of resistant cells, yet strategies to manipulate these fates are underdeveloped.	Investigate senolytic and autophagy-modulating agents in TNBC; study interplay with immune response; develop biomarkers for senescence-associated resistance.	Non-apoptotic survival pathways contribute to relapse; targeting them may enhance chemotherapy efficacy [103].	Low
Biomarker-driven patient stratification	Lack of robust predictive biomarkers hampers personalized therapy and clinical trial success in chemoresistant TNBC.	Integrate multi-omics data to identify and validate biomarkers predicting resistance and therapeutic response; implement biomarker-driven clinical trials.	Patient heterogeneity necessitates precision medicine approaches to improve outcomes [54].	High

research remains constrained by small sample sizes, limited clinical validation, and oversimplified experimental models that fail to capture the disease's full complexity. The heterogeneity of TNBC subtypes and inconsistent definitions of resistance further complicate comparisons across studies and hinder therapeutic advancements. Future research must prioritize larger, longitudinal clinical studies and more sophisticated models to bridge these gaps and translate findings into effective treatments (Table 2).

Conclusion

Chemoresistance in TNBC reveals a deeply intricate and multifactorial landscape driven by interconnected molecular signaling, CSC dynamics, epigenetic regulation, and metabolic rewiring. Central to chemoresistance are aberrations in key signaling pathways including PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, and NF-κB, which orchestrate survival, proliferation, and therapeutic evasion. These pathways often exhibit compensatory crosstalk and feedback loops that undermine the efficacy of monotherapies, necessitating combinatorial approaches targeting multiple nodes simultaneously to circumvent resistance. CSCs emerge as pivotal contributors to therapeutic failure and disease relapses, characterized by their plasticity, heterogeneity, and resistance to conventional chemotherapeutics. Enriched CSC populations display distinct surface markers and activate stemness-associated signaling such as Notch, Hedgehog, TGF-β, and epithelial-to-mesenchymal transition programs. The TME, particularly cancer-associated fibroblasts and hypoxia-induced factors, further modulates CSC maintenance and drug resistance phenotypes, underscoring the need to consider niche interactions in therapeutic design.

Epigenetic modifications, including DNA methylation, histone modifications, and chromatin remodeling, play essential roles in establishing drug-tolerant states and sustaining chemoresistance. These reversible yet stable alterations influence gene expression programs

and enhance landscapes, regulating resistance-associated transcription factors and pathways. Targeting epigenetic regulators such as bromodomain proteins, histone deacetylases, and deubiquitinases has demonstrated potential to re-sensitize resistant TNBC cells, offering a promising avenue to address non-genetic resistance mechanisms. Metabolic adaptations constitute another layer of resistance, with chemoresistant TNBC cells displaying reprogrammed lipid metabolism, enhanced oxidative phosphorylation, and altered nucleotide biosynthesis. These metabolic shifts provide survival advantages under therapeutic stress and represent exploitable vulnerabilities. Inhibition of metabolic enzymes and pathways has shown efficacy in preclinical models, suggesting metabolic targeting as a complementary strategy to conventional therapy.

The integration of molecular biomarkers, including MLK4, RASAL2, USP51, CYR61, and epigenetic signatures-facilitates patient stratification and informs personalized treatment regimens. Despite promising preclinical and early clinical evidence, challenges remain in translating these insights due to TNBC's heterogeneity, adaptive resistance mechanisms, and toxicity concerns associated with combination therapies. Future research should emphasize multi-omics integration, robust biomarker validation, and development of adaptive clinical trial designs to optimize therapeutic outcomes. Overall, a comprehensive and integrative approach targeting molecular signaling, CSCs, epigenetic states, and metabolic pathways is essential to overcome chemoresistance and improve prognosis for patients with TNBC.

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None.

Conflict of Interest

None.

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