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UNDERSTANDING DRUG RESISTANCE IN ER-POSITIVE BREAST CANCER: A REVIEW OF FIBROBLAST-CANCER CELL INTERACTIONS

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ABSTRACT

Endocrine therapy remains the cornerstone of treatment for estrogen receptor–positive (ER-positive) breast cancer; however, therapeutic resistance continues to limit long-term clinical success. While earlier studies primarily focused on tumor-intrinsic genetic alterations, emerging evidence highlights the tumor microenvironment as a decisive regulator of drug response. Among stromal components, cancer-associated fibroblasts (CAFs) have gained prominence as key drivers of tumor progression and endocrine resistance. This qualitative secondary review synthesizes peer-reviewed literature published between 2010 and 2025 to elucidate the mechanistic role of fibroblast–cancer cell interactions in shaping therapeutic outcomes. Data were systematically analyzed to identify recurring biological themes, including paracrine survival signaling, extracellular matrix remodeling, metabolic reprogramming, and induction of estrogen-independent growth pathways. Findings reveal that CAFs promote resistance through activation of PI3K/AKT and MAPK signaling, enhancement of cancer stem–like phenotypes, metabolic coupling via lactate exchange, and biomechanical alterations of the extracellular matrix that restrict drug penetration. Heterogeneous co-culture models further demonstrate that these stromal-mediated processes operate synergistically to confer tumor plasticity and sustained survival under endocrine stress. Collectively, this review underscores fibroblasts as central orchestrators of resistance in ER-positive breast cancer and emphasizes the necessity of incorporating tumor microenvironment dynamics into pharmaceutical research. The

integration of stromal-targeted therapies with conventional endocrine agents, alongside the adoption of co-culture platforms in preclinical screening, may offer more durable therapeutic strategies.

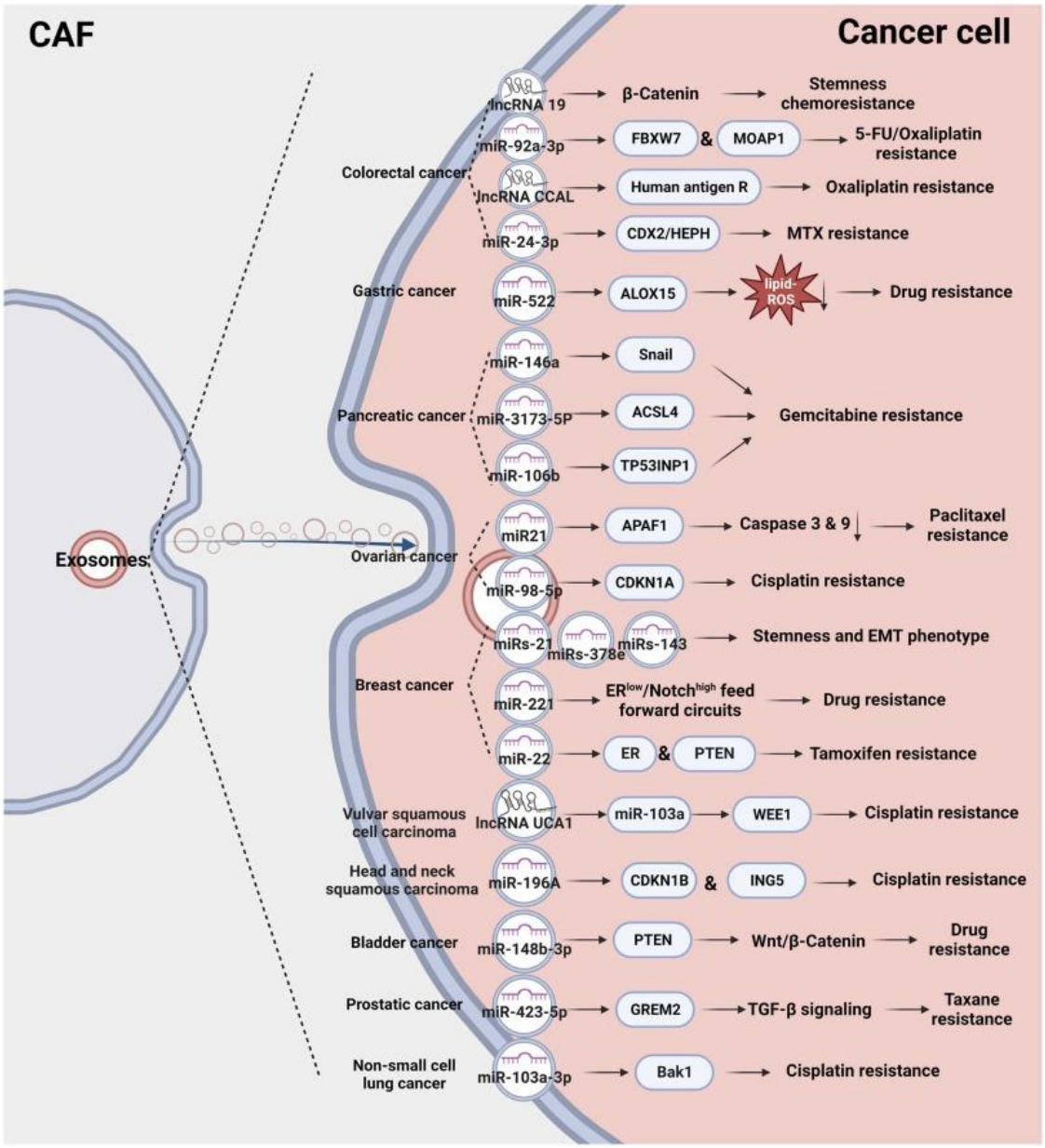
KEYWORDS: Cancer-associated fibroblasts; ER-positive breast cancer; endocrine resistance; tumor microenvironment; co-culture models; metabolic reprogramming; extracellular matrix remodelling.

INTRODUCTION

Estrogen receptor–positive (ER-positive) breast cancer represents the most prevalent molecular subtype, accounting for nearly 70% of all diagnosed breast malignancies. Endocrine-based therapies, including selective estrogen receptor modulators and aromatase inhibitors, remain the cornerstone of treatment and often achieve meaningful initial tumor control. Despite these early benefits, a substantial proportion of patients ultimately experience therapeutic resistance, resulting in disease progression, metastatic spread, and clinical relapse (Siegel et al., 2024; Osborne & Schiff, 2011). Earlier investigations primarily attributed endocrine resistance to intrinsic genetic and epigenetic alterations within cancer cells. However, growing evidence indicates that tumor behavior cannot be fully understood in isolation. Instead, the tumor microenvironment (TME)—a complex ecosystem comprising immune cells, endothelial cells, adipocytes, extracellular matrix (ECM), and stromal fibroblasts—actively shapes therapeutic outcomes. The illustrated schematic highlights how inflammatory mediators, reactive oxygen species, immune checkpoints, and metabolic by-products collectively influence tumor survival, emphasizing that drug response emerges from dynamic multicellular interactions rather than cancer cell autonomy alone (Hanahan, 2022).

Among stromal components, fibroblasts undergo profound phenotypic reprogramming within tumors, transforming into cancer-associated fibroblasts (CAFs). These CAFs acquire enhanced secretory and matrix-modifying capabilities, producing cytokines (e.g., IL-6, TGF-β), chemokines, growth factors, and ECM proteins such as fibronectin and laminin. As depicted in the figure, CAF-mediated remodelling promotes immune evasion, angiogenesis, and activation of pro-survival signalling pathways in adjacent ER-positive cancer cells. Such paracrine and mechanical cues have been shown to directly attenuate endocrine sensitivity while fostering adaptive resistance states (Kalluri, 2016; Sahai et al., 2020). Importantly, CAFs also regulate immune polarisation and metabolic reprogramming within the TME. Crosstalk between fibroblasts, macrophages, T cells, and adipocytes generates an

immunosuppressive milieu characterised by elevated VEGF, IL-10, and PGE2, alongside altered lipid and ketone metabolism. These processes collectively enhance tumor plasticity and protect malignant cells from therapeutic stress, reinforcing the concept that resistance is a systems-level phenomenon rather than a single-gene event (Binnewies et al., 2018).

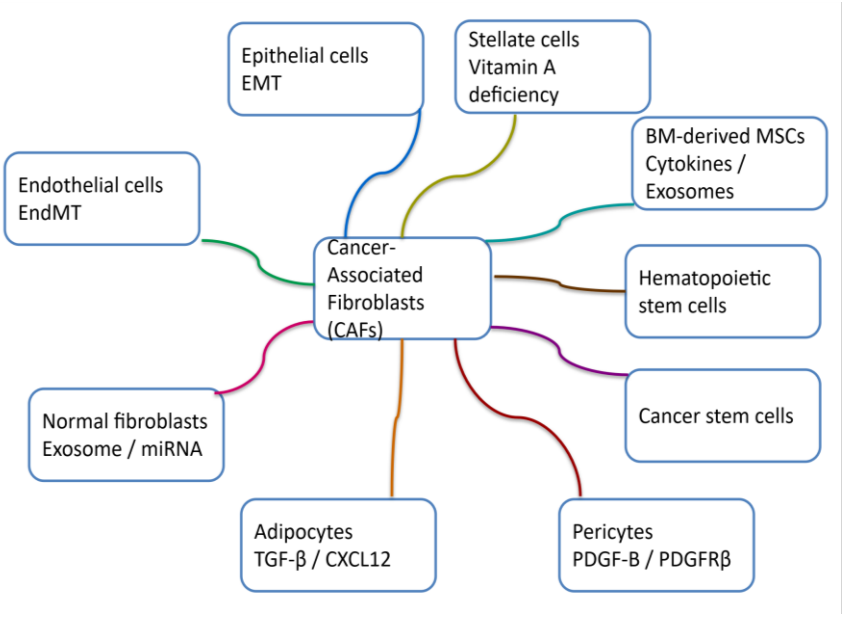


Source: (Feng B., et al. 2022. Cancer-associated fibroblasts and resistance to anticancer therapies).

To better capture this complexity, heterogeneous co-culture platforms integrating fibroblasts with ER-positive breast cancer cells have emerged as critical experimental models. These systems recapitulate stromal–epithelial signalling, ECM dynamics, and immune modulation observed in vivo, enabling mechanistic exploration of resistance pathways that remain

invisible in monoculture settings. Such approaches have revealed that fibroblast–cancer cell communication significantly alters drug response profiles, highlighting CAFs as both biomarkers and potential therapeutic targets (Hirata & Sahai, 2017).

Against this background, the present review synthesizes secondary literature to qualitatively examine how fibroblast-mediated interactions within the tumor microenvironment contribute to endocrine resistance in ER-positive breast cancer. By integrating insights from studies on CAF biology, immune regulation, and metabolic signaling—as conceptually summarized in the accompanying figure—this work aims to clarify the central role of stromal heterogeneity in shaping treatment failure and to identify future directions for combination strategies targeting both cancer cells and their supportive niches.



Fibroblasts within the tumor microenvironment actively modulate malignant progression through multiple coordinated mechanisms. These include the release of paracrine growth factors that support tumor cell proliferation, secretion of pro-inflammatory cytokines that sustain chronic signaling networks, and remodeling of the extracellular matrix leading to increased tissue rigidity. In parallel, fibroblast–cancer cell crosstalk stimulates key survival pathways such as PI3K/AKT and MAPK, while also facilitating epithelial–mesenchymal transition, thereby enhancing cellular motility and invasiveness. Collectively, these fibroblast-driven processes contribute to therapeutic resistance by promoting tumor cell adaptability, reducing responsiveness to anticancer agents, and strengthening survival signaling cascades.

This study employed a qualitative secondary data review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to synthesize existing scientific literature on the role of cancer-associated fibroblasts (CAFs) in endocrine resistance in estrogen receptor–positive (ER-positive) breast cancer. The review aimed to identify mechanistic insights into fibroblast–cancer cell interactions and their implications for drug resistance and pharmaceutical research. Literature Search Strategy; A systematic literature search was conducted across major biomedical databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify peer-reviewed studies published between January 2010 and March 2025. The search strategy combined Medical Subject Headings (MeSH) terms and relevant keywords related to breast cancer biology, tumor microenvironment interactions, and therapeutic resistance. The following representative search string was used: “ER-positive breast cancer” AND “cancer-associated fibroblasts” OR “tumor microenvironment” AND “endocrine resistance” OR “drug resistance” AND “extracellular matrix remodeling” OR “metabolic reprogramming”. Additional articles were identified through reference list screening of key review papers and relevant primary research articles to ensure comprehensive coverage of the topic. Studies were included if they met the following criteria:[1] Published in peer-reviewed journals between 2010 and 2025. $_2$Investigated cancer-associated fibroblasts or stromal fibroblasts within the tumor microenvironment.[3] Focused on breast cancer, particularly ER-positive subtypes.[4] Examined mechanisms related to endocrine resistance, drug resistance, metabolic interactions, or ECM remodeling.[5] Provided experimental, clinical, or mechanistic insights relevant to fibroblast–tumor interactions. Studies were excluded if they: Focused solely on non-breast cancers without transferable mechanisms. Were conference abstracts without full peer-reviewed publications. Lacked mechanistic or pharmacological relevance.

All retrieved studies were screened using a two-stage selection process. Initially, titles and abstracts were evaluated for relevance. Subsequently, full-text articles meeting the inclusion criteria were reviewed in detail. Duplicates were removed during the screening process. Following PRISMA guidelines, the study selection involved: Identification: Retrieval of records through database searches. Screening: Removal of duplicate and irrelevant articles. Eligibility: Full-text assessment of potentially relevant studies. Inclusion: Final selection of articles for qualitative synthesis.

Relevant information from selected studies was systematically extracted, including

Mechanisms of CAF activation, ECM remodeling pathways, Metabolic interactions between fibroblasts and cancer cells, Signaling pathways involved in endocrine resistance, Implications for targeted therapeutic strategies. The extracted information was analyzed using thematic synthesis, allowing recurring biological mechanisms to be categorized into major conceptual themes such as paracrine survival signaling, extracellular matrix remodeling, metabolic reprogramming, and endocrine therapy resistance. Because the objective of the review was mechanistic interpretation rather than statistical comparison, a qualitative analytical framework was adopted rather than a quantitative meta-analysis.

Recent studies on endocrine resistance in estrogen receptor positive breast cancer

Previous research on endocrine resistance in estrogen receptor–positive (ER-positive) breast cancer initially focused on tumor-intrinsic genetic and epigenetic alterations; however, recent studies increasingly emphasize the decisive role of the tumor microenvironment (TME) in regulating therapeutic outcomes (Osborne & Schiff, 2011; Hanahan, 2022). Among stromal components, cancer-associated fibroblasts (CAFs) have been identified as key regulators of tumor progression, influencing cancer cell survival, proliferation, and resistance through cytokine secretion, extracellular matrix remodeling, and activation of signaling pathways such as PI3K/AKT and MAPK (Kalluri, 2016; Sahai et al., 2020). Evidence also suggests that fibroblast–cancer cell interactions promote metabolic coupling and immune modulation, generating an immunosuppressive microenvironment that enhances tumor adaptability under endocrine stress (Binnewies et al., 2018; Lyssiotis & Kimmelman, 2017). Furthermore, co-culture and stromal-interaction studies demonstrate that CAF-mediated paracrine signaling can induce estrogen-independent growth pathways, thereby reducing responsiveness to endocrine therapies and contributing to long-term therapeutic resistance (Hirata & Sahai, 2017). Collectively, the literature highlights fibroblasts as central mediators of resistance mechanisms and underscores the importance of targeting tumor–stromal interactions to improve therapeutic effectiveness.

Cancer-Associated Fibroblast and Mechanisms of CAF's Activation

Cancer-Associated Fibroblasts (CAFs) are specialized fibroblast cells present in the tumor microenvironment that support cancer progression. They promote tumor growth by secreting growth factors, remodeling the extracellular matrix, and enhancing angiogenesis and immune suppression. As a result, CAFs play a crucial role in tumor development, metastasis, and resistance to therapy. Cancer-associated fibroblasts (CAFs) arise from multiple cellular

origins and undergo extensive phenotypic reprogramming within the tumor microenvironment (TME). In breast cancer, CAFs may originate from resident tissue fibroblasts, mesenchymal stem cells, adipocytes, pericytes, or epithelial cells undergoing epithelial–mesenchymal transition (EMT). The activation of fibroblasts is primarily driven by persistent exposure to tumor-derived signaling molecules such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), interleukin-6 (IL-6), and reactive oxygen species (ROS). One of the most well-characterized drivers of fibroblast activation is TGF-β signaling, which induces the differentiation of normal fibroblasts into myofibroblast-like cells expressing markers such as α-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), and platelet-derived growth factor receptor-β (PDGFR-β). These activated fibroblasts acquire enhanced contractility and secretory capabilities that allow them to remodel the extracellular matrix and influence tumor behavior.

Additionally, chronic inflammatory signaling contributes significantly to CAF activation. Cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) activate transcription factors including NF-κB and STAT3, which promote a pro-tumorigenic fibroblast phenotype. These pathways stimulate the secretion of chemokines, growth factors, and matrix-remodeling enzymes that reinforce tumor progression. Mechanical stress within the tumor microenvironment also contributes to CAF activation. Increased matrix stiffness and mechanical tension activate integrin signaling and focal adhesion kinase (FAK), further promoting fibroblast differentiation and ECM production. Once activated, CAFs become persistent stromal regulators that sustain tumor growth through multiple mechanisms, including cytokine secretion, metabolic support, ECM remodeling, and immune modulation. Importantly, CAFs rarely revert to their normal fibroblast state, making them stable components of the tumor microenvironment and important contributors to therapeutic resistance.

THEMATIC DISCUSSION

Paracrine Survival Signalling

The reviewed literature consistently demonstrates that cancer-associated fibroblasts (CAFs) function as dynamic regulators of tumour cell survival through potent paracrine signalling networks. In estrogen receptor–positive (ER^+) breast cancer, CAF-derived cytokines—including interleukin-6 (IL-6), transforming growth factor-β (TGF-β), and an array of growth

factors—activate critical pro-survival cascades such as the PI3K/AKT and MAPK pathways. These signaling axes converge to suppress apoptosis, enhance stress adaptability, and sustain proliferative signaling under endocrine therapeutic pressure.

Importantly, stromal-mediated activation of these pathways diminishes tumor cell reliance on estrogen signaling, thereby attenuating the cytostatic and cytotoxic effects of endocrine agents. The persistent exposure to CAF-derived soluble mediators promotes transcriptional reprogramming and survival plasticity, fostering adaptive resistance phenotypes. Thus, paracrine survival signaling represents a foundational mechanism by which the tumor microenvironment reinforces therapeutic tolerance and tumor persistence.

Extracellular Matrix Remodeling

A central and reproducible finding across studies is the extensive remodeling of the extracellular matrix (ECM) orchestrated by CAFs. Through augmented collagen deposition, matrix crosslinking, and structural reorganization, CAFs substantially increase tissue stiffness and alter the architectural integrity of the tumor microenvironment. These biomechanical transformations generate a desmoplastic and highly fibrotic niche that actively influences cancer cell behavior. ECM stiffening enhances mechanotransduction signaling, facilitating epithelial–mesenchymal transition (EMT), invasion, and metastatic dissemination. Simultaneously, dense matrix architecture impairs effective drug diffusion, creating a physical barrier that limits endocrine therapy penetration. Beyond its structural role, the remodeled ECM also modulates biochemical signaling, amplifying growth factor availability and integrin-mediated survival pathways. Consequently, ECM remodeling functions as both a mechanical and molecular determinant of endocrine therapy resistance and metastatic progression.

Extracellular Matrix (ECM) Function, Components and Remodeling

The extracellular matrix (ECM) is a dynamic structural network composed of proteins, glycoproteins, and polysaccharides that provide mechanical support and biochemical signaling cues to surrounding cells. In breast cancer, the ECM is extensively remodeled by cancer-associated fibroblasts, creating a tumor-promoting microenvironment that supports tumor growth, invasion, and resistance to therapy. Major ECM components include collagens (particularly type I and III), fibronectin, laminin, elastin, and proteoglycans such as hyaluronan. These molecules interact with cell surface receptors such as integrins, which transmit mechanical and biochemical signals into the cell through pathways including FAK,

PI3K/AKT, and MAPK signaling.

CAFs play a central role in ECM remodeling by secreting matrix proteins and matrix-modifying enzymes such as matrix metalloproteinases (MMPs) and lysyl oxidase (LOX). MMPs degrade existing ECM components, allowing tumor cells to migrate and invade surrounding tissues. Meanwhile, LOX enzymes promote collagen crosslinking, leading to increased matrix stiffness and tissue rigidity. This altered mechanical environment activates mechanotransduction pathways, where tumor cells sense changes in ECM stiffness through integrins and cytoskeletal structures. Activation of mechanotransduction signaling promotes epithelial–mesenchymal transition (EMT), enhanced motility, and increased metastatic potential.

In addition to structural modifications, ECM remodeling affects drug delivery and therapeutic efficacy. Dense collagen fibers and fibrotic stroma create physical barriers that limit drug penetration into tumor tissue. As a result, endocrine therapies and chemotherapeutic agents may fail to reach effective concentrations within tumor cells. Furthermore, ECM components can function as reservoirs for growth factors such as TGF-β and VEGF, which are released during matrix degradation and further stimulate tumor progression. Thus, ECM remodeling represents both a structural and biochemical mechanism by which the tumor microenvironment promotes cancer survival and therapy resistance.

Metabolic Reprogramming

Metabolic reprogramming is a fundamental hallmark of cancer and plays a crucial role in the interaction between cancer cells and stromal fibroblasts. Within the tumor microenvironment, CAFs undergo metabolic alterations that support tumor growth through a phenomenon known as metabolic symbiosis. Activated fibroblasts often exhibit increased glycolytic activity, a process sometimes referred to as the reverse Warburg effect. In this metabolic state, CAFs convert glucose into lactate and other metabolites, which are subsequently released into the tumor microenvironment. Cancer cells then utilize these metabolites as alternative energy sources for mitochondrial oxidative phosphorylation and biosynthetic processes.

This metabolic coupling allows cancer cells to maintain high levels of ATP production and macromolecule synthesis even under conditions of therapeutic stress or nutrient deprivation. CAF-derived metabolites such as lactate, pyruvate, ketone bodies, and amino acids serve as

essential substrates that support tumor survival and proliferation. In addition to nutrient exchange, CAFs also influence metabolic pathways through the secretion of cytokines and growth factors that regulate cellular metabolism. For example, IL-6 and TGF-β signaling can activate metabolic regulators such as mTOR and AMPK, which coordinate cellular energy homeostasis. Metabolic reprogramming also contributes to the development of endocrine resistance in ER-positive breast cancer. Under endocrine therapy, cancer cells experience metabolic stress due to disrupted estrogen signaling. However, CAF-mediated metabolic support compensates for this stress by providing alternative energy sources, allowing tumor cells to sustain proliferation despite hormonal deprivation.

These findings highlight the importance of targeting tumor metabolism and stromal metabolic interactions as potential therapeutic strategies for overcoming drug resistance. Emerging evidence underscores the critical role of metabolic symbiosis between CAFs and cancer cells in sustaining tumor survival during endocrine treatment. CAFs undergo metabolic reprogramming characterized by enhanced glycolysis and altered nutrient processing, generating metabolites such as lactate, pyruvate, and specific amino acids. These substrates are subsequently transferred to adjacent cancer cells, fueling mitochondrial oxidative phosphorylation and biosynthetic pathways.

This fibroblast–cancer cell metabolic coupling supports energy homeostasis and macromolecular synthesis under conditions of estrogen deprivation or pharmacologic inhibition. By compensating for endocrine-induced metabolic stress, CAF-derived nutrients enable malignant cells to maintain proliferation and survival despite disrupted estrogen receptor signaling. Such stromal metabolic support exemplifies tumor microenvironment–driven plasticity and highlights metabolic reprogramming as a central contributor to therapy tolerance.

Induction of Endocrine Resistance

The cumulative impact of CAF-derived signaling culminates in the progressive induction of endocrine resistance. Persistent exposure to stromal cytokines and growth factors activates alternative mitogenic pathways, including PI3K/AKT, MAPK, and receptor tyrosine kinase signaling, thereby reducing cellular dependence on estrogen receptor–mediated transcriptional programs. This shift toward estrogen-independent growth is accompanied by enhanced growth factor receptor responsiveness, survival pathway amplification, and transcriptional reconfiguration. Over time, ER^+ breast cancer cells acquire a resistant

phenotype characterized by sustained proliferation despite endocrine blockade. These findings collectively position CAFs not merely as passive structural components but as active drivers of therapeutic failure. Endocrine therapies such as tamoxifen, fulvestrant, and aromatase inhibitors are designed to inhibit estrogen receptor signaling, which is the primary driver of proliferation in ER-positive breast cancer. However, the tumor microenvironment significantly influences the effectiveness of these therapies. Cancer-associated fibroblasts promote endocrine resistance through multiple mechanisms. One key process involves the secretion of cytokines and growth factors that activate alternative survival pathways, including PI3K/AKT, MAPK/ERK, and JAK/STAT signaling. Activation of these pathways allows cancer cells to maintain proliferation even when estrogen signaling is inhibited.

CAF-derived growth factors such as hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and fibroblast growth factors (FGFs) can activate receptor tyrosine kinases on tumor cells, leading to estrogen-independent cell growth. This signaling bypass reduces the reliance of tumor cells on ER-mediated transcriptional programs. Another mechanism involves epigenetic modifications and transcriptional reprogramming induced by stromal signaling. Prolonged exposure to CAF-derived cytokines alters gene expression patterns within cancer cells, promoting the development of resistant phenotypes characterized by enhanced survival and stem-like properties. Furthermore, CAFs influence endocrine resistance through exosome-mediated communication. Exosomes released by fibroblasts can transfer microRNAs, proteins, and metabolites that modulate signaling pathways in cancer cells. These extracellular vesicles contribute to adaptive responses that enable tumor cells to withstand endocrine therapy. Collectively, these processes illustrate how fibroblast-mediated stromal interactions transform ER-positive breast cancer into a therapy-resistant disease.

Taken together, these themes reveal a multidimensional framework in which CAFs orchestrate endocrine resistance through interconnected mechanisms involving paracrine signaling, ECM remodeling, metabolic reprogramming, and estrogen-independent pathway activation. The tumor microenvironment thus emerges as a critical determinant of therapeutic outcome, underscoring the necessity of combinatorial strategies targeting both cancer cells and stromal components to overcome resistance in ER-positive breast cancer.

Summary Table of Key Mechanisms

Fibroblast Function	*Impact on Cancer Cells*	*Therapeutic Consequence*
Cytokine secretion	Survival pathway activation	Reduced drug sensitivity
ECM remodeling	Increased invasion	Poor drug penetration
Metabolic support	Enhanced energy availability	Therapy tolerance
Growth factor signaling	ER pathway bypass	Endocrine resistance

Drug resistance

Representation of Resistance Development; Drug Resistance Mechanisms**;** Drug resistance in breast cancer is a multifactorial process involving genetic, molecular, and microenvironmental factors. CAFs contribute significantly to these resistance mechanisms through several interconnected biological processes.

Drug Efflux

One important mechanism involves the upregulation of ATP-binding cassette (ABC) transporters, which actively pump chemotherapeutic drugs out of cancer cells. CAF-derived cytokines such as IL-6 and CXCL12 stimulate the expression of efflux transporters including P-glycoprotein (ABCB1) and multidrug resistance proteins (MRPs), thereby reducing intracellular drug concentrations and limiting therapeutic effectiveness.

Immune Evasion

CAFs also reshape the immune microenvironment by promoting immunosuppressive conditions that protect tumor cells from immune-mediated destruction. Fibroblasts secrete factors such as TGF-β, CXCL12, and prostaglandin E2 (PGE2), which inhibit cytotoxic T-cell activity and recruit regulatory immune cells such as myeloid-derived suppressor cells and regulatory T cells. This immune suppression allows tumor cells to evade immune surveillance and sustain tumor progression.

Anti-Apoptotic Signaling

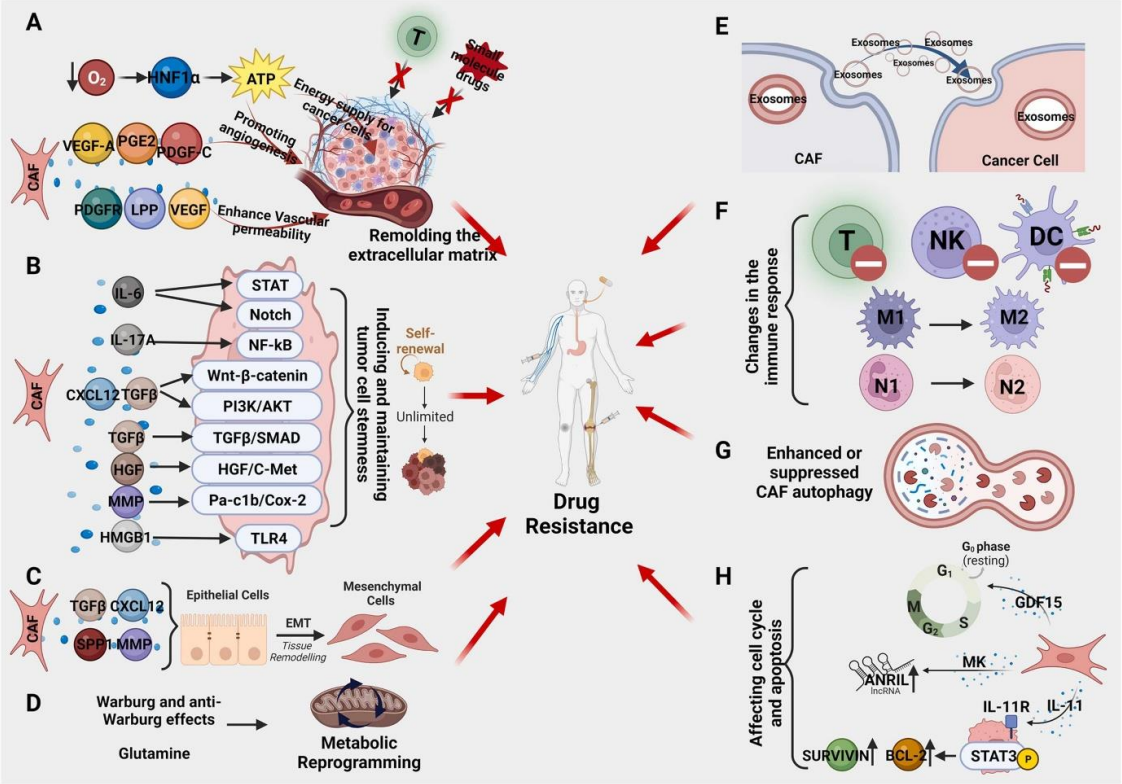
Resistance to apoptosis is another key mechanism contributing to treatment failure. CAF-mediated signaling activates anti-apoptotic proteins including BCL-2, survivin, and MCL-1 through pathways such as PI3K/AKT and NF-κB. These proteins inhibit programmed cell death and allow cancer cells to survive under therapeutic stress.

Genetic Mutations and Epigenetic Alterations

Genetic mutations within cancer cells can also drive drug resistance. Mutations in genes such as ESR1, PIK3CA, and TP53 have been associated with resistance to endocrine therapy.

Additionally, epigenetic modifications including DNA methylation and histone acetylation can alter gene expression patterns that promote survival and therapy tolerance.

Together, these mechanisms demonstrate that drug resistance arises from complex interactions between tumor cells and their microenvironment rather than from single molecular events.



Source: (Feng B., et al. 2022. Cancer-associated fibroblasts and resistance to anticancer therapies).

Figure, Multifactorial mechanisms of cancer-associated fibroblast (CAF)–mediated drug resistance in the tumor microenvironment. Cancer-associated fibroblasts promote therapeutic resistance through multiple coordinated biological processes that collectively enhance tumor survival. (A) CAF-derived growth factors such as VEGF, PDGF, and PGE2 stimulate angiogenesis, increase vascular permeability, and remodel the extracellular matrix (ECM), thereby facilitating tumor progression and limiting drug penetration. (B) Secretion of cytokines and chemokines, including IL-6, IL-17A, CXCL12, TGF-β, and HGF, activates pro-survival signaling pathways such as STAT3, PI3K/AKT, NF-κB, Notch, and Wnt/β-catenin, promoting cancer stem-cell maintenance and long-term resistance. (C) CAF signaling induces epithelial–mesenchymal transition (EMT), enhancing tumor invasiveness

and metastatic potential. (D) Metabolic reprogramming driven by CAF-mediated nutrient exchange supports tumor bioenergetics under therapeutic stress. (E) Bidirectional transfer of resistance-associated molecules occurs via CAF- and tumor-derived exosomes. (F) CAF activity reshapes the immune microenvironment by suppressing cytotoxic immune responses and promoting immunosuppressive cell polarization. (G) Regulation of autophagy further enhances tumor cell survival during treatment. (H) CAF-induced alterations in cell-cycle control and apoptosis signaling sustain malignant cell persistence. Together, these interconnected stromal mechanisms establish a protective tumor niche that drives endocrine and chemotherapeutic resistance.

Clinical Relevance of CAF-Targeted Therapy

Increasing evidence indicates that cancer-associated fibroblasts are central regulators of therapeutic resistance in breast cancer, making them attractive targets for clinical intervention. Unlike tumor cells, which often undergo rapid genetic evolution, CAFs represent relatively stable stromal components that maintain tumor-supportive signaling networks. Consequently, targeting fibroblast activity has emerged as a promising strategy to enhance treatment responses in ER-positive breast cancer.

One clinically relevant approach involves inhibiting CAF activation pathways, particularly those mediated by transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) signaling. Pharmacological inhibition of these pathways may reduce fibroblast-mediated ECM remodeling and suppress pro-tumorigenic cytokine secretion. For instance, TGF-β inhibitors have been investigated for their ability to disrupt fibroblast activation and improve drug penetration within fibrotic tumor tissue.

Another therapeutic strategy focuses on targeting fibroblast-derived signaling molecules that promote tumor survival. CAF-secreted cytokines such as interleukin-6 (IL-6) and hepatocyte growth factor (HGF) activate downstream pathways including JAK/STAT, PI3K/AKT, and MAPK signaling, which contribute to estrogen-independent tumor growth. Inhibitors targeting these pathways may therefore restore endocrine sensitivity.

In addition, extracellular matrix–modifying therapies are gaining attention in clinical oncology. Agents that reduce collagen crosslinking or degrade dense stromal matrices can enhance drug penetration and improve therapeutic efficacy. Enzymatic strategies targeting hyaluronan and collagen deposition have shown potential in improving the delivery of

anticancer drugs within stromal-rich tumors.

Recent clinical advances in combination therapies further underscore the clinical relevance of targeting stromal interactions. For example, CDK4/6 inhibitors and PI3K inhibitors are increasingly combined with endocrine therapy in advanced ER-positive breast cancer. Although these drugs primarily target tumor cell signaling, emerging evidence suggests that they may also indirectly influence tumor–stromal interactions within the microenvironment. Collectively, these developments suggest that integrating CAF-targeted therapies with endocrine treatment may represent a promising strategy for overcoming resistance and improving long-term clinical outcomes in breast cancer patients.

Emerging Pharmaceutical Strategies

The recognition that tumor progression is strongly influenced by stromal interactions has led to the development of novel pharmaceutical strategies aimed at targeting the tumor microenvironment alongside cancer cells. Several emerging therapeutic approaches are currently being explored in preclinical and clinical research.

CAF-Targeted Therapeutics

One emerging strategy involves directly targeting fibroblast-specific markers such as fibroblast activation protein (FAP), platelet-derived growth factor receptors (PDGFR), and α-smooth muscle actin–positive fibroblasts. Therapeutic approaches include monoclonal antibodies, small-molecule inhibitors, and CAR-T cell therapies designed to eliminate or modulate tumor-promoting fibroblast populations.

Targeting Tumor Metabolism

Another promising avenue involves disrupting metabolic interactions between CAFs and cancer cells. Inhibitors targeting glycolysis, lactate transporters (such as MCT1 and MCT4), and mitochondrial metabolism are being investigated to interrupt the metabolic symbiosis that supports tumor survival during endocrine therapy.

ECM-Modulating Therapies

Pharmaceutical research is also exploring drugs that alter extracellular matrix composition and stiffness. Agents targeting lysyl oxidase (LOX), matrix metalloproteinases (MMPs), and integrin signaling pathways may reduce stromal rigidity and inhibit metastatic progression while improving drug delivery to tumor tissue.

Immunomodulatory Approaches

Since CAFs contribute to immune suppression within the tumor microenvironment, immunomodulatory therapies are being investigated to reverse these effects. These include immune checkpoint inhibitors, cytokine signaling inhibitors, and therapies targeting stromal immune regulators. By restoring immune surveillance, such treatments may improve the effectiveness of conventional anticancer therapies.

Advanced Drug Screening Models

Innovative experimental platforms such as three-dimensional tumor organoids, patient-derived xenografts, and microfluidic tumor-on-a-chip systems are increasingly used in pharmaceutical research. These models more accurately replicate the complexity of tumor–stromal interactions and allow researchers to evaluate drug responses in physiologically relevant environments.

Together, these emerging strategies highlight the importance of integrative therapeutic approaches that simultaneously target tumor cells and their supporting microenvironment.

Implications for Pharmaceutical Research

This review highlights the necessity for a paradigm shift in anticancer drug development, emphasizing the tumor microenvironment as a critical therapeutic target. From a pharmaceutical standpoint, effective treatment strategies should incorporate agents capable of modulating stromal activity alongside conventional tumor-directed therapies. Targeting cancer-associated fibroblasts as adjunctive interventions may enhance endocrine responsiveness and limit adaptive resistance mechanisms. Furthermore, the incorporation of heterogeneous co-culture platforms into early-stage drug screening workflows offers a more predictive assessment of therapeutic efficacy by capturing stromal–epithelial interactions. These insights support the development of combination treatment approaches that simultaneously disrupt malignant cells and their supportive microenvironment, underscoring the importance of systems-based drug discovery frameworks rather than cancer cell–centric models alone. The growing recognition of stromal contributions to therapeutic resistance necessitates a shift in pharmaceutical research toward microenvironment-inclusive drug development strategies. Traditional anticancer drug discovery has largely focused on targeting tumor cells directly, often neglecting the supportive stromal components that enable tumor survival.

Future therapeutic strategies should therefore aim to simultaneously target cancer cells and stromal interactions. Potential approaches include inhibitors of CAF activation, ECM-modifying agents, metabolic inhibitors, and immunomodulatory therapies that restore effective immune responses. Additionally, preclinical drug testing should incorporate three-dimensional co-culture systems, patient-derived organoids, and microfluidic tumor-on-a-chip models that better replicate the complexity of the tumor microenvironment. These advanced platforms allow researchers to evaluate drug responses in physiologically relevant contexts and improve the predictive accuracy of preclinical studies. Ultimately, integrating tumor biology with microenvironmental dynamics may lead to the development of more effective combination therapies capable of overcoming endocrine resistance.

Future Research Directions

Although substantial progress has been made in understanding fibroblast-mediated therapeutic resistance, several key questions remain unresolved and represent important avenues for future research.

First, greater efforts are needed to characterize the heterogeneity of cancer-associated fibroblasts. Recent studies suggest that CAFs consist of multiple functional subtypes with distinct roles in tumor progression, immune modulation, and therapy resistance. Advanced techniques such as single-cell RNA sequencing and spatial transcriptomics may help identify specific fibroblast populations that are most relevant for therapeutic targeting.

Second, future studies should focus on identifying reliable biomarkers for CAF activity. Such biomarkers would enable clinicians to stratify patients based on stromal characteristics and tailor treatment strategies accordingly. Molecular markers related to fibroblast activation, ECM composition, and stromal signaling pathways could potentially serve as predictive indicators of endocrine therapy response.

Third, further research is required to evaluate the clinical effectiveness of CAF-targeted therapies in combination with existing anticancer treatments. Well-designed clinical trials are necessary to determine whether targeting fibroblast activity can significantly improve patient outcomes in ER-positive breast cancer.

Fourth, advances in systems biology and computational modeling may provide new insights into the complex signaling networks operating within the tumor microenvironment.

Integrating multi-omics data—including genomic, transcriptomic, proteomic, and metabolomic datasets—could help identify critical regulatory nodes that control tumor–stromal interactions.

Finally, continued development of microenvironment-inclusive experimental models, such as organoid cultures and patient-derived tumor explants, will be essential for improving translational research. These models offer a more realistic representation of tumor biology and may enhance the predictive accuracy of preclinical drug testing. In summary, future research should aim to integrate molecular biology, clinical investigation, and advanced experimental technologies to develop comprehensive therapeutic strategies capable of overcoming endocrine resistance in ER-positive breast cancer.

Limitations

Despite offering an integrative synthesis of contemporary evidence, this review is subject to several methodological and conceptual limitations that warrant consideration. First, the study relies exclusively on secondary data derived from published literature. Although systematic thematic synthesis enables comprehensive interpretation, the absence of primary experimental validation limits the ability to directly confirm causality or quantify the magnitude of fibroblast-mediated resistance mechanisms. The conclusions are therefore interpretative rather than empirically tested within a controlled experimental framework. Second, substantial heterogeneity exists across the included studies in terms of fibroblast origin (primary patient-derived CAFs versus immortalized cell lines), experimental platforms (2D monocultures, 3D spheroids, organoids, and in vivo xenografts), and analytical endpoints. Variations in culture conditions, molecular markers, and signaling readouts complicate direct cross-study comparability and may influence the reproducibility of reported mechanisms. This methodological diversity, while reflecting biological complexity, introduces interpretative variability. Third, the absence of universally standardized biomarkers for defining and subclassifying cancer-associated fibroblast (CAF) populations remains a significant challenge. CAFs are increasingly recognized as a heterogeneous and functionally diverse stromal population. Without consensus markers to distinguish pro-tumorigenic, immunomodulatory, or potentially tumor-restraining subtypes, mechanistic interpretations risk oversimplification. This heterogeneity may also partly explain inconsistent translational outcomes observed in stromal-targeted therapeutic trials. Fourth, although robust preclinical evidence supports the mechanistic involvement of fibroblasts in

endocrine resistance, clinical translation remains comparatively limited. Few clinical trials have successfully integrated CAF-targeted strategies with endocrine therapy in a standardized manner. Consequently, the clinical applicability of several proposed mechanisms remains to be validated through patient-derived models, longitudinal studies, and biomarker-driven stratification approaches. Finally, the qualitative design of this review emphasizes thematic integration rather than quantitative meta-analysis. While this approach is well-suited for mechanistic exploration, it does not provide pooled effect sizes or statistical measures of association. Future studies incorporating systematic meta-analytic techniques may further refine the strength of evidence linking fibroblast activity to therapeutic resistance.

CONCLUSION

This qualitative secondary analysis reinforces the central role of fibroblast–cancer cell interactions in the development and maintenance of endocrine resistance in estrogen receptor–positive breast cancer. The evidence consistently demonstrates that cancer-associated fibroblasts function not merely as passive structural components but as dynamic regulators of tumor adaptability. Through coordinated mechanisms—including paracrine survival signaling, extracellular matrix remodeling, metabolic coupling, immune modulation, and activation of estrogen-independent growth pathways—CAFs create a protective stromal niche that sustains malignant persistence under therapeutic pressure. Importantly, resistance emerges as a systems-level phenomenon rather than a consequence of isolated tumor-cell mutations. The reciprocal signaling between stromal and epithelial compartments generates adaptive plasticity, enabling cancer cells to bypass endocrine inhibition and sustain long-term survival. This paradigm shift—from a tumor-centric to a microenvironment-integrated model of resistance—has profound implications for therapeutic development.

Future pharmaceutical strategies must therefore move beyond monotherapeutic endocrine targeting and adopt combinatorial approaches that simultaneously disrupt malignant signaling and stromal support systems. The integration of CAF-modulating agents, immune-targeted therapies, and metabolically directed interventions with conventional endocrine treatments may offer more durable clinical outcomes. Furthermore, incorporation of heterogeneous co-culture platforms, patient-derived organoids, and tumor microenvironment–inclusive screening systems into preclinical pipelines will enhance translational predictability. In conclusion, a comprehensive therapeutic framework that addresses both cancer cells and their supportive stromal ecosystem holds substantial promise for overcoming endocrine resistance.

Advancing this systems-based approach represents a critical step toward improving treatment durability, minimizing relapse, and achieving sustained clinical benefit for patients with ER-positive breast cancer.

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