

TUMOR PLASTICITY AND PHENOTYPIC SWITCHING AS DRIVERS OF THERAPEUTIC RESISTANCE IN BREAST CANCER

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ABSTRACT

Breast cancer remains one of the most extensively treated yet persistently recurrent malignancies in oncology, and much of that persistence traces back to a single unresolved problem: tumors that respond to therapy often find a way back. For decades the dominant explanation was genetic, resistance following classic Darwinian logic as mutations accumulate and the fittest clone survives. That is true, but it is not the whole story. Breast cancer cells can also survive treatment by changing what they are, temporarily, without changing their genetic material. They can adopt mesenchymal features, slip into stem-like states, enter a dormant drug-tolerant condition, lean on a supportive tissue environment, or rewire how they generate energy. This review brings together evidence on these five reversible mechanisms in breast cancer, arguing that they represent facets of one underlying phenomenon, a flexible tumor cell state that treatment pushes cells across, and sometimes back over. Therapies aimed only at a genetic target may be treating the wrong problem, and future strategies may need to address timing and cell state, not just molecular targets.

KEYWORDS: breast cancer, phenotypic plasticity, epithelial-mesenchymal transition, cancer stem cells, drug-tolerant persister cells, tumor microenvironment, metabolic reprogramming, therapeutic resistance.

BACKGROUND

Breast cancer treatment decisions still largely follow the molecular subtype a tumor is assigned at diagnosis: hormone receptor-positive disease treated with endocrine therapy, human epidermal growth factor receptor 2 (HER2)-amplified disease treated with HER2-directed agents, and triple-negative disease treated with cytotoxic chemotherapy and, increasingly, immunotherapy. Each of these approaches has genuinely extended survival. Yet across all three categories, the same pattern recurs: an encouraging early response gives way, months or years later, to relapse. In the metastatic setting this is close to universal for hormone receptor-positive disease treated with sequential endocrine therapies.^[1]

The traditional explanation for this pattern rests on clonal selection. A tumor is genetically heterogeneous from the outset; treatment kills off the sensitive majority and leaves behind rare pre-existing or newly acquired resistant subclones, which then repopulate the tumor. This model has strong support in breast cancer. Mutations in the ligand-binding domain of the estrogen receptor gene *ESR1* arise under the selective pressure of aromatase inhibition and confer ligand-independent receptor activity that blunts the effect of most endocrine agents.^[2,3,4,5] These mutations are essentially absent in treatment-naïve tumors and become common only after prolonged endocrine exposure.^[1,6] Mutations in *PIK3CA*, present in a substantial fraction of hormone receptor-positive advanced disease, contribute similarly to endocrine resistance.^[7]

This genetic account leaves real gaps. *ESR1* mutations explain resistance in only a subset of relapsing patients, and many tumors regain sensitivity to therapy after a drug holiday, behavior difficult to reconcile with a permanent, heritable genetic lesion.^[8] Lineage-tracing experiments in estrogen receptor (ER)-positive breast cancer models have shown that a portion of endocrine-tolerant cells emerge stochastically, without any genetic marker predicting in advance which cells would survive.^[9] Single-cell profiling of primary and metastatic breast tumors repeatedly finds transcriptional and epigenetic diversity among cells that share essentially the same genome.^[10,11]

This review examines an alternative and complementary explanation: phenotypic plasticity, the reversible capacity of a cancer cell to shift between functional states in response to a changing environment. A search of the recent literature was conducted around five recurring, interlinked expressions of plasticity in breast cancer therapy resistance: epithelial-mesenchymal transition (EMT), cancer stem cell (CSC) interconversion, drug-tolerant persister (DTP) states, tumor microenvironment (TME) signaling, and metabolic adaptation. The aim is to evaluate whether these mechanisms form a coherent, non-genetic axis of resistance distinct from clonal selection, and to consider what that distinction means for how resistance might eventually be targeted.

Conceptual framework: plasticity versus mutation

Reversibility is what separates a plasticity-based mechanism from a mutation-based one. A resistant clone carrying an *ESR1* mutation remains resistant once treatment is withdrawn, because the mutation is fixed in its genome. A cell in a drug-tolerant persister state will often regain sensitivity once the drug is removed, because nothing in its DNA has changed.^[8,12] This distinction has practical weight: if resistance is reversible in principle for some fraction of cells, the window for intervening before that resistance becomes permanent is a genuine and actionable therapeutic target.

A useful way to picture this borrows Waddington's landscape metaphor from developmental biology, in which a cell's identity is a ball resting in one of several valleys separated by ridges. Genetic and epigenetic instability in cancer flattens some of those ridges, making transitions between valleys, epithelial to mesenchymal, differentiated to stem-like, proliferative to dormant, easier to cross than in a healthy cell.^[13,14] Treatment itself often supplies the force that pushes cells over a ridge, since chemotherapy, endocrine deprivation, and targeted kinase inhibition all act as both selective and inductive pressures.^[15,16]

What physically flattens these ridges is epigenetic remodeling, changes in DNA methylation, histone modification, and chromatin accessibility, combined with post-transcriptional regulation, stochastic gene

expression, and signals arriving from outside the cell.^[16,17] Single-cell chromatin profiling of breast cancer patient-derived xenografts has shown that tumor cells with near-identical genomes can carry substantially different chromatin states, and that this epigenetic diversity, not genetic diversity, tracks with functional heterogeneity in the tumor.^[11]

Epithelial-mesenchymal transition

EMT is a normal developmental program that breast cancer cells repurpose. Cells undergoing EMT lose polarity and cell-cell adhesion, downregulate E-cadherin, and adopt a migratory, mesenchymal appearance, driven by transcription factors including Snail, Slug, Zeb1, and Twist that repress epithelial genes and activate mesenchymal ones.^[18,19,20] These factors are not redundant: Snail typically appears first, while Zeb1 and Twist sustain the migratory phenotype over time.^[19]

EMT confers resistance beyond its role in invasion. Mesenchymal-shifted cells proliferate more slowly, which blunts therapies targeting rapidly dividing cells, and often show altered drug transporter and anti-apoptotic protein expression.^[20] A meta-analysis pooling data from over three thousand metastatic breast cancer patients found high EMT transcription factor expression consistently associated with worse prognosis, with Slug showing the strongest effect.^[18] Snail-driven repression of p53 expands tumor-initiating populations in breast cancer models, and even transient Snail expression grants lasting metastatic competence.^[21]

Circulating tumor cells from metastatic breast cancer patients frequently co-express epithelial, mesenchymal, and stem markers simultaneously, consistent with a spectrum of hybrid states rather than a one-way switch.^[22] It is increasingly this partial, hybrid phenotype, rather than a fully mesenchymal one, that correlates most closely with resistance and metastatic capacity^[17], and cell populations retaining the ability to move between epithelial and mesenchymal states show greater resistance than those locked into either state.^[23] Findings vary across model systems, and whether EMT causes resistance or simply correlates with some other resistance-conferring change remains unresolved in places^[11,14], but the overall evidence for a causal, reversible contribution is substantial.

Cancer stem cells and interconversion

The CSC model holds that a subpopulation defined by markers such as CD44^{high}/CD24^{low/-} or high activity of the enzyme aldehyde dehydrogenase (ALDH1) disproportionately drives tumor initiation, metastasis, and resistance.^[24,25] CD44⁺/CD24⁻ breast cancer cells are more tumorigenic in xenograft models than their CD44⁺/CD24⁺ counterparts, and ALDH1 positivity independently marks enhanced self-renewal and detoxification capacity.^[25,26]

Two observations complicate a strictly hierarchical reading of this model. The CD44/CD24 marker set and ALDH1 activity frequently identify largely non-overlapping cell populations within the same tumor^[24,27,28], and stemness itself appears to be a state that non-stem cells can enter and exit under treatment pressure rather than a fixed, heritable identity. Cells forced through partial EMT acquire CD44^{high}/CD24^{low}, ALDH^{high} characteristics, linking stemness acquisition to the same transcription factor networks that drive EMT.^[29] This interconversion model has largely replaced the older view of fixed stem and non-stem compartments.^[30]

The functional consequences are considerable. CSC-enriched populations show enhanced DNA repair, altered handling of reactive oxygen species (ROS), upregulated ATP-binding cassette (ABC) drug efflux transporters, and quiescence that protects them from cytotoxic agents.^[26] Higher baseline CD44⁺/CD24⁻ and ALDH1 expression predicts poorer trastuzumab response in HER2-positive disease.^[31] In oral squamous cell carcinoma, a useful cross-tumor illustration if not a breast-specific data point, stem-like cells retaining active plasticity, the capacity to move between epithelial and post-EMT states, were markedly more resistant than cells locked into either state, and this plastic subpopulation could be selectively targeted through endoplasmic reticulum stress and autophagy inhibition.^[23] This helps explain why CSC-directed therapy has underdelivered clinically: eliminating today's marker-defined stem cells does not prevent tomorrow's non-stem cells from repopulating that compartment under selective pressure.

Drug-tolerant persister states

Where EMT and CSC biology describe what cells become, DTP biology describes how a subpopulation survives long enough to become anything at all. Persister cells, first characterized clearly in EGFR-mutant lung cancer and since documented in breast cancer, survive acute drug exposure by entering a slow-cycling or quiescent state without acquiring classical resistance mutations.^[12,32] Unlike a resistant clone, persisters generally regain full drug sensitivity once the drug is withdrawn for long enough.^[8,33]

The persister state involves coordinated epigenetic remodeling, transcriptional reprogramming, and metabolic adaptation.^[8,12] Whether persisters arise through selection of pre-existing tolerant cells or through drug-induced reprogramming of otherwise identical cells remains debated, though lineage tracing in ER-positive breast cancer models undergoing endocrine deprivation supports a largely stochastic, induction-leaning picture.^[9,33,34]

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, now standard in hormone receptor-positive advanced breast cancer, arrest cells in G1 phase; depending on dose and context this arrest resolves as either reversible

quiescence or stable senescence, regulated partly through mechanistic target of rapamycin (mTOR) signalling.^[35,36,37] Cells held in quiescence retain the capacity to re-enter the cell cycle once therapy is interrupted, which underlies current maintenance dosing strategies.^[12,36] Growth factor receptor signaling separately supports persister-like tolerance in metastatic breast cancer, offering another point of intervention.^[30]

Perhaps most consequentially, persister cells appear to function as a reservoir from which permanent resistance later emerges. Erlotinib-resistant lung cancer colonies traced back to a single persister origin acquired a strikingly diverse range of resistance mechanisms, suggesting the persister bottleneck broadens rather than constrains the eventual paths to resistance.^[32] If this generalizes to breast cancer, as early evidence suggests,^[34] the persister window becomes a genuinely time-limited target: eliminate or hold cells here, and the genetic diversification that produces stable resistance may never occur.

Tumor microenvironment-mediated plasticity

None of these transitions occur in isolation. Breast tumor cells sit within a dense microenvironment of cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), immune cells, vasculature, and extracellular matrix, and this environment actively drives plasticity rather than merely surrounding it.^[16,38] Single-cell sequencing shows both CAFs and TAMs are more heterogeneous than older marker-based classifications suggested, with distinct subtypes occupying different spatial niches.^[16,39]

CAFs influence plasticity through paracrine signaling and exosomal cargo. A CD63⁺ CAF subpopulation in tamoxifen-resistant breast tumors secretes exosomal microRNA-22, which downregulates estrogen receptor- α and the tumor suppressor PTEN in neighboring tumor cells, driving endocrine resistance directly.^[40] TAMs contribute differently: tamoxifen-resistant cells upregulate the glucose transporter SGLT1, become more glycolytic, and secrete lactate that polarizes nearby macrophages toward an immunosuppressive M2 state; those macrophages then signal back through EGFR/PI3K/Akt signaling, reinforcing the resistance phenotype that recruited them.^[41] This bidirectional signaling, tumor cells reshaping their environment and being reshaped in turn, recurs throughout the microenvironment literature and helps explain the durability of established resistance.^[39,42]

Hypoxia is a particularly potent non-cellular driver of plasticity. Hypoxia-inducible factors (HIF), principally HIF-1 α and HIF-2 α , directly upregulate Snail, Twist, and Zeb1 while promoting stemness through Wnt and Notch signalling.^[43,44] In HER2-positive breast cancer, hypoxic HIF-1 α stabilization sustains extracellular signal-regulated kinase (ERK) signaling downstream of HER2 even during lapatinib treatment, bypassing the drug's

mechanism entirely until HIF-1 α or ERK signaling is separately blocked.^[45] HIF-1 α overexpression more broadly correlates with resistance across drug classes, earlier relapse, and worse prognosis through effects spanning metabolism, apoptosis resistance, and immune evasion.^[46,47]

EMT also upregulates the immune checkpoint ligand PD-L1 through phosphoinositide 3-kinase and protein kinase B (PI3K/AKT) and ERK signaling, adding immune protection to mesenchymal-shifted cells^[29,48], and signal transducer and activator of transcription 3 (STAT3) signaling, frequently hyperactivated in triple-negative disease, simultaneously promotes EMT and expression of PD-L1 and interleukin-10.^[49] Immune checkpoint inhibitors accordingly underperform in tumors with a strong EMT signature, and resistance to blockade of programmed cell death protein 1 (PD-1) and PD-L1 in triple-negative disease has been linked to reduced antigen presentation, checkpoint co-expression, and CAF-mediated immune exclusion.^[49,50]

Metabolic adaptation

Plasticity also operates at the level of energy metabolism. The Warburg effect, the tendency of cancer cells to favor glycolysis even with adequate oxygen, is increasingly understood as a setting tumor cells can adjust under selective pressure rather than a fixed signature, shifting toward oxidative phosphorylation (OXPHOS) when advantageous.^[51,52]

The clearest breast cancer evidence comes from endocrine therapy persisters. ER-positive cells surviving estrogen deprivation become newly and heavily dependent on mitochondrial OXPHOS to meet their energy needs, a dependency absent in the drug-sensitive parental population.^[9,53] In a phase II clinical trial, residual proliferative tumor cells remaining after neoadjuvant letrozole showed increased mitochondrial content compared to fully suppressed tumors, and pharmacologic inhibition of mitochondrial complex I selectively suppressed persister regrowth in patient-derived xenografts, synergizing with fulvestrant.^[9] Metastatic ER-positive cancers resistant to both endocrine therapy and palbociclib show elevated OXPHOS dependency, with *PIK3CA/AKT1* mutation status predicting sensitivity to OXPHOS-directed treatment, a direct convergence of the genetic and metabolic-plasticity models of resistance.^[54]

Cross-tumor evidence clarifies the underlying mechanism. In lung adenocarcinoma persisters, the glycolysis-to-OXPHOS switch depends on PINK1-mediated mitophagy, a process that clears damaged mitochondria to sustain oxidative metabolism; blocking mitophagy eliminates the persister population.^[55] Persister cells across cancer types also depend on redox-buffering systems, aldehyde dehydrogenase activity and glutathione peroxidase 4, to manage the reactive oxygen species generated by heavy oxidative metabolism, and

inhibiting these systems can push persisters toward oxidative or iron-dependent cell death.^[56]

Metabolic reprogramming feeds back into the epigenetic machinery governing plasticity generally, since histone-modifying enzymes depend directly on metabolite availability, meaning shifts in central metabolism reshape chromatin and alter how easily cells move between EMT, stem-like, and persister states.^[13,16]

Convergence of plasticity mechanisms

Read separately, these five bodies of literature can look like loosely related fields that happen to share vocabulary. Read together, a more coherent picture emerges. The same signaling pathways, transforming growth factor beta (TGF-beta)/SMAD, Wnt/beta-catenin, Notch, and hypoxia-responsive HIF signaling, recur as upstream drivers of EMT, stemness, and microenvironment-mediated resistance.^[16,43,44] The same transcription factors, particularly Snail, Zeb1, and Twist, sit at the intersection of EMT and stemness^[21,29], and the same epigenetic regulators, chromatin remodelers and histone-modifying enzymes, execute all of these transitions, with metabolic state feeding directly into that machinery.^[11,13,17]

A provisional temporal model follows from this convergence. Acute therapeutic stress first triggers a persister or dormant state, often with partial EMT and a metabolic shift toward OXPHOS. That state is stabilized by supportive signals from CAFs, TAMs, and hypoxic niches. Only after this plasticity-supported survival window has bought sufficient time does a subset of surviving cells acquire the stable genetic alterations, an *ESR1* mutation, for instance, that lock in permanent resistance.^[8,9,32,34] Plasticity and mutation are, on this model, sequential phases of one process rather than competing explanations, with plasticity providing the bridge that lets a tumor survive long enough for genetic resistance to catch up.

This model is not yet proven end to end in breast cancer. Much mechanistic detail comes from cell lines and patient-derived xenografts, which capture cell-intrinsic biology well but reproduce microenvironmental complexity imperfectly.^[14] Single-cell and spatial transcriptomic technologies reveal cell-state heterogeneity directly but largely provide static snapshots of transient states^[10,57,58], and genuinely longitudinal human data, serial biopsies or circulating tumor cell monitoring tracking a single patient through relapse, remain comparatively rare despite being what the model most needs for validation.^[22]

Therapeutic implications

If plasticity functions as a reversible bridge to permanent resistance, timing matters as much as target selection. Epigenetic inhibitors targeting histone deacetylases, bromodomain and extraterminal domain (BET) proteins, or histone demethylases aim to prevent cells from

completing the chromatin remodeling that persisters or EMT transitions require, and BET inhibition has shown promise in blocking clonal outgrowth of *ESR1*-mutant cells before that population becomes established.^[2]

A second approach exploits vulnerabilities created by plastic states rather than preventing them. Mitochondrial complex I inhibition selectively targets OXPHOS-dependent endocrine persisters while sparing other cells and shows synergy with standard endocrine agents preclinically^[9,53,54], and post-EMT, plasticity-retaining stem-like cells show selective sensitivity to endoplasmic reticulum stress and autophagy inhibition once enriched.^[23]

A third, more clinically mature approach involves scheduling. CDK4/6 inhibitor maintenance regimens already implicitly rest on persister biology, holding cells in a reversible quiescent state rather than attempting outright elimination^[36,37], and whether more deliberately adaptive dosing could further prevent persister populations from stabilizing into permanent resistance remains an open question. Newer modalities, including proteolysis-targeting chimeras (PROTACs) and antibody-drug conjugates (ADCs), are being explored to reach previously undruggable resistance-associated targets in triple-negative disease, offering a route around some plasticity-driven escape mechanisms.^[59]

A recurring obstacle across all these strategies is the absence of validated biomarkers able to identify a plastic, persister, or hybrid-EMT population in a patient in real time rather than retrospectively.^[8] Developing such biomarkers, alongside the longitudinal sampling needed to validate them, may be the most consequential gap between current mechanistic insight and changed clinical practice.

CONCLUSIONS

Breast cancer resistance has too often been framed as binary: a tumor is either sensitive, or it has acquired a resistance mutation and become resistant. The evidence reviewed here supports a messier but more actionable picture, in which resistance frequently unfolds as a dynamic continuum, cells moving reversibly through mesenchymal, stem-like, dormant, and metabolically rewired states before some eventually acquire a permanent genetic change. EMT, CSC interconversion, DTP biology, TME signaling, and metabolic adaptation are not five independent mechanisms so much as five visible expressions of one underlying property, a tumor cell population's capacity to change what it is under pressure. For the field, this reframing matters because it identifies a genuinely reversible, time-limited window in the course of resistance, one that existing drugs and scheduling strategies are only beginning to be designed around. Recognizing plasticity as a target in its own right, alongside genetic drivers, may be one of the more promising directions available for improving durability of response in breast cancer treatment.

List of abbreviations

ABC: ATP-binding cassette
 ADC: antibody-drug conjugate
 ALDH1: aldehyde dehydrogenase 1
 BET: bromodomain and extraterminal domain
 CAF: cancer-associated fibroblast
 CDK4/6: cyclin-dependent kinase 4 and 6
 CSC: cancer stem cell
 DTP: drug-tolerant persister
 EGFR: epidermal growth factor receptor
 EMT: epithelial-mesenchymal transition
 ER: estrogen receptor
 ERK: extracellular signal-regulated kinase
 HER2: human epidermal growth factor receptor 2
 HIF: hypoxia-inducible factor
 IL-10: interleukin-10
 mTOR: mechanistic target of rapamycin
 OXPHOS: oxidative phosphorylation
 PD-1: programmed cell death protein 1
 PD-L1: programmed death-ligand 1
 PI3K/AKT: phosphoinositide 3-kinase / protein kinase B
 PROTAC: proteolysis-targeting chimera
 PTEN: phosphatase and tensin homolog
 ROS: reactive oxygen species
 SGLT1: sodium-glucose cotransporter 1
 STAT3: signal transducer and activator of transcription 3
 TAM: tumor-associated macrophage
 TGF-beta: transforming growth factor beta
 TME: tumor microenvironment

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