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From Bench to Community: Translating Breast Cancer Stem Cell Biology into Practical Oncology

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Abstract

Breast cancer stem cells (BCSCs) are a resilient subpopulation driving recurrence, metastasis, and therapy resistance. Recent research has revealed three mechanistic pillars of BCSC survival: lysine succinylation, which enables metabolic flexibility; nuclear filamentous actin, which provides structural protection and genomic stability; and ribosome biogenesis, which sustains translational capacity and protein synthesis under stress. Together, these processes form an interconnected network that allows BCSCs to withstand oxidative, metabolic, and genotoxic challenges that defeat conventional therapies. However, the translation of such insights from laboratory discoveries to real-world oncology practice remains limited, especially in community settings where most patients receive care. This Perspective highlights how understanding these mechanistic pillars can inform biomarker-guided strategies, therapeutic repurposing, and policy-driven initiatives that integrate BCSC-targeted approaches into community oncology. By bridging laboratory discovery and clinical application, these efforts may enable more durable disease control, improved survival, and reduced recurrence across diverse breast cancer patient subpopulations.

Keywords: Breast Cancer Stem Cells; Lysine Succinylation; Nuclear Filamentous Actin; Ribosome Biogenesis; Drug Repurposing

Introduction

Breast cancer remains the most common malignancy among women and a leading cause of cancer-related mortality worldwide [1]. Despite major advances in early detection, surgery, and targeted therapies, recurrence and resistance such as the relapse of estrogen receptor positive (ER+) breast cancers after initial response to endocrine therapy continue to undermine long-term survival [2]; mechanistically, this acquired resistance involves ESR1 mutations, ligand-independent signaling, activation of alternate pathways like HER2 and PI3K/AKT/mTOR, and epigenetic reprogramming that enables residual tumor cells to evade treatment pressure [3]. At the core of this persistence lies a distinct subpopulation, i.e., breast cancer stem cells (BCSCs), which possess defining stemness features (self-renewal, differentiation potential, dormancy) to regenerate tumors post-therapy [4]. Their adaptability is further reinforced by a supportive tumor microenvironment (TME) comprising immune and stromal components that provide trophic and protective signals [5]. Moreover, enrichment of BCSCs is often observed following chemotherapy or endocrine therapy—consistent with their role as the "seed" of relapse. Extensive research has delineated key signaling pathways, Notch, Wnt/β-catenin, Hedgehog, STAT3, and Hippo-YAP, that sustain stemness and epithelial–mesenchymal transition (EMT) in BCSCs [6]. These cascades converge on transcription factors such as SOX2, OCT4, and NANOG, preserving pluripotency and drug resistance. Beyond signaling, metabolic rewiring allows BCSCs to flexibly switch between glycolysis and oxidative phosphorylation (OXPHOS), depending on environmental and therapeutic conditions [7]. Epigenetic mechanisms, DNA methylation, histone modifications, and noncoding RNAs, provide an additional regulatory layer that fine-tunes stemness and survival [8]. Recent discoveries expand this framework by introducing three mechanistic pillars crucial to BCSC persistence: (1) Lysine succinylation, a reversible post-translational modification that integrates metabolic and epigenetic control; (2) Nuclear filamentous actin (F-actin), a structural scaffold protecting nuclear integrity and coordinating DNA repair; and (3) Ribosome biogenesis, which sustains the translational machinery required for rapid adaptation and growth. Together, these processes shape a triad of metabolic, structural, and translational resilience. Yet, despite these mechanistic insights, their translation into community oncology practice remains slow [9]. Most breast cancer patients are treated outside tertiary academic centers, underscoring the need to integrate molecular discoveries into accessible, equitable care frameworks. This Perspective explores how targeting lysine succinylation, nuclear F-actin, and ribosome biogenesis can reshape breast cancer management across research and community domains.

Lysine Succinylation as a Metabolic Nexus in BCSCs

Metabolic adaptability defines the survival advantage of BCSCs. Unlike bulk tumor cells that rely primarily on glycolysis, BCSCs dynamically shift between glycolysis and OXPHOS to sustain energy production under fluctuating oxygen or nutrient conditions [10]. This metabolic plasticity is central to stemness, therapy resistance, and metastatic competence. Lysine succinylation, a reversible acylation of mitochondrial and cytoplasmic proteins, regulates key enzymes within the tricarboxylic acid (TCA) cycle and fatty acid oxidation [11]. By altering enzymatic charge and structure, succinylation reprograms metabolic flux, influencing mitochondrial fission and reactive oxygen species (ROS) homeostasis. Succinylation of mitochondrial fission factor (MFF), for instance, promotes mitochondrial fragmentation, a hallmark of stem-like adaptability [12]. SIRT5, the major mitochondrial desuccinylase, fine-tunes this process. Overexpression of SIRT5 maintains metabolic balance, while its inhibition increases oxidative stress and reduces tumorigenicity [13]. Pharmacologic or genetic inhibition of SIRT5 destabilizes BCSC metabolism and enhances chemosensitivity, making it a promising therapeutic target. Targeting the succinylation pathway extends beyond SIRT5. Limiting succinyltransferase activity or restricting succinyl-CoA availability can further reduce BCSC fitness. In ovarian cancer stem cells, CPT1A inhibition disrupts succinyltransferase function, impairs mitochondrial fission, and diminishes stemness [12]. Additionally, blocking secretion of migration inhibitory factor (MIF), a succinylation-related cytokine, can remodel the TME from an immunosuppressive to an antitumor state [7]. Together, these findings identify lysine succinylation as a metabolic–epigenetic checkpoint linking mitochondrial function, redox control, and transcriptional

regulation. Because metabolic pathways are highly druggable, targeting succinylation may represent a feasible strategy for repurposing FDA-approved agents or developing novel therapeutics.

Nuclear Filamentous Actin: The Structural Shield of BCSCs

Triple-negative breast cancer (TNBC) represents one of the most aggressive subtypes, characterized by early relapse and limited targeted therapy options. BCSCs are disproportionately abundant in TNBC, where nuclear filamentous actin (F-actin) has emerged as an unexpected yet critical survival determinant. Within the nucleus, F-actin filaments serve as stress-responsive structures that regulate DNA repair, replication, and transcription. They recruit repair proteins to sites of DNA damage [14], stabilize replication forks under genotoxic stress [15], and maintain chromatin architecture to sustain transcriptional programs promoting EMT and stemness [16]. These functions collectively create a nuclear "stress shield", protecting BCSCs from cytotoxic damage. From a therapeutic standpoint, targeting nuclear actin dynamics offers an innovative vulnerability. Potential strategies include inhibition of actin-bundling proteins such as α-actinin 4 [17], interference with filament-severing proteins like INF2 [18], or disruption of upstream stress pathways (e.g., ATR–mTOR-C1–WASP/ARP2/3) that drive nuclear actin assembly [15]. Emerging translational evidence links lovastatin, a widely used cholesterol-lowering drug, to disruption of nuclear F-actin networks. Lovastatin induces nuclear translocation and polymerization of F-actin in TNBC stem cells, leading to nucleolar stress, suppression of rRNA synthesis, and downregulation of stemness-associated genes [19]. Given its safety profile and affordability, lovastatin exemplifies how drug repurposing could translate mechanistic insights into practical community oncology applications. By destabilizing nuclear actin organization, these approaches may sensitize BCSCs to genotoxic agents, reduce relapse risk, and extend treatment efficacy, particularly in underserved clinical environments.

Ribosome Biogenesis: Translational Powerhouse of BCSCs

High rates of protein synthesis are essential for BCSC proliferation, adaptation, and resistance. Compared with non-stem tumor cells, BCSCs display hyperactive ribosome biogenesis, especially within TNBC [20, 21]. Enhanced nucleolar activity facilitates rRNA synthesis and ribosomal assembly, supporting rapid proteome remodeling in response to stress. Key regulators, such as mitochondrial ribosomal protein S27 (MRPS27) and nucleolar phosphoprotein NOLC1, coordinate mitochondrial translation and rRNA transcription, linking energy metabolism to protein synthesis [21]. This coupling allows BCSCs to maintain a high biosynthetic rate even under metabolic constraint. Therapeutically, the nucleolus presents an emerging "stress amplifier" target. Inhibitors that disrupt rRNA transcription (e.g., RNA polymerase I blockers) or ribosomal protein interactions can trigger nucleolar stress and apoptosis preferentially in cancer stem cells. Moreover, ribosome biogenesis inhibitors synergize with DNA-damaging agents by overwhelming the proteostatic capacity of BCSCs. In line with its role in disrupting nuclear F-actin, lovastatin targets the ribosome biogenesis pathway in TNBC, offering a metabolic vulnerability suitable for drug repurposing. Because ribosomal hyperactivation is metabolically expensive, normal cells are comparatively spared, widening the therapeutic window.

Translating Mechanistic Insights into Community Oncology

Integrating Mechanistic Pillars

The triad of lysine succinylation, nuclear F-actin, and ribosome biogenesis reflects the metabolic, structural, and translational dimensions of BCSC resilience. Targeting these axes simultaneously could overcome compensatory feedback mechanisms that undermine monotherapies. Combining metabolic inhibitors with drugs inducing nucleolar or structural stress may offer synergistic efficacy.

Community-Centered Implementation

Translating such mechanistic advances into community oncology requires pragmatic steps: (1) Biomarker-guided risk stratification using minimally invasive assays to identify patients with high BCSC burden; (2) Incorporation of drug repurposing, such as statins or mitochondrial modulators, into

adjuvant therapy trials; (3) Expansion of community trial networks to improve access to BCSC-targeted interventions; and (4) Tele-oncology integration, linking molecular testing hubs with local clinics for real-time decision support. Educational initiatives for oncologists, nurses, and primary care providers can foster awareness of BCSC biology, enabling more personalized surveillance and treatment adaptation.

Policy and Collaborative Frameworks

Policy reform and intersectoral collaboration will be critical. Reimbursement models for molecular diagnostics, regulatory support for repurposed drugs, and public funding for translational community trials can accelerate clinical adoption. Collaboration between academic researchers and community oncologists will ensure that new discoveries reach patients promptly and equitably.

Concluding Remarks

BCSCs lie at the heart of therapeutic resistance and recurrence in breast cancer. Sustained by lysine succinylation, nuclear F-actin, and ribosome biogenesis, they form a triad of metabolic, structural, and translational defenses that conventional therapies rarely eliminate. By integrating these mechanistic insights into community oncology, we can bridge the gap between discovery and delivery. Accessible diagnostics, repurposed therapeutics, and supportive policy frameworks are essential to bring BCSC-targeted strategies from the bench to the bedside, and from the laboratory to the community. This integrative approach offers a roadmap for achieving durable remission, reducing disparities, and transforming the management of breast cancer worldwide.

Graphical Abstract

Graphical Abstract

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