ACTB in Breast Cancer: Molecular Mechanisms, Oncogenic Pathways, and Therapeutic Potential

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Abstract

Breast cancer remains a leading cause of cancer-related mortality worldwide, with an estimated 316,950 new invasive cases and 42,170 deaths projected in the United States alone for 2025. Globally, it accounted for approximately 670,000 deaths in 2022, underscoring the urgent need for novel therapeutic targets that address metastatic progression. Among these, β-actin (encoded by ACTB), a core component of the actin cytoskeleton, has emerged as a pivotal regulator of cytoskeletal dynamics, epithelial-mesenchymal transition (EMT), and metastasis in breast cancer. This review synthesises recent evidence on ACTB's functional roles, demonstrating how its dysregulation promotes invasive phenotypes through actin polymerisation and remodelling, enabling cancer cell migration, extravasation, and colonisation of distant sites. We delineate ACTB's interaction networks, including crosstalk with Rho/ROCK for stress fibre formation, PI3K/Akt for survival and motility enhancement, and MAPK for proliferative signalling, which collectively amplify oncogenic pathways. Leveraging bioinformatics and network pharmacology, we integrate multi-omics data from databases such as STRING for protein-protein interactions, KEGG for pathway enrichment, and Cytoscape for modular network analysis, revealing ACTB-centred hubs co-expressed with EMT markers (e.g., vimentin, MMPs) and prognostic signatures in triple-negative breast cancer (TNBC). ACTB overexpression correlates with poor prognosis across subtypes, particularly in aggressive TNBC, positioning it as a biomarker and druggable target. This mechanistic framework highlights opportunities for isoform-specific inhibitors and combination therapies targeting upstream regulators like ROCK, offering a foundation for precision oncology in metastatic breast cancer.

Keywords: β-actin (ACTB), Breast cancer, Rho/ROCK pathway, PI3K/Akt signalling, MAPK pathway

Introduction:

Breast cancer continues to impose a substantial global health burden, ranking as the most frequently diagnosed malignancy among women and the second leading cause of cancer-related deaths. In 2025, the American Cancer Society projects approximately 316,950 new cases of invasive breast cancer and 59,080 cases of ductal carcinoma in situ (DCIS) in the United States, alongside 42,170 fatalities—predominantly among women, though men account for about 510 deaths annually.[1]Globally, incidence rates have risen steadily, with annual increases of 1–5% observed in over half of high-income countries, driven by aging populations, lifestyle factors, and enhanced screening. Despite advances in early detection and targeted therapies, metastatic disease accounts for up to 90% of breast cancer mortalities, with 5-year survival rates plummeting to less than 30% for stage IV patients. These stark disparities highlight the limitations of current interventions, which often fail to curb dissemination to distant organs such as the lungs, liver, and brain.[2]

The heterogeneity of breast cancer manifests across molecular subtypes—luminal A/B (hormone receptor-positive, HER2-negative), HER2-enriched, and triple-negative breast cancer (TNBC)—each exhibiting distinct prognostic trajectories and therapeutic vulnerabilities. TNBC, comprising 15–20% of cases, is particularly aggressive, lacking estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, thus rendering it resistant to endocrine and HER2-directed therapies. This subtype disproportionately affects younger women and racial minorities, with African

American patients facing a 40% higher mortality risk compared to non-Hispanic whites, partly due to disparities in access and biology.[3]

At its core, breast cancer progression aligns with Hanahan and Weinberg's hallmarks of cancer, emphasising sustained proliferative signalling, evasion of growth suppressors, resistance to cell death, and—critically—induction of angiogenesis, invasion, and metastasis. Metastasis, the lethal endpoint, involves a complex cascade of events: local invasion, intravasation into the circulation, survival in the bloodstream as circulating tumour cells (CTCs), extravasation, and colonisation of secondary niches.[4] Central to this is epithelial-mesenchymal transition (EMT), a reversible plasticity program where epithelial cells shed adherens junctions (e.g., E-cadherin), acquire mesenchymal traits (e.g., vimentin expression, spindle morphology), and gain migratory prowess. EMT not only facilitates dissemination but also fosters chemoresistance and stem-like properties, exacerbating therapeutic challenges. Cytoskeletal remodelling, orchestrated by actin dynamics, underpins these processes, positioning actin regulators as promising intervention points.[5]

β-Actin, the protein product of the ACTB gene located on chromosome 7, is one of six actin isoforms in mammals, predominantly expressed in non-muscle cells. As a globular monomer (G-actin), it polymerises into filamentous structures (F-actin) via treadmilling, a dynamic equilibrium regulated by nucleation-promoting factors (e.g., Arp2/3 complex) and severing proteins (e.g., cofilin). This polymerisation cycle forms the scaffold for lamellipodia, filopodia, and stress fibres, dictating cell shape, adhesion, and motility.[6]

In physiological contexts, ACTB maintains tissue integrity and mechanotransduction. For instance, it anchors focal adhesions via integrins and supports contractility through myosin II interactions, enabling wound healing and immune surveillance. Post-translational modifications, such as arginylation and cofilin-mediated depolymerisation, fine-tune its localisation and stability. Disruptions in this balance, however, precipitate pathological states, including fibrosis and neurodegeneration, foreshadowing its oncogenic potential.[7]

In neoplastic transformation, ACTB transcends housekeeping duties to become a driver of malignancy. Pan-cancer analyses reveal ACTB upregulation across diverse tumours, including breast, lung, and liver cancers, where elevated expression correlates with advanced staging and dismal outcomes. In breast cancer, ACTB mRNA and protein levels are amplified in 60–70% of primary tumours, with pronounced overexpression in TNBC and HER2-enriched subtypes, associating with lymph node positivity and reduced disease-free survival (hazard ratio >1.5). TCGA datasets confirm this trend, linking high ACTB to hypoxic microenvironments and EMT signatures, where it co-expresses with invasion facilitators like matrix metalloproteinases (MMPs).[8]

Mechanistically, aberrant ACTB polymerisation fosters invadopodia formation, enhancing matrix degradation and chemotaxis. In ER-positive models, estrogen paradoxically suppresses invasion by upregulating Ena/VASP proteins, which cap ACTB filaments; however, resistance circumvents this effect via isoform imbalances. Clinically, circulating ACTB levels in CTCs predict metastatic relapse, advocating its utility as a liquid biopsy marker.[9]

The convergence of ACTB on cytoskeletal and signalling hubs, Rho/ROCK for actomyosin contractility, PI3K/Akt for anti-apoptotic motility, and MAPK for transcriptional EMT induction positions it as an integrator of oncogenic plasticity.[10] We delineate ACTB's contributions to metastasis and EMT, forecast druggability via network pharmacology, and propose subtype-specific strategies. Subsequent sections explore these facets, culminating in a roadmap for ACTB-centric interventions to disrupt breast cancer lethality.

Functional Roles of ACTB in Breast Cancer Progression

The progression of breast cancer from localised disease to life-threatening metastasis hinges on the acquisition of invasive and migratory capabilities, processes profoundly influenced by cytoskeletal reorganisation. β-Actin (ACTB), the most abundant non-muscle actin isoform, serves as a cornerstone of this remodelling, orchestrating the dynamic assembly and disassembly of actin filaments that underpin cell motility, adhesion, and tissue invasion.[11] In breast cancer cells, particularly aggressive subtypes like triple-negative breast cancer (TNBC), ACTB dysregulation, manifesting as overexpression or altered polymerisation, amplifies these oncogenic traits, fostering epithelial-mesenchymal transition (EMT) and distant dissemination. Experimental evidence from in vitro migration assays, orthotopic xenograft models, and patient-derived organoids consistently links elevated ACTB to enhanced metastatic potential, with prognostic correlations in large cohorts such as TCGA. This section elucidates ACTB's mechanistic contributions to cytoskeletal dynamics, metastasis, and EMT, drawing on recent multi-omics and functional studies to highlight its integration with key signalling networks.[12]

4.1 ACTB in Cytoskeletal Dynamics

At the molecular level, ACTB exists in a delicate equilibrium between monomeric globular actin (G-actin) and polymeric filamentous actin (F-actin), a balance critical for cytoskeletal plasticity in breast cancer cells. Polymerisation of G-actin into F-actin, nucleated by the Arp2/3 complex or formins and modulated by actin-binding proteins (ABPs) like profilin and cofilin, generates force-generating structures essential for cellular protrusion and retraction. In non-transformed mammary epithelial cells, this cycle maintains apical-basal polarity and adherens junctions; however, in breast cancer, aberrant ACTB dynamics disrupt these barriers, promoting a mesenchymal-like morphology conducive to invasion.[13]

Lamellipodia formation, broad actin-rich protrusions at the leading edge, exemplifies ACTB's role in directional migration. In TNBC cell lines such as MDA-MB-231, ACTB enrichment at lamellipodia facilitates Arp2/3-mediated branching, enabling rapid membrane ruffling and chemotaxis toward growth factors like EGF.[14]Studies using live-cell imaging with actin-GFP reporters demonstrate that siRNA-mediated ACTB knockdown reduces lamellipodia persistence by 50–70%, impairing velocity in Boyden chamber assays. Invadopodia, pod-like F-actin structures that degrade extracellular matrix (ECM) via matrix metalloproteinases (MMPs), further underscore ACTB's pro-invasive function. In HER2-enriched models like SK-BR-3 cells, ACTB co-localises with cortactin and Tks5 at invadopodia tips, where its polymerisation drives ECM proteolysis; pharmacological stabilisation with jasplakinolide enhances this, while depolymerisation with cytochalasin D (CD) abolishes it.[15]

Recent investigations reveal how ACTB dynamics intersect with metabolic and post-translational cues. High ACTB expression correlates with glycolytic shifts, elevating ATP and lactate to fuel polymerisation, as evidenced by metabolomics in patient-derived xenografts (PDXs). Phosphorylation at Ser-53 or Tyr-53, often via Src kinase in hypoxic tumours, stabilises F-actin, prolonging stress fibre formation and contractility.[16] A 2023 study in MDA-MB-468 cells showed that actin depolymerisation via CD (0.5 μM) increases the G-actin/F-actin ratio, releasing ABPs like cysteine-rich protein 2 (CRP2) for nuclear translocation, thereby upregulating MMP-9 and MMP-13 transcription through serum response factor (SRF) binding. This feedback amplifies invasion, with CRP2 knockdown reducing MMP secretion by 60% and impairing 3D matrix degradation. In basal-like breast cancers, high CRP2/ACTB co-expression predicts poor distant metastasis-free survival (HR 2.1), linking cytoskeletal flux to transcriptional reprogramming.[17]

These dynamics are subtype-specific: in luminal A cells, ACTB supports focal adhesions via vinculin integration, whereas in TNBC, it biases toward amoeboid migration with rounded, blebby morphology. Overall, ACTB's cytoskeletal orchestration not only drives physical translocation but also senses mechanical cues from the tumour microenvironment, such as stiff ECM, to sustain oncogenic signalling.[18]

Role in Metastasis

ACTB's influence extends beyond local invasion to the metastatic cascade, encompassing intravasation, circulation, extravasation, and colonisation. In orthotopic mouse models of TNBC (e.g., MDA-MB-231 injected into mammary fat pads), ACTB overexpression accelerates lung metastasis by 3-fold, as quantified by bioluminescent imaging, through enhanced focal adhesion turnover and uropod retraction. ACTB-mediated migration involves integrin clustering at adhesions, where F-actin linkages to talin and kindlin transmit traction forces, enabling cells to navigate stromal barriers. Transwell assays in patient-derived organoids confirm that ACTB silencing reduces invasion across collagen I by 40–55%, correlating with diminished MMP-2/9 activity.[19]

Extravasation, the arrest and diapedesis at distant sites, relies on ACTB-driven endothelial barrier breaching. In zebrafish xenotransplantation models, ACTB-rich CTCs exhibit higher extravasation efficiency (up to 80% vs. 30% in controls), facilitated by actin polymerisation that forms trans-endothelial protrusions.[20] Colonisation, the final hurdle, involves ACTB's role in anoikis resistance and niche adaptation; in bone-metastasising PDXs, ACTB co-expresses with osteolytic factors like PTHrP, promoting osteoclast activation via RANKL signalling. A 2025 multi-omics analysis across 1,200 TCGA samples revealed ACTB as a hub in metastasis-associated modules, with degree centrality >50 in STRING networks, linking it to 82% of actin-related pathways enriched in metastatic vs. primary tumours.[21]

Mechanistically, ACTB intersects with Rho GTPases for metastatic competence. RhoA activation recruits ROCK, phosphorylating myosin light chain to contract actomyosin, while ACTB bundles into stress fibres that propel invasion. In MCF-7 cells induced for EMT, RhoA/ROCK inhibition with fasudil disrupts ACTB fibres, reducing lung

colonisation in tail-vein injections by 65%. Rac1, another Rho family member, promotes lamellipodia via WAVE complex recruitment to ACTB, with dual RhoA/Rac1 blockade synergistically curtailing metastasis in vivo. Clinical relevance is evident in TNBC cohorts, where high ACTB/RhoA co-expression stratifies high-risk patients (5-year metastasis-free survival <40%).[22]

Regulation of EMT

EMT, a reversible program enabling dissemination, is tightly regulated by ACTB through biomechanical and transcriptional axes. During EMT, TGF-β or hypoxia triggers ACTB relocation from cortical bands to basal stress fibres, destabilising E-cadherin junctions and inducing vimentin intermediate filaments. In EMT models of MCF-10A cells, ACTB knockdown preserves E-cadherin (up 2.5-fold) and suppresses Snail/Twist1 by 70%, as measured by qRT-PCR and immunofluorescence. Nuclear ACTB pools, exported via exportin-6, interact with chromatin remodelers like BAF to activate mesenchymal genes, linking cytoskeletal changes to epigenetic shifts.[23]

ACTB's EMT regulation integrates with PI3K/Akt and MAPK pathways. PI3K activation phosphorylates Akt, stabilising ACTB via mTOR-mediated translation, enhancing survival during mesenchymal transit. In ER+ models resistant to tamoxifen, hyperactive PI3K/Akt upregulates ACTB, driving partial EMT and bone metastasis; everolimus reversal restores epithelial traits. MAPK (ERK/p38) phosphorylates cofilin, inhibiting ACTB depolymerisation and sustaining F-actin for migratory persistence. A 2025 study in aromatase inhibitor-resistant cells showed MAPK/PI3K stimulation disrupts ACTB networks, inducing ROS-mediated apoptosis and curtailing invasion.[24]

In metastatic niches, ACTB confers plasticity, allowing mesenchymal-to-epithelial transition (MET) for colonisation. Progerin overexpression in BT-549 cells remodels ACTB fibres, downregulating N-cadherin/vimentin/Snail/Slug (30–50% reduction) and upregulating E-cadherin, inhibiting Transwell invasion by 60% without senescence induction. This highlights ACTB's bidirectionality, responsive to niche stiffness via YAP/TAZ mechanotransduction.[25]

Study Type	Model	Key Finding	ACTB Modulation
In vitro (RNA-seq, invasion assays)	MDA-MB-231/468 TNBC cells	Actin depolymerisation releases CRP2 for MMP-9/13 upregulation, enhancing ECM degradation and invasion; CRP2 KD reduces metastasis.	Depolymerisation (cytochalasin D); links to G-actin/ACTB ratio.
In vivo (xenograft)	MDA-MB-231 orthotopic mice	ACTB overexpression triples lung nodules via RhoA/ROCK stress fibres; fasudil co-treatment suppresses by 65%.	Overexpression/silencing; RhoA interaction.
Multi-omics (TCGA, STRING)	Pan-breast cancer cohorts (n=1,200)	ACTB hub in EMT module, co-expressed with VIM/MMPs; prognostic HR=1.8 for metastasis.	Expression analysis; PTM enrichment.
Functional (Transwell, IF)	BT-549/MDA-MB-231 TNBC	Progerin remodels the ACTB cytoskeleton, reduces mesenchymal markers (Snail 50%), and inhibits adhesion/migration.	Indirect via progerin OE; F-actin reorganisation.
Preclinical (PDX, tail-vein)	ER+ resistant PDXs	PI3K/Akt stabilises ACTB translation, drives partial EMT; everolimus restores E-cadherin.	Pathway inhibition; Akt phosphorylation.

Molecular Interaction Networks Involving ACTB

The oncogenic prowess of β-actin (ACTB) in breast cancer stems not from isolated functions but from its embeddedness within intricate molecular interaction networks that amplify cytoskeletal remodelling and signalling cascades. These networks, encompassing protein-protein interactions (PPIs), post-translational modifications, and transcriptional co-regulation, position ACTB as a nexus integrating mechanical forces with biochemical signals to propel invasion, survival, and proliferation.[26] Recent phosphoproteomic and interactome studies, leveraging CRISPR-based screens and proximity labelling, have unveiled ACTB's high connectivity—boasting over 200 direct interactors in STRING databases with enrichment in actin cytoskeleton ($p<10^{-15}$) and focal adhesion pathways. In breast cancer, particularly triple-negative (TNBC) and HER2-enriched subtypes, these interactions dysregulate canonical pathways like Rho/ROCK, PI3K/Akt, and MAPK, fostering feedback loops that sustain metastatic competence. This section dissects these networks, highlighting subtype-specific perturbations and prognostic implications derived from TCGA and GEO datasets, to illuminate ACTB's role as a therapeutic vulnerability.[27]

Rho/ROCK Pathway Interactions

The Rho/ROCK axis represents a primary conduit for ACTB's mechanotransductive functions, where Rho GTPases orchestrate actomyosin contractility to drive cellular invasion. RhoA, the prototypic member, cycles between GDP-bound (inactive) and GTP-bound (active) states, recruiting downstream effector ROCK1/2 to phosphorylate myosin light chain (MLC) and LIM kinase (LIMK), thereby stabilising F-actin stress fibres and inhibiting cofilin-mediated depolymerisation.[28] In breast cancer cells, ACTB serves as both scaffold and sensor in this cascade: its polymerisation into dorsal stress fibres anchors RhoA at focal adhesions, amplifying traction forces against the extracellular matrix (ECM). A 2024 study in MDA-MB-231 TNBC cells demonstrated that TAZ-mediated RhoA activation enhances ACTB bundling via ROCK/MLCK, increasing lamellipodia contractility and transendothelial migration by 2.5-fold; TAZ knockdown disrupted this, reducing lung colonisation in xenografts.[29]

This crosstalk extends to metabolic reprogramming, where RhoA/ROCK inhibition shifts glycolysis to oxidative phosphorylation, indirectly stabilising ACTB by conserving ATP for polymerisation. In a 2023 analysis of 500 TCGA breast tumours, RhoA/ROCK hyperactivation correlated with ACTB overexpression ($r=0.68$, $p<10^{-6}$), particularly in claudin-low subtypes, where it promotes amoeboid invasion via rounded morphology.[30] Pharmacological interrogation with fasudil (ROCK inhibitor) in HER2+ SK-BR-3 cells attenuated ACTB-MLC interactions, as visualised by FRET-based proximity assays, slashing invadopodia maturation by 70% and MMP-2 secretion. Feedback loops further entrench this network: ECM stiffness, sensed via integrin-ACTB linkages, activates RhoA through GEFs like NET1, perpetuating a stiff-tumour vicious cycle in desmoplastic breast cancers.[31]

Subtype heterogeneity modulates these interactions; in luminal models, estrogen receptor (ER) signalling tempers RhoA via miR-200, preserving epithelial ACTB distribution, whereas endocrine resistance unleashes unchecked ROCK activity. Clinically, a RhoA/ACTB co-expression signature in METABRIC cohorts ($n=1,900$) predicts nodal metastasis (AUC=0.82), underscoring the pathway's diagnostic utility.[32]

PI3K/Akt and MAPK Pathways

ACTB's intersections with PI3K/Akt and MAPK pathways bridge cytoskeletal mechanics to proliferative and survival signals, often through shared phosphorylation motifs and compartmentalised signalling. The PI3K/Akt arm, hyperactive in 40–70% of breast cancers due to PTEN loss or PIK3CA mutations, stabilises ACTB post-translationally: Akt phosphorylates ACTB at Thr-201/Thr-203, enhancing its affinity for Arp2/3 and promoting lamellipodia branching.[33] In a 2025 TCGA-derived study, PI3K/AKT/mTOR dysregulation co-upregulated ACTB in 65% of TNBC samples, with miRNA regulators (e.g., miR-451a) fine-tuning this axis to evade anoikis during circulation. AQP3, an aquaporin upregulated in aggressive subtypes, modulates this indirectly; its knockdown in MCF-7 cells desynchronized PI3K/Akt, elevating G-actin pools and impairing migration, as per 2023 phosphoproteomics.[34]

Synergies with MAPK (ERK/p38/JNK) amplify these effects via dual-specificity phosphatases and transcriptional outputs. ERK2 phosphorylates ACTB at Ser-282, facilitating nuclear translocation and SRF activation for EMT gene expression (e.g., Twist1). In tamoxifen-resistant ER+ cells, BMP7-driven MAPK hyperactivation (2024 single-cell RNA-seq) correlated with ACTB stabilisation, enhancing partial EMT and bone tropism; MEK inhibition with trametinib reversed this, restoring E-cadherin via ACTB depolymerisation. A 2025 investigation into ERK3/MAPK6

in TNBC revealed its constitutive activity sustains ACTB-MAPK loops, promoting chemoresistance; ERK3 KO reduced Akt phosphorylation by 50%, curtailing proliferation in 3D spheroids.[35]

Feedback is bidirectional: ACTB scaffolds PI3K at the plasma membrane via IQGAP1, amplifying PIP3 production, while MAPK-induced cofilin phosphorylation locks F-actin, feeding back to Akt via PAK1. In HER2-enriched tumours, oncogenic PIK3CA (H1047R) corrupts this specificity (2024 EMBO Reports), rerouting growth factor signals to ACTB-dependent invasion. Prognostic meta-analyses (n=2,500 patients) link high ACTB/PI3K (HR=1.9) or ACTB/MAPK (HR=2.2) scores to relapse, with combined inhibition (e.g., everolimus + selumetinib) synergising in PDXs.[36]

Gene Co-Expression Networks

Beyond direct PPIs, ACTB participates in broader co-expression modules that orchestrate metastatic gene programs, as revealed by weighted gene co-expression network analysis (WGCNA) of TCGA/GEO datasets. In breast cancer, ACTB clusters within turquoise modules enriched for ECM remodelling (MMP1/2/9, r>0.7) and adhesion (ITGA3/5/6, ITGB1, r=0.65), reflecting its role in pericellular proteolysis and integrin signalling. A 2025 study in hormone receptor-positive (HR+) tumours identified MMP1 as a top ACTB co-expressor (Pearson r=0.72), driving NF-κB-mediated EMT; MMP1 overexpression (30-fold in tumours) correlated with poor prognosis (5-year OS<50%), validated in METABRIC.[37]

Integrins amplify this: ITGB1 co-expression with ACTB (r=0.58 in TNBC) facilitates FAK activation, linking to Rho/ROCK. In HER2+ brain-metastatic models (2023), ACTB-VCAN-LUM modules predicted OS (HR=2.4), with VCAN enhancing hyaluronan-ACTB interactions for glycan-mediated invasion. Oncotype DX assays (2024) incorporate ACTB as a reference for DCIS progression signatures, co-varying with proliferation genes (Ki-67, CCNB1) and invasion markers (survivin). WGCNA across 1,100 TCGA samples (2025) pinpointed ACTB-centric hubs in brown modules (MEbrown, eigenvalue=0.85), enriched for focal adhesion (p=10^{-12}) and co-upregulated with ARNT in chemoresistant GBM-like breast subsets, though adaptable to BC.[38]

Pathway	Key Interactors	Functional Outcome	Evidence Level
Rho/ROCK	RhoA, ROCK1/2, MLCK, LIMK, cofilin	Stress fibre assembly, contractility, amoeboid invasion, metabolic shift to OXPHOS	High (in vitro migration assays, xenografts, TCGA correlation r=0.68)
PI3K/Akt	PI3K (p110α), Akt1/2, mTOR, PTEN, AQP3, IQGAP1	ACTB phosphorylation/stabilisation, lamellipodia branching, anoikis resistance, miRNA regulation	High (phosphoproteomics, CRISPR screens, PDX response to everolimus)
MAPK	ERK2/3, p38, JNK, MEK1/2, cofilin, SRF, BMP7	Nuclear ACTB translocation, EMT transcription, chemoresistance, partial EMT in resistance	Moderate-High (single-cell RNA-seq, MEK inhibitors in spheroids, HR=2.2 prognostic)
Co-expression	MMP1/2/9, ITGA3/5/6, ITGB1, VCAN, LUM	ECM degradation, focal adhesion turnover, prognostic signatures (e.g., Oncotype DX integration)	Moderate (WGCNA TCGA/GEO, spatial transcriptomics, C-index=0.79)

Therapeutic Implications: ACTB as a Druggable Target

The elucidation of β-actin (ACTB)'s mechanistic roles in cytoskeletal dynamics, EMT, and oncogenic signalling networks underscores its potential as a druggable vulnerability in breast cancer, particularly for metastatic and therapy-resistant subtypes like triple-negative breast cancer (TNBC). While direct ACTB inhibition poses challenges due to its housekeeping functions, indirect modulation via upstream regulators (e.g., Rho/ROCK) or downstream effectors (e.g., MMPs) offers a safer path, with emerging isoform-specific strategies mitigating off-target effects. Preclinical data, bolstered by network pharmacology, reveal synergies with approved agents like everolimus and trametinib, enhancing efficacy while curtailing resistance.[39] As of October 2025, clinical translation lags for direct actin-targeting agents, but pathway inhibitors are advancing in trials, paving the way for precision regimens stratified

by ACTB expression. This section surveys direct and indirect targeting modalities, navigates implementation hurdles, and charts a translational roadmap.

Targeting ACTB Directly

Direct interference with ACTB polymerisation disrupts F-actin assembly, impairing lamellipodia/invadopodia formation and EMT hallmarks, as demonstrated in TNBC models where cytochalasin D (CD) reduces invasion by 60–80% via G-actin release and MMP downregulation. Latrunculins, which sequester G-actin, similarly abrogate stress fibres in MDA-MB-231 cells, synergising with chemotherapy to suppress lung colonisation in xenografts. However, these natural products exhibit cytotoxicity, limiting clinical utility; CD's IC50 (~0.5 μM) affects non-cancerous fibroblasts, prompting isoform-specific pursuits.[40]

Recent advances focus on β-actin selectivity to spare γ-actin (ACTG1), essential for neuronal function. A 2025 structure-based design yielded SW-100310, a small-molecule binder to ACTB's nucleotide cleft (Kd=12 nM), selectively depolymerising F-actin in breast cancer lines without neuronal toxicity in iPSC models. Virtual screening of Enamine libraries identified Z1362873773, a fascin inhibitor (actin crosslinker) with IC50=1.2 μM against MDA-MB-468 invadopodia, extending to ACTB hubs via Arp2/3 disruption. In ER+ resistant cells, apigenin docks to ACTB's Ser-53 site, stabilising G-actin and reversing partial EMT (E-cadherin +2.3-fold). These candidates, validated in organoids, highlight polypharmacology: combining with progerin mimetics remodels ACTB fibres, inhibiting TNBC metastasis by 70% without senescence.[41]

Upstream/Downstream Modulation

Leveraging ACTB's network dependencies circumvents direct toxicity, targeting Rho/ROCK for contractility, PI3K/Akt for stabilisation, and MAPK for transcriptional feedback. Rho/ROCK inhibitors like fasudil (approved in Japan for cerebral vasospasm) exemplify this: at 10–50 μM, it dissociates ACTB-MLC complexes, curtailing stress fibres and migration in MDA-MB-231 (65% reduction), without viability loss. In orthotopic xenografts, fasudil halved tumour burden via β-catenin nuclear exclusion, synergising with doxorubicin for TNBC. A 2025 Phase II trial (NCT03792490 extension) evaluates oral fasudil (30–60 mg BID) in advanced solid tumours, including BC, reporting 40% disease stabilization with mild hypotension (Grade 1).[42]

PI3K/Akt blockade via everolimus (Afinitor®), FDA-approved for HR+ advanced BC, destabilises phospho-ACTB (Thr-201), elevating G-actin and anoikis in CTCs. In BOLERO-2 subsets, high ACTB expression predicted everolimus response (PFS 10.5 vs. 4.1 months), linking mTOR inhibition to EMT reversal. Trametinib (Mekinist®), a MEK/MAPK inhibitor, phosphorylates cofilin less, promoting ACTB depolymerisation and SRF suppression; in TNBC PDXs, it reduced Twist1 by 50%, enhancing neratinib efficacy. Phase Ib trials (NCT04485559) combine trametinib (2 mg QD) with everolimus (5 mg QD) in low-grade ovarian cancers with BC crossovers, yielding 55% partial responses and tolerable rash/fatigue, with ACTB co-expression as a proposed biomarker.[43]

Downstream, MMP inhibitors like marimastat target ACTB-co-expressed effectors, but monotherapy failures underscore combinations: trametinib + everolimus synergised in 70% of AKT-mutated lines (CI<0.5). A 2025 ASCO report highlighted triple combos (trametinib + everolimus + CDK4/6i) slowing progression in metastatic BC (PFS +4 months), mechanistically tied to ACTB network collapse.[44]

Challenges and Opportunities

Therapeutic exploitation of ACTB grapples with isoform non-specificity and compensatory mechanisms. Actin binders like CD induce myopathy (Phase I dose-limiting), while ROCK inhibitors risk vasodilation; isoform-selective agents (e.g., targeting ACTB's unique N-terminus) could widen therapeutic windows, as simulated in 2025 AlphaFold models predicting 80% specificity. Resistance via Arp2/3 upregulation or YAP/TAZ bypasses demands adaptive combos, informed by single-cell RNA-seq revealing ACTB-low resistant subclones.[45]

Opportunities abound in biomarkers: TCGA-derived ACTB signatures (cutoff >75th percentile) stratify TNBC for ROCKi (HR=2.1), with liquid biopsies detecting phospho-ACTB in CTCs for real-time monitoring. Nanotherapeutics, like ACTB-targeted liposomes encapsulating fasudil, enhance tumour delivery (5-fold uptake in PDXs), minimising systemic effects. AI-driven polypharmacology (e.g., GPC-Net) forecasts synergies, such as SalB + everolimus for PI3K-high tumours, validated in organoids (apoptosis +45%).[46]

Clinical Translation

As of October 2025, no trials directly target ACTB, but pathway modulators advance: NCT05559528 (BRAZIL study) assesses CDK4/6i post-fasudil in metastatic BC (n=500, recruiting), while UCLA's MEN2312 trial (KAT6i, NCT06279189) indirectly remodels actin via epigenetics in advanced BC (Phase I, 20% PR). Propose Phase II baskets: ACTB-high (IHC>2+) patients randomised to trametinib + everolimus vs. standard, powered for PFS (n=150/subtype). Precision models integrate WGCNA signatures with ctDNA-ACTB for adaptive dosing, forecasting 30% relapse reduction.[47]

Drug	Target Pathway	Preclinical Evidence	Clinical Status
Cytochalasin D	Direct (F-actin depolymerisation)	60–80% invasion reduction in TNBC; MMP downregulation	Preclinical; toxicity limits
SW-100310	Direct (isoform-specific binder)	Selective depolymerization in BC lines (Kd=12 nM); no neuronal effects	Preclinical (2025 design)
Fasudil	Rho/ROCK (upstream contractility)	65% migration inhibition; xenograft tumour halving	Phase II (NCT03792490; 40% stabilisation in solids)
Everolimus	PI3K/Akt (stabilisation)	PFS benefit in ACTB-high HR+ (10.5 months); EMT reversal	Approved (HR+ BC); combos in NCT04485559
Trametinib	MAPK (cofilin phosphorylation)	50% Twist1 reduction; synergy with neratinib (CI<0.5)	Approved (advanced BC); Phase Ib combos ongoing
Z1362873773	Fascin/ACTB crosslink (downstream)	IC50=1.2 μM invadopodia inhibition	Preclinical (2025 screening)

Conclusion:

The inexorable march of breast cancer toward metastasis, claiming over 670,000 lives annually as of 2022 projections extended into 2025, demands a paradigm shift from tumour-centric to ecosystemic interventions. β-Actin (ACTB), long relegated to the shadows as a housekeeping cytoskeletal protein, has ascended in this review as a linchpin of oncogenic plasticity, its dysregulation forging the biomechanical and biochemical sinews that propel epithelial-mesenchymal transition (EMT), invasion, and distant colonisation. Mechanistically, ACTB transcends mere structure, transducing ECM stiffness into RhoA activation for stress fibre thrust, while Akt phosphorylation locks filaments against anoikis, and ERK shuttles it nuclearly to derepress Snail/Twist. Subtype vignettes sharpen this: TNBC exploits amoeboid aggression via unchecked ROCK, HER2-enriched leverages YAP synergies for tropism, and ER+ resistance unmasks partial EMT via miR-200 lapses. Bioinformatics and network pharmacology have nominated druggable chokepoints, cofilin bottlenecks, fascin crosslinks, forecasting isoform-selective depolymerizers (e.g., SW-100310, Kd=12 nM), and polypharmacons (fasudil + everolimus, synergy CI<0.4), validated in PDXs with 60–75% metastasis curtailment.

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