β-Actin (ACTB): From Housekeeping Gene to Clinical Biomarker – Insights into Diagnostic, Prognostic, and Predictive Applications

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Abstract:

Beta-actin (ACTB), a highly conserved cytoskeletal protein, plays essential roles in cell migration, adhesion, and transcriptional regulation. Traditionally used as a housekeeping gene for normalization in gene expression studies, emerging evidence reveals dysregulated ACTB expression and mutations in various diseases, including cancers and dystrophies, challenging its benign reference status. This review synthesizes the diagnostic, prognostic, and predictive values of ACTB across oncology and non-oncology contexts. ACTB expression alterations serve as early detection biomarkers detected via liquid biopsies in cancers, and as indicators of fibrosis or neurodegeneration. Prognostically, elevated ACTB correlates with aggressive phenotypes and poor survival in colorectal and other cancers, driven by mechanisms linked to epithelial-mesenchymal transition, metastasis, and immune evasion. Predictively, ACTB polymorphisms and expression levels influence chemotherapy response in ovarian cancer and immunotherapy effectiveness through modulation of T-cell migration. Translational progress from preclinical models, including CRISPR-based knockouts, to emerging clinical trials highlights potential clinical applications while underscoring gaps like assay standardization, ethnic variability, and prospective validation needs. Ethical and regulatory considerations stress equitable access and rigorous biomarker validation. Future directions involve AI-driven analytics, nanotechnology-enabled targeting, and multi-omics biomarker integration to harness ACTB's full potential. Overall, ACTB represents a versatile yet underexploited biomarker promising to enhance precision diagnostics and therapeutics.

Keywords: ACTB, β-Actin, Biomarker, Diagnostics, Prognostics, Predictive value, Translational medicine, Cancer biomarkers

Introduction:

ACTB, encoding beta-actin, is a fundamental component of the cytoskeleton and plays a vital role in various cellular processes. It exists as one of six different actin isoforms, with ACTB specifically classified as a nonmuscle cytoskeletal actin. Its main functions include maintaining cell shape, facilitating cell motility, enabling cell adhesion, and regulating gene transcription, especially in dynamic cellular contexts such as migration and tissue development.[1]

Isoforms and Biological Roles

Among the six isoforms of actin in humans, ACTB (beta-actin) is highly conserved and ubiquitously expressed across tissues. Its role is essential in providing structural support, organizing intracellular compartments, and driving cell motility through actin filament polymerization. Beta-actin's involvement extends to key cellular processes such as cell migration, adhesion, and gene regulation—crucial during development, immune responses, and wound healing.[2]

Traditional Use as Housekeeping Gene

Due to its stable and abundant expression, ACTB is extensively used as a housekeeping gene in qPCR and RNA-seq experiments to normalize gene expression data, serving as a control for variations in sample input and quality. However, recent evidence suggests that ACTB expression can vary significantly across different cell types and disease states, particularly in cancers, highlighting the importance of context-specific validation.[3]

Clinical and Disease Associations

Dysregulation of ACTB has been implicated in multiple diseases. Its overexpression is well-documented in various cancers such as breast, colon, and liver, where it often correlates with increased tumor invasion, metastasis, and poorer prognosis.[4] Conversely, mutations leading to loss of function, including heterozygous deletions and nonsense mutations, cause developmental disorders characterized by malformations, intellectual disability, and organ malformations, exemplified by Baraitser-Winter syndrome and other congenital malformation syndromes.In muscle-related diseases like dystrophies, mutations affecting actin stability have also been observed, further emphasizing its importance in cellular integrity and function.[5]

Translational and Diagnostic Context

Research has extended into clinical applications, utilizing ACTB in various diagnostic and prognostic modalities. For instance, actin polymerization assays help investigate actin dynamics in disease models, while immunohistochemistry and liquid biopsy approaches leverage ACTB as a stable marker for tissue origin and tumor progression.[6]

Scope and Objectives

The aim of this review is to synthesize current evidence on ACTB's molecular functions and its clinical implications, focusing on its roles as an early diagnostic marker, a prognostic indicator, and a predictor of therapy response in various diseases, notably cancer. The review also seeks to identify gaps in knowledge, especially regarding the mechanisms of ACTB dysregulation and its potential as a therapeutic target, culminating in proposals for future research directions.[7]

Diagnostic Value of ACTB

Overview: ACTB as a Biomarker for Early Detection

Beta-actin (ACTB) has emerged as a promising biomarker candidate for early disease detection by virtue of its expression patterns, genetic mutations, and post-translational modifications in pathological conditions. ACTB's ubiquitous expression and fundamental cellular roles make it readily detectable in biological samples, including blood, tissue, and liquid biopsy specimens. [8]Detection of altered ACTB expression levels, aberrant mutations, or specific modifications can serve as early indicators signaling disease onset or progression. These alterations may be identified through various molecular platforms such as quantitative PCR (qPCR), next-generation sequencing (NGS), and immunoassays like enzyme-linked immunosorbent assays (ELISA).[9]

While historically used as a housekeeping gene, growing evidence highlights that ACTB expression is not universally stable across disease states, particularly cancers, underscoring its potential utility as a diagnostic biomarker rather than a mere normalization control. Moreover, distinct mutations or epigenetic alterations impacting ACTB, or its protein's post-translational profile, provide additional layers of diagnostic information.[10]

Disease-Specific Evidence

Oncology: Circulating ACTB mRNA in Liquid Biopsies

Liquid biopsy, an emerging minimally invasive technique, analyzes circulating nucleic acids and proteins shed by tumors into body fluids. Circulating ACTB mRNA and protein expression have been evaluated in liquid biopsies from cancer patients, including lung and breast cancers. Studies demonstrate that increased circulating ACTB mRNA correlates with tumor presence and burden, making it a viable early detection marker.[11] In lung cancer, assays detecting ACTB transcripts alongside mutation analysis of circulating tumor DNA (ctDNA) enable sensitive stratification and monitoring of disease progression. Similarly, breast cancer liquid biopsies use circulating ACTB mRNA levels for real-time tumor monitoring, complementing detection of other oncogenic markers.[12]

These liquid biopsy approaches benefit from high-throughput, sensitive methods like NGS and qPCR, allowing precise quantification of ACTB alterations. However, variations in normalization strategies and biological noise present challenges for consistency across studies and clinical use.[13]

Non-Oncology: ACTB in Fibrosis and Neurodegeneration

Beyond cancer, ACTB dysregulation also shows diagnostic relevance in fibrotic and neurodegenerative diseases. For idiopathic pulmonary fibrosis (IPF), ACTB expression has been studied in lung tissue biopsies and extracellular

vesicles, highlighting its potential as a marker of fibroblast activation and disease severity. Targeting pathways regulating ACTB dynamics could inform diagnostic or therapeutic strategies in fibrosis.[14]

In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), the formation of actin aggregates, including altered ACTB interactions, associates with cellular toxicity and disease progression. Detection of these aggregates or changes in actin-binding protein profiles in cerebrospinal fluid or tissue may provide early diagnostic clues for ALS and related conditions.[15]

Technologies and Challenges

Several molecular and immunological platforms exist for detecting ACTB expression and modifications for diagnostic purposes:

- qPCR: Widely used for quantifying ACTB mRNA expression, qPCR offers sensitivity and specificity but requires careful normalization strategies due to observed variability of ACTB expression in disease contexts.[16]
- Next-Generation Sequencing (NGS): NGS provides comprehensive mutation and expression profiling of ACTB and its isoforms in tissues and circulating nucleic acids, aiding detection of rare variants and subtle expression changes relevant for early diagnosis.[17]
- ELISA and Immunoassays: These enable detection of ACTB protein levels and post-translational modifications in blood or other fluids. Commercial ACTB ELISA kits support quantitative protein biomarker studies but face challenges such as cross-reactivity and standardization.[18]

Despite these advances, key challenges hinder clinical translation. Normalization of ACTB expression remains problematic due to its variable expression in different tissues, disease stages, and treatment conditions, complicating data interpretation in qPCR and RNA-seq assays. Biological variability in liquid biopsy analytes and low abundance in early disease stages demand highly sensitive and standardized detection methods. Furthermore, post-translational modifications affecting antibody binding pose risks for immunoassay accuracy.[19]

Prognostic Value of ACTB

Overview: ACTB Expression and Mutations as Prognostic Indicators

Beta-actin (ACTB), integral to cytoskeletal structure and cellular motility, has increasingly been recognized as a significant prognostic biomarker in multiple diseases, particularly cancer and cardiovascular conditions.[20] Elevated or aberrant ACTB expression and mutations often correlate with disease aggressiveness and poor clinical outcomes such as reduced overall survival (OS) and relapse-free survival (RFS). This prognostic potential is driven by ACTB's involvement in cellular processes that underpin tumor progression, metastasis, and tissue remodeling, positioning it as a critical molecular indicator for patient stratification and outcome prediction.[21]

Disease-Specific Evidence

Oncology: Colorectal Cancer and Broader Cancer Prognostics

A comprehensive pan-cancer analysis leveraging TCGA (The Cancer Genome Atlas) data has highlighted that overexpression of ACTB correlates with poor OS across multiple tumor types, including colorectal cancer. Meta-analyses reveal that high ACTB mRNA and protein levels significantly associate with aggressive disease phenotypes and shortened survival times. Kaplan-Meier survival plots demonstrate that patients with elevated ACTB exhibit diminished OS and RFS, underscoring its value as a prognostic marker.[22]

In colorectal cancer specifically, elevated ACTB expression correlates strongly with increased risk of metastasis and recurrence, which is linked mechanistically to ACTB’s role in cytoskeletal remodeling that facilitates tumor cell migration and invasion. The hazard ratio (HR) quantifies this prognostic risk, with studies reporting HR values greater than 1.5 for high ACTB expression groups compared to low expression cohorts, indicating significantly increased mortality risk. This prognostic insight supports ACTB measurement as part of patient risk stratification to guide follow-up and therapeutic decisions.[23]

Non-Oncology: Cardiovascular Disease

ACTB’s prognostic relevance extends into cardiovascular disease, where actin cytoskeletal dynamics influence vascular remodeling in conditions such as atherosclerosis. Studies demonstrate that disturbed ACTB expression and methylation patterns in peripheral blood are associated with disease severity and outcomes in coronary heart disease

and heart failure. For example, hypermethylation of ACTB CpG sites correlates with higher risk and poor prognosis in patients, with odds ratios indicating a 1.2- to 1.4-fold increased risk of adverse events.[24]

This remodeling of the actin cytoskeleton affects vascular smooth muscle cell apoptosis, plaque stability, and arterial remodeling, all of which impact the progression and prognosis of atherosclerotic disease. Thus, ACTB serves as a molecular link between cytoskeletal integrity and cardiovascular clinical outcomes.[25]

Mechanistic Insights: EMT, Metastasis, and Immune Evasion

ACTB's prognostic importance derives from its mechanistic roles in critical cellular pathways:

- Epithelial-Mesenchymal Transition (EMT): EMT is essential for cancer metastasis, involving loss of cell adhesion molecules such as E-cadherin and cytoskeletal remodeling. ACTB regulates actin filament assembly/disassembly, driving morphological changes necessary for EMT and increased motility. ACTB overexpression promotes EMT, thereby facilitating invasion and metastasis.[26]
- Metastasis Facilitation: ACTB supports cytoskeletal rearrangements that facilitate tumor cell invasion, dissemination, and colonization of distant organs. Enhanced ACTB expression encourages formation of cellular protrusions and migration structures critical for metastatic potential.[27]
- Immune Evasion: Emerging evidence links ACTB cytoskeleton remodeling to tumor immune evasion. Accumulation of filamentous actin at the immune synapse between tumor and immune cells can increase resistance to immune cell-mediated lysis, including Natural Killer cell attacks, thereby contributing to metastatic cell survival in host tissues.[28]

Quantitative Evidence: Survival Analyses and Hazard Ratios

Consolidated survival analyses from TCGA and other databases consistently show associations between elevated ACTB expression and poorer clinical outcomes:

- Kaplan-Meier analyses report statistically significant lower OS for high ACTB expression groups in cancers such as colorectal (READ), lung adenocarcinoma (LUAD), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), and others (p-values typically <0.05).[29]
- Hazard ratios for mortality in patients with high ACTB expression often range between 1.3 and 2.0, indicating 30% to 100% increased risk of death compared to patients with lower expression, supporting ACTB's role as a prognostic risk factor.[30]
- Relapse-free survival analyses reinforce these findings, highlighting ACTB's utility in predicting disease recurrence risk, particularly in breast and colorectal cancers.[31]

In cardiovascular disease, odds ratios above 1.2 for ACTB methylation patterns associate with worsened event-free survival, delineating ACTB's prognostic capacity beyond oncology.[32]

Predictive Value of ACTB

Overview: ACTB as a Companion Biomarker for Therapy Response

Beta-actin (ACTB), a pivotal cytoskeletal protein involved in cell structure and motility, has gained attention as a companion biomarker to predict therapy responses across diverse clinical settings. Its expression level, polymorphisms, and interactions with signaling pathways modulate cellular resistance or sensitivity to treatments such as chemotherapy and immunotherapy.[33] ACTB-mediated alterations in actin dynamics impact drug uptake, intracellular trafficking, cell survival, and immune cell functions, making it a critical determinant of treatment efficacy. Consequently, measuring ACTB status in tumors or immune cells has potential utility in tailoring precision therapies for improved patient outcomes.[34]

Disease-Specific Evidence

Oncology: ACTB Polymorphisms and Chemotherapy Response in Ovarian Cancer

In ovarian cancer, research has identified that polymorphisms and differential expression of ACTB correlate with patient responses to taxane-based chemotherapy one of the mainstays for treating this malignancy.[35] Lower ACTB expression associates strongly with multi-drug resistance and poor overall survival, as evidenced by experimental and clinical data. Specifically, downregulation of ACTB renders ovarian cancer cells less sensitive to platinum and taxane agents by modifying actin cytoskeleton architecture and influencing drug efflux mechanisms.[36]

MicroRNA regulation also titrates ACTB levels, with miRNA-450b-5p negatively regulating ACTB expression and impacting chemoresistance and prognosis. High miRNA-450b-5p and consequent low ACTB expression correspond to reduced sensitivity to carboplatin and shorter progression-free survival, framing ACTB as a functional and predictive biomarker.[37]

In hepatocellular carcinoma (HCC), low ACTB expression predicts improved response to targeted therapy with lenvatinib. Patient-derived xenograft models confirmed that tumors exhibiting low ACTB levels were more responsive to lenvatinib, highlighting ACTB's potential for guiding therapeutic decisions in liver cancer.[38]

Non-Oncology: ACTB and Predictive Roles in Immunotherapy

The success of immunotherapies, particularly immune checkpoint inhibitors targeting PD-1/PD-L1, partially depends on effective T-cell migration and immune synapse formation, processes intrinsically governed by actin cytoskeletal dynamics. ACTB plays a key role in regulating T-cell motility and function, thus modulating immune responsiveness.[39]

Altered ACTB expression influences the tumor immune microenvironment by affecting infiltration of immune cells such as CD8+ cytotoxic T-cells and macrophages, which are critical mediators of immunotherapy efficacy. ACTB expression correlates with immune checkpoints and regulators across multiple tumor types, suggesting it may predict response to checkpoint blockade therapy.[40]

Integration with Other Biomarkers: Multi-Omics Panels

ACTB's predictive power is further enhanced when integrated within multi-omics biomarker panels that combine genomic, transcriptomic, and proteomic data. For example, combining ACTB expression with tumor suppressor gene TP53 mutation status refines prediction models for therapy response and patient survival in various cancers.[41] TP53 has emerged as a robust molecular biomarker outperforming some androgen receptor markers, and its interaction with ACTB-driven cytoskeletal functions suggests a synergistic role in modulating treatment sensitivity.[42]

Multi-gene regulatory indices incorporating ACTB alongside immune and metabolism-related genes also improve predictive accuracies for immunotherapy responses, enabling personalized treatment stratification. Integration of ACTB into such comprehensive panels is crucial to overcome limitations due to tumor heterogeneity and dynamic treatment adaptation.[43]

Challenges: Heterogeneity and Validation Needs

Despite promising evidence, ACTB's predictive biomarker applications face key challenges:

- Expression Heterogeneity: ACTB expression shows marked variability across tumor types, cellular subpopulations, and disease stages, complicating interpretation of single-timepoint measurements.[44]
- Prospective Validation: Most current findings derive from retrospective analyses or preclinical models; prospective clinical trials are urgently needed to validate ACTB-based predictive models before clinical deployment.[45]
- Assay Standardization: Diverse detection platforms (qPCR, immunohistochemistry, NGS) require harmonization to ensure reproducibility and comparability across clinical laboratories.[46]
- Biological Complexity: ACTB-mediated therapy resistance involves multifactorial pathways, necessitating multi-marker approaches rather than reliance on ACTB alone.[47]

Translational Perspectives and Challenges

From Bench to Bedside: Preclinical Models to Clinical Trials

The pivotal roles of beta-actin (ACTB) in cellular architecture, motility, and signaling underpin its emerging translational potential as a biomarker and therapeutic target. Preclinical models have been instrumental in dissecting ACTB's functional relevance and therapeutic applicability.[48]CRISPR-Cas9 gene editing technology has enabled targeted generation of ACTB knockout and knock-in models in cell lines and animals, elucidating its indispensability for cell survival, migration, and response to therapies. These models reveal that manipulating ACTB expression or function alters tumor invasiveness, drug sensitivity, and immune interactions, supporting its utility as both a biomarker and actionable target.[49]

Animal models including orthotopic tumor xenografts with ACTB modulation recapitulate human disease phenotypes, allowing study of therapeutic response dynamics linked to ACTB expression. Additionally, in vitro assays of actin polymerization/depolymerization have enhanced mechanistic understanding of how ACTB alterations influence chemoresistance and immune evasion.[50]

In the clinical domain, ACTB's biomarker roles are increasingly evaluated in ongoing and recently completed clinical trials (e.g., NCT07060365) involving ovarian and hepatocellular carcinoma, where ACTB expression guides targeted therapy selection or monitors treatment response. Although direct ACTB-targeted therapies in humans remain nascent, its inclusion in multi-parameter biomarker panels for precision oncology and immunotherapy exemplifies its translational progression.[51]

Current Gaps: Standardization, Variability, and Validation

Despite promising preclinical and emerging clinical evidence, significant gaps hinder ACTB's full clinical adoption.

- Lack of Standardized Assays: There is no universally accepted, standardized assay for clinical quantification of ACTB at the mRNA or protein levels. Methodological heterogeneity in qPCR normalization, antibody specificity in immunohistochemistry, and detection platforms complicate data harmonization and inter-study comparisons.[52]
- Ethnic and Population Variability: Limited data exist on how ethnic and genetic backgrounds influence ACTB expression, polymorphisms, or post-translational modifications. This variability may affect biomarker performance and predictive accuracy across diverse populations, necessitating inclusive cohort studies and validations.[53]
- Prospective Randomized Controlled Trials (RCTs): Most ACTB-based biomarker validations stem from retrospective cohorts or preclinical studies. Prospective RCTs explicitly evaluating diagnostic, prognostic, and predictive utilities of ACTB are scarce but critical for regulatory approval and clinical confidence.[54]
- Biological Complexity and Heterogeneity: ACTB's ubiquitous expression and involvement in fundamental cellular functions pose challenges in distinguishing pathological alterations from physiological variation, requiring sophisticated multi-omics and integrative bioinformatics for robust clinical translation.[55]

Ethical and Regulatory Considerations

Clinical biomarker development including ACTB is governed by stringent ethical and regulatory frameworks ensuring safety, efficacy, and equitable access.

- Biomarker Validation Pathways: The FDA and EMA provide comprehensive guidelines detailing the phases of biomarker development—from analytical validation (accuracy, precision), clinical validation (association with clinical outcomes), to clinical utility (impact on patient management). Meeting regulatory rigor requires controlled studies, reproducible assays, and demonstration of improved clinical decision-making.[56]
- Data Privacy and Informed Consent: Biomarker research often involves genomic and multi-omics data, necessitating robust policies for data privacy, storage, and participant informed consent, especially when involving diverse populations or clinical trial participants.[57]
- Equity in Access: Ethical frameworks underscore the imperative to ensure biomarker testing and associated therapies are accessible across socioeconomic strata and geographic regions, to prevent disparities in health outcomes. Strategies include affordable assay development, reimbursement policies, and global clinical trial inclusivity.[58]
- Transparency and Communication: Clear communication of biomarker test limitations, possible false positives/negatives, and implications for patient care is morally essential to maintain trust and informed healthcare decisions.[59]

Future Directions and Conclusions

Emerging Opportunities: AI-Driven Analytics, Nanotechnology, and Combination Biomarkers

The future landscape of ACTB research and clinical application is poised for transformational advances driven by cutting-edge technologies. Artificial intelligence (AI) and machine learning (ML) algorithms offer unprecedented

opportunities for extracting complex, multidimensional insights from large-scale ACTB datasets, including transcriptomic, proteomic, and epigenomic profiles. AI-driven analytics can facilitate precise stratification of patient subgroups based on subtle ACTB expression patterns or mutation signatures, enhancing diagnostic accuracy and the predictive value of ACTB-centered biomarkers.[60]

Nanotechnology also presents promising avenues for ACTB-targeted diagnostics and therapeutics. Nanoengineered probes and delivery systems can enable highly sensitive detection of ACTB protein or mRNA at single-cell resolution in liquid biopsies, improving early detection capabilities. Moreover, nanocarriers targeting the actin cytoskeleton could allow delivery of actin-modulating agents specifically to cancerous or fibrotic tissue, minimizing off-target effects and overcoming drug resistance.[61]

Combination biomarker panels integrating ACTB with other molecular markers such as TP53 mutations, immune checkpoints, and metabolic enzymes are another vital development. Multi-omics approaches combining genomics, epigenetics, and proteomics increase the robustness of biomarker assays and better capture tumor and disease complexity. These composite panels provide comprehensive prognostic and predictive frameworks, unlocking precision medicine opportunities unavailable from single-gene markers alone.[62]

Research Priorities: Large-Scale Cohorts, Longitudinal Studies, and Therapeutic Targeting

To translate these technological promises into clinical reality, focused research efforts are essential. Large-scale, ethnically diverse cohort studies are required to validate ACTB as a biomarker across different populations and disease contexts. Longitudinal designs will elucidate dynamic changes in ACTB expression and function during disease progression and treatment, informing optimal intervention timing and monitoring.[63]

Parallel research should explore therapeutic targeting of ACTB and actin cytoskeleton regulators. Development of small molecule inhibitors or stabilizers of actin dynamics holds potential for novel treatments in oncology, fibrosis, and immune modulation. These therapies could disrupt ACTB-mediated mechanisms underlying metastasis, drug resistance, and immune evasion, providing innovative avenues beyond traditional cytotoxic drugs.[64]

Conclusion:

Beta-actin (ACTB) remains an underexplored yet potent biomarker at the intersection of cell biology, clinical diagnostics, and therapeutic innovation. Its fundamental roles in cytoskeletal regulation, cell motility, and transcriptional processes underpin its diagnostic, prognostic, and predictive utilities across a spectrum of diseases ranging from cancer to fibrotic and neurodegenerative disorders. Emerging technologies and integrated multi-omics approaches promise to overcome historical challenges of variability and specificity.

Harnessing ACTB's full potential requires concerted efforts to standardize assays, incorporate advanced analytics, and validate findings prospectively within large-scale diverse cohorts. Concurrently, ethical frameworks must ensure equitable access to ACTB biomarker testing and incorporate patient-centered communication strategies. Ultimately, ACTB is poised to be a cornerstone biomarker facilitating precision medicine approaches, enabling earlier detection, more accurate prognostication, and tailored therapeutic interventions, thus improving patient outcomes and quality of life.

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