Applied Cell Biology

ISSN : 2320-1991 Online
ISSN : 2320-1983 Print
Volume 13 Issue 3
DOI: https://dx.doi.org/10.53043/2320-1991.acb13012

Review Article
Appl Cell Biol, 13(3), 2025 [65-73]
Published: July 25, 2025

Regulatory Complexity of the Actin Cytoskeleton and Its Contribution to Human Disorders

Brennan Gerlach*

Department of Molecular and Cellular Physiology, Albany Medical College, 47 New Scotland Avenue, MC-8, Albany, NY 12208, USA

***Corresponding author:** Brennan Gerlach, Department of Molecular and Cellular Physiology, Albany Medical College, 47 New Scotland Avenue, MC-8, Albany, NY 12208, USA.

ABSTRACT

The actin cytoskeleton constitutes one of the most dynamic and versatile structural systems within eukaryotic cells, underpinning a broad range of essential biological processes including cell shape maintenance, migration, intracellular transport, signal transduction, and mechanical force generation. Far from being a static scaffold, actin filaments undergo continuous remodeling governed by a complex network of regulatory proteins, signaling cascades, and biomechanical cues. The precise spatial and temporal control of actin dynamics is fundamental to tissue development, homeostasis, and adaptive cellular responses. Disruption of this finely tuned regulatory system has increasingly been recognized as a central contributor to the pathogenesis of numerous human disorders, ranging from cancer and neurodegenerative diseases to cardiovascular, immunological, and developmental abnormalities. This review provides a comprehensive and integrative analysis of the molecular mechanisms governing actin cytoskeleton regulation and examines how their dysregulation drives disease-associated cellular phenotypes. Emphasis is placed on the interplay between actin-binding proteins, upstream signaling pathways, and mechanotransduction processes that collectively orchestrate cytoskeletal behavior. Furthermore, the emerging therapeutic potential of targeting actin-associated regulatory networks is critically discussed, highlighting both current limitations and future opportunities. By synthesizing insights from cell biology, molecular pathology, and translational research, this review underscores the actin cytoskeleton as a pivotal regulatory hub in human disease and a promising frontier for therapeutic intervention.

Keywords

Actin cytoskeleton
Cytoskeletal dynamics
Actin-binding proteins
Cellular mechanics
Disease mechanisms
Signal transduction
Therapeutic targeting

INTRODUCTION

The actin cytoskeleton represents a fundamental organizational framework of eukaryotic cells, providing both structural integrity and dynamic adaptability required for cellular function. Actin exists primarily in two interconvertible states: monomeric globular actin (G-actin) and polymerized filamentous actin (F-actin). The rapid and reversible assembly of actin filaments allows cells to respond to internal cues and external stimuli with remarkable precision. Unlike other cytoskeletal systems, such as microtubules or intermediate filaments, the actin network exhibits an exceptional degree of plasticity, enabling continuous reorganization on timescales ranging from seconds to minutes [1].

Historically, actin was regarded largely as a structural component essential for muscle contraction and basic cellular architecture. However, advances in molecular and imaging technologies have profoundly reshaped this view, revealing actin as a central regulator of diverse biological processes. Actin filaments form specialized structures including stress fibers, lamellipodia, filopodia, cortical networks, and contractile

rings, each tailored to specific functional demands. The formation and maintenance of these structures are governed by an intricate regulatory system composed of actin-binding proteins (ABPs), nucleation factors, severing proteins, motor proteins, and signaling intermediates [2].

The regulatory complexity of the actin cytoskeleton arises from the need to integrate biochemical signals with mechanical forces. Actin dynamics are tightly controlled by signaling pathways involving small GTPases, kinases, phosphoinositides, and calcium-dependent modulators, which collectively determine filament nucleation, elongation, branching, and disassembly [3-5]. This multilayered regulation allows actin networks to function as both effectors and sensors of cellular signaling, positioning the cytoskeleton as a bidirectional interface between intracellular processes and the extracellular environment.

Perturbations in actin regulation can profoundly alter cellular behavior. Aberrant actin remodeling has been implicated in uncontrolled cell migration and invasion in cancer, synaptic dysfunction in neurological disorders, impaired contractility in cardiac disease, and defective immune responses. Importantly, many disease-associated mutations and pathological signaling alterations converge on actin-regulatory pathways, highlighting the cytoskeleton as a common denominator across seemingly disparate disorders.

Despite its central role in cellular physiology and pathology, the actin cytoskeleton presents unique challenges as a therapeutic target. The ubiquitous expression and essential nature of actin raise concerns regarding toxicity and specificity [6]. Consequently, current research efforts have shifted toward targeting upstream regulators, signaling modulators, and context-specific actin-associated pathways rather than actin itself. Understanding the regulatory logic that governs actin dynamics in both normal and diseased states is therefore critical for the development of effective and selective therapeutic strategies.

This review aims to provide a detailed and integrative examination of the regulatory mechanisms controlling actin cytoskeleton dynamics and to elucidate how their disruption contributes to human disease. By emphasizing theoretical frameworks and mechanistic insights, this work seeks to bridge fundamental cell biology with translational implications, offering a cohesive perspective on the actin cytoskeleton as a central player in health and disease.

MOLECULAR ORGANIZATION OF THE ACTIN CYTOSKELETON

At the molecular level, actin cytoskeleton organization is dictated by the coordinated action of polymerization dynamics and regulatory protein interactions. Actin polymerization is inherently polarized, with a fast-growing barbed (+) end and a slow-growing pointed (−) end [7-10]. This polarity enables directional filament growth, a property exploited during processes such as cell migration and intracellular trafficking. The ATP-bound state of actin monomers favors filament assembly, while ATP hydrolysis and phosphate release destabilize older filament regions, promoting turnover.

The intrinsic properties of actin filaments are modulated by a diverse repertoire of ABPs that bind actin monomers, filament sides, or filament ends. These proteins regulate filament nucleation, elongation rates, branching geometry, crosslinking, and severing, thereby generating functionally distinct actin architectures. The spatial distribution of ABPs within cells further contributes to regional specialization of actin networks, allowing different cytoskeletal structures to coexist and operate simultaneously.

Actin nucleation represents a rate-limiting step in filament formation and is tightly regulated by specialized nucleator complexes. The Arp2/3 complex generates branched actin networks critical for membrane protrusion, while formin proteins promote the assembly of long, unbranched filaments characteristic of stress fibers and contractile structures. The balance between these nucleation pathways determines the overall architecture and mechanical properties of the actin cytoskeleton [11].

Beyond nucleation and elongation, filament disassembly is equally essential for cytoskeletal remodeling. Severing proteins such as cofilin induce filament fragmentation, accelerating turnover and enabling rapid reorganization. The coordinated regulation of assembly and disassembly ensures that actin networks remain dynamic and responsive rather than static and rigid.

Importantly, actin filaments do not function in isolation but interact extensively with other cytoskeletal elements and cellular components. Crosstalk with microtubules, intermediate filaments (Table 1), membrane lipids, and adhesion complexes integrates actin dynamics into broader cellular systems. This interconnectedness amplifies the impact of actin dysregulation, as local perturbations can propagate across multiple structural and signaling domains [12].

MOLECULAR REGULATORS GOVERNING ACTIN CYTOSKELETON DYNAMICS

The dynamic behavior of the actin cytoskeleton is orchestrated by an extensive network of regulatory proteins that

Table 1: Major Actin Cytoskeletal Structures and Their Functional Roles.

Actin Structure	Predominant Organization	Key Regulatory Proteins	Principal Cellular Functions
Cortical actin network	Dense, mesh-like	Arp2/3, cofilin, profilin	Cell shape maintenance, membrane tension
Stress fibers	Bundled, contractile	Formins, myosin II, α-actinin	Force generation, mechanotransduction
Lamellipodia	Branched network	Arp2/3, WAVE complex	Cell migration, leading-edge protrusion
Filopodia	Parallel bundles	Formins, fascin	Environmental sensing, guidance
Contractile ring	Circumferential bundle	Formins, myosin II	Cytokinesis

collectively control actin polymerization, depolymerization, spatial organization, and mechanical output. These regulators function in a highly coordinated manner to ensure that actin remodeling is precisely matched to cellular demands. Rather than acting as isolated factors, actin regulators operate within interconnected molecular circuits, allowing rapid adaptation to biochemical and biomechanical signals.

Central to act in regulation is the control of monomer availability. Actin monomers are sequestered, recycled, and delivered to sites of filament growth through the actions of specific actin-binding proteins. Profilin plays a critical role in maintaining a pool of polymerization-competent ATP–actin monomers while simultaneously inhibiting spontaneous nucleation. By facilitating the exchange of ADP for ATP on G-actin and delivering monomers to barbed ends, profilin promotes controlled filament elongation in response to upstream signals [13].

In contrast, thymosin β4 acts as a monomer-sequestering protein, binding G-actin and preventing its incorporation into filaments. The balance between profilin and thymosin β4 activities determines the size and availability of the actin monomer pool, thereby exerting global control over cytoskeletal dynamics. Disruption of this balance has been linked to altered cell motility, impaired wound healing, and pathological tissue remodeling [14].

Filament nucleation represents another critical regulatory checkpoint. The Arp2/3 complex is the primary mediator of branched actin network formation, a structure essential for membrane protrusion and cell migration. Activation of Arp2/3 requires nucleation-promoting factors such as WASP and WAVE proteins, which integrate signals from small GTPases, phosphoinositides, and kinases [15-17]. The spatial restriction of Arp2/3 activity ensures that branched networks are generated selectively at the leading edge of migrating cells or at sites of endocytosis.

Formin proteins constitute a second major class of actin nucleators and are responsible for the assembly of long, unbranched filaments. Unlike Arp2/3, formins remain processively associated with the growing barbed end, protecting it from capping proteins and enabling sustained filament elongation. This activity is particularly important for the formation of stress fibers, filopodia, and the contractile ring during cytokinesis [18,19]. Mutations or dysregulation of formins have been implicated in developmental disorders, cardiomyopathies, and cancer progression [20].

Actin filament turnover is driven primarily by severing and depolymerizing proteins, among which cofilin is the most extensively studied. Cofilin binds preferentially to ADP-actin regions within filaments, inducing conformational changes that weaken inter-subunit interactions and promote filament severing. This activity generates new filament ends, accelerating actin turnover and enabling rapid cytoskeletal remodeling [21,22]. Cofilin activity is tightly regulated by phosphorylation, pH, and phosphoinositide binding, reflecting its central importance in maintaining cytoskeletal homeostasis.

Crosslinking proteins such as α-actinin, filamin, and fascin further modulate actin architecture by organizing filaments into higher-order structures. These proteins determine filament spacing, bundle stiffness, and network elasticity, thereby influencing the mechanical properties of cells. Changes in crosslinker expression or function can profoundly alter cell mechanics and have been associated with diseases characterized by altered tissue stiffness and mechanosensitivity [23].

Motor proteins, particularly myosin II, introduce contractile forces into actin networks. Myosin-driven sliding of actin filaments underlies cellular processes such as migration, adhesion maturation, and cytokinesis. The coordination between actin polymerization and myosin contractility enables cells to generate force while maintaining dynamic flexibility. Dysregulation of this balance contributes to pathological states including fibrosis, hypertension, and tumor invasion [16].

INTEGRATION OF ACTIN DYNAMICS WITH CELLULAR SIGNALING PATHWAYS

Actin cytoskeleton remodeling is inseparably linked to intracellular signaling networks that translate extracellular cues into mechanical and structural responses. Small Rho family GTPases, including RhoA, Rac1, and Cdc42, function

as master regulators of actin organization. These molecular switches cycle between active and inactive states in response to receptor activation, thereby directing distinct actin assembly programs [24].

RhoA signaling promotes the formation of stress fibers and focal adhesions through activation of formins and myosin II. In contrast, Rac1 primarily drives lamellipodia formation by stimulating Arp2/3-mediated branching, while Cdc42 regulates filopodia assembly and cell polarity [18,19]. The spatial and temporal coordination of these GTPases enables cells to adopt complex morphologies and directional behaviors.

Downstream of Rho GTPases, multiple kinase cascades further refine actin regulation. Rho-associated protein kinases (ROCKs) modulate actomyosin contractility by phosphorylating myosin light chains and inhibiting myosin phosphatase activity. Meanwhile, LIM kinases regulate cofilin activity through phosphorylation, linking upstream signaling to filament turnover rates [25].

Phosphoinositide signaling provides an additional layer of regulation by modulating the localization and activity of actin-binding proteins at the plasma membrane. Phosphatidylinositol 4,5-bisphosphate serves as a key lipid regulator, binding to numerous ABPs and influencing actin assembly at membrane interfaces. Alterations in phosphoinositide metabolism have been linked to defects in membrane trafficking, cell migration, and neuronal function [26].

Calcium signaling also intersects with actin regulation through calcium-sensitive proteins such as gelsolin and calmodulin-dependent kinases. These pathways enable rapid cytoskeletal responses to changes in intracellular calcium levels, particularly in excitable cells and muscle tissue (Table 2) [27].

ACTIN CYTOSKELETON AS A MECHANOSENSITIVE SYSTEM

Beyond its biochemical regulation, the actin cytoskeleton functions as a primary mediator of cellular mechanosensing and mechanotransduction. Cells continuously experience mechanical forces from their environment, including shear stress, tension, and compression. Actin networks respond to these forces by reorganizing their architecture and altering signaling outputs.

Actin filaments and associated proteins form direct physical connections between the extracellular matrix and intracellular signaling hubs through adhesion complexes. These structures enable cells to sense substrate stiffness and adjust their behavior accordingly. Changes in actin tension influence gene expression, cell differentiation, and survival, underscoring the cytoskeleton's role as a mechanochemical integrator [25–27].

Mechanical stress can also modulate actin dynamics by altering filament stability and regulator binding. This bidirectional relationship between mechanics and biochemistry amplifies the consequences of actin dysregulation, particularly in diseases characterized by abnormal tissue mechanics such as cancer and fibrosis.

PATHOPHYSIOLOGICAL CONSEQUENCES OF ACTIN CYTOSKELETON DYSREGULATION

Precise regulation of the actin cytoskeleton is indispensable for cellular homeostasis, tissue organization, and organismal development. Perturbations in actin dynamics—whether arising from genetic mutations, aberrant signaling, or environmental stress—can disrupt fundamental cellular processes and contribute directly to disease pathogenesis. Increasing evidence indicates that actin dysfunction is not merely a secondary consequence of disease but often represents a primary molecular driver that initiates and sustains pathological states.

Because actin networks integrate biochemical signaling, mechanical force generation, and spatial organization, their dysregulation produces pleiotropic effects that propagate across multiple cellular systems. These effects manifest differently depending on cell type, tissue context, and the nature of the underlying molecular defect, yet common mechanistic themes can be identified across diverse disease categories.

Table 2: Principal Actin-Regulatory Proteins and Their Molecular Functions.

Regulatory Protein	Primary Function	Mode of Action	Disease Associations
Profilin	Monomer regulation	Promotes ATP–actin incorporation	Cancer, cardiovascular disease
Thymosin β4	Monomer sequestration	Prevents spontaneous polymerization	Impaired tissue repair
Arp2/3 complex	Branched nucleation	Generates dendritic actin networks	Immunodeficiency, cancer
Formins	Linear nucleation	Processive barbed-end elongation	Developmental disorders
Cofilin	Filament turnover	Severing and depolymerization	Neurodegeneration
Myosin II	Contractility	Actin filament sliding	Fibrosis, hypertension

Review Article

ACTIN CYTOSKELETON ALTERATIONS IN CANCER PROGRESSION AND METASTASIS

One of the most extensively studied pathological contexts of actin dysregulation is cancer. Tumor progression and metastasis depend critically on the ability of cancer cells to remodel their cytoskeleton, detach from primary tissues, migrate through extracellular matrices, and invade distant organs. These processes require coordinated actin polymerization, adhesion turnover, and force generation, all of which are frequently altered in malignant cells.

Cancer cells often exhibit upregulated activity of actin nucleators and polymerization factors, leading to enhanced formation of lamellipodia, invadopodia, and other protrusive structures. Overexpression or hyperactivation of Arp2/3 complex components and formins has been correlated with increased invasive potential and poor clinical prognosis in multiple cancer types [28–30]. Similarly, deregulated cofilin activity promotes excessive actin turnover, enabling rapid cytoskeletal remodeling that supports directional migration and invasion.

The actin cytoskeleton also plays a central role in epithelial–mesenchymal transition (EMT), a process through which epithelial cells acquire mesenchymal characteristics and increased motility. During EMT, extensive reorganization of actin structures accompanies changes in cell–cell adhesion and polarity. These cytoskeletal alterations are driven by oncogenic signaling pathways that converge on Rho GTPases and downstream actin regulators [31].

Beyond migration, actin dynamics influence cancer cell proliferation and survival. Actin-mediated mechanotransduction regulates transcriptional programs through pathways such as YAP/TAZ, linking cytoskeletal tension to gene expression. Dysregulated actin mechanics can therefore alter cell cycle control and resistance to apoptosis, further promoting tumor growth [32,33].

NEUROLOGICAL DISORDERS LINKED TO ACTIN DYSREGULATION

The nervous system is particularly sensitive to alterations in actin dynamics due to the central role of actin in neuronal morphology, synaptic plasticity, and intracellular transport. Actin filaments are essential components of growth cones, dendritic spines, and synaptic terminals, where they regulate axon guidance, synapse formation, and activity-dependent remodeling.

Mutations in genes encoding actin-regulatory proteins have been implicated in a wide range of neurodevelopmental and neurodegenerative disorders. Defects in Arp2/3 complex function and its regulatory factors disrupt dendritic spine morphology, leading to impaired synaptic connectivity and cognitive dysfunction [34]. Similarly, altered cofilin regulation has been associated with abnormal actin aggregation in neurodegenerative diseases, contributing to synaptic loss and neuronal death [35].

In Alzheimer's disease and related tauopathies, aberrant actin–cofilin rod formation has been observed in affected neurons. These structures interfere with axonal transport and synaptic function, exacerbating neuronal dysfunction and degeneration [36]. Actin dysregulation has also been linked to Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis, highlighting its broad relevance in neurological pathology.

CARDIOVASCULAR AND MUSCULAR DISORDERS INVOLVING ACTIN NETWORKS

In striated and smooth muscle tissues, actin filaments form the structural backbone of the contractile apparatus. Precise organization and regulation of actin–myosin interactions are required for effective force generation and coordinated contraction. Disruption of actin filament assembly or stability can therefore have profound consequences for cardiovascular and muscular function.

Inherited mutations in actin isoforms or actin-associated proteins have been linked to cardiomyopathies and congenital myopathies. These mutations often impair filament stability or interaction with myosin, leading to weakened contractile force and progressive tissue dysfunction [37,38]. In vascular smooth muscle cells, altered actin dynamics contribute to abnormal contractility and vascular remodeling, which are hallmarks of hypertension and atherosclerosis.

Actin-mediated mechanotransduction also plays a critical role in cardiac remodeling in response to mechanical stress. Dysregulated actin signaling can lead to maladaptive hypertrophy and heart failure by altering cellular stiffness and gene expression profiles [39].

IMMUNE SYSTEM DYSFUNCTIONS AND ACTIN REGULATION

Immune cell function relies heavily on rapid and precise actin remodeling. Processes such as immune synapse formation, phagocytosis, chemotaxis, and antigen presentation all depend on dynamic actin reorganization. Consequently, defects in actin regulatory pathways can severely compromise immune responses.

Primary immunodeficiency disorders have been linked to mutations in actin-regulatory proteins such as WASP, which is essential for Arp2/3-mediated actin assembly in hematopoietic cells. Loss of WASP function results in impaired immune cell migration, defective signaling, and increased susceptibility to infections [40].

Actin dysregulation also contributes to inflammatory and autoimmune diseases. Aberrant cytoskeletal remodeling can alter immune cell activation thresholds and cytokine production (Table 3), promoting chronic inflammation and tissue damage [41].

SYSTEMS-LEVEL CONSEQUENCES OF ACTIN DYSREGULATION

At the systems level, actin cytoskeleton dysfunction disrupts the integration of mechanical, biochemical, and transcriptional networks. Because actin structures influence nuclear architecture and chromatin organization, alterations in cytoskeletal tension can lead to widespread changes in gene expression. This coupling between cytoskeletal state and transcriptional regulation amplifies the pathological impact of actin defects beyond immediate structural abnormalities [42].

Furthermore, actin dysregulation often triggers compensatory responses that may initially preserve function but ultimately exacerbate disease progression. Chronic activation of stress pathways, altered metabolic states, and sustained inflammatory signaling are common secondary consequences of cytoskeletal imbalance.

THERAPEUTIC TARGETING OF THE ACTIN CYTOSKELETON

Given the central role of the actin cytoskeleton in disease pathogenesis, considerable effort has been directed toward developing therapeutic strategies that modulate actin dynamics. However, because actin is essential for virtually all eukaryotic cells, therapeutic intervention must strike a careful balance between correcting pathological dysregulation and preserving physiological function. As a result, most current approaches focus on targeting upstream regulators, signaling pathways, or context-specific actin remodeling events rather than actin filaments themselves.

Early pharmacological agents such as cytochalasins, latrunculins, and phalloidin derivatives demonstrated the feasibility of manipulating actin polymerization but were limited by high toxicity and lack of specificity. These compounds disrupt fundamental cellular processes, making them unsuitable for systemic therapeutic use [43]. Nevertheless, they provided foundational insights into actin biology and continue to serve as important experimental tools.

More recent strategies aim to modulate actin dynamics indirectly by targeting regulatory proteins and signaling nodes. In cancer, inhibitors of Rho GTPases, ROCK kinases, and downstream effectors have shown promise in reducing tumor cell invasion and metastasis. By attenuating actomyosin contractility and protrusive activity, these agents can impair malignant cell motility without completely abolishing actin function [44,45].

In neurological disorders, therapeutic interest has focused on stabilizing synaptic actin structures to preserve neuronal connectivity. Small molecules that modulate cofilin activity or enhance actin filament stability have been explored as potential interventions for neurodegenerative diseases characterized by synaptic loss [46]. Although clinical translation remains limited, these approaches underscore the therapeutic potential of fine-tuning actin dynamics in a tissue-specific manner.

ACTIN MODULATION IN CARDIOVASCULAR AND IMMUNE THERAPIES

In cardiovascular disease, targeting actin-associated signaling pathways offers a means to influence cardiac remodeling and vascular function. Modulators of mechanotransduction pathways, including those that regulate cytoskeletal tension and focal adhesion signaling, have been investigated for their ability to prevent maladaptive hypertrophy and fibrosis [47]. These interventions aim to normalize actin-mediated force transmission rather than directly altering filament assembly.

Similarly, immune-related therapies increasingly recognize the importance of actin regulation in immune cell activation and migration. In primary immunodeficiencies linked to actin regulatory defects, gene therapy approaches have

Table 3: Actin Cytoskeleton Dysregulation in Human Diseases.

Disease Category	Key Actin Defect	Affected Processes	Representative Outcomes
Cancer	Enhanced actin polymerization	Migration, invasion	Metastasis
Neurodegeneration	Actin aggregation	Synaptic plasticity	Cognitive decline
Cardiomyopathy	Filament instability	Muscle contraction	Heart failure
Immunodeficiency	Impaired nucleation	Immune cell motility	Recurrent infections
Fibrosis	Excessive actomyosin tension	ECM remodeling	Tissue stiffening

demonstrated encouraging results. Restoration of functional actin regulators can rescue immune cell function and improve clinical outcomes, highlighting the feasibility of correcting cytoskeletal defects at their genetic origin [48].

In autoimmune and inflammatory conditions, modulating actin-dependent signaling pathways may help recalibrate immune responses. By influencing immune synapse formation and cytoskeletal organization, targeted therapies can potentially reduce pathological inflammation while preserving host defense mechanisms [49].

EMERGING MOLECULAR AND TECHNOLOGICAL APPROACHES

Advances in molecular biology and bioengineering are expanding the therapeutic landscape for actin-related diseases. RNA-based therapies, including siRNA and antisense oligonucleotides, offer the possibility of selectively downregulating aberrant actin regulators in specific tissues. These approaches provide high specificity but require efficient delivery systems and careful control to avoid off-target effects [50].

Genome-editing technologies such as CRISPR-Cas systems present another promising avenue for correcting inherited actin-related disorders. Precise editing of pathogenic mutations in actin genes or regulatory factors has shown success in preclinical models, although ethical, safety, and delivery challenges must be addressed before widespread clinical application [51].

In parallel, mechanobiology-driven therapeutic strategies are gaining attention (Table 4). By manipulating the physical properties of the cellular microenvironment—such as substrate stiffness or extracellular matrix composition—it is possible to indirectly influence actin organization and cellular behavior. These approaches are particularly relevant in fibrosis and cancer, where altered tissue mechanics play a central role in disease progression [52].

TRANSLATIONAL CHALLENGES AND LIMITATIONS

Despite significant progress, several challenges hinder the clinical translation of actin-targeted therapies. The ubiquitous expression and essential nature of actin impose inherent constraints on systemic interventions. Even modest perturbations of actin dynamics can have widespread consequences, underscoring the need for highly selective and context-dependent strategies.

Another major limitation lies in the complexity and redundancy of actin regulatory networks. Multiple pathways often converge on the same cytoskeletal outcomes, allowing cells to compensate for the inhibition of individual components. This redundancy can reduce therapeutic efficacy and necessitates combination approaches or targeting of central regulatory hubs.

Furthermore, differences in actin organization across cell types and tissues complicate the extrapolation of findings from experimental models to human disease. Improved in vivo models and patient-derived systems are essential for accurately assessing therapeutic potential and safety.

FUTURE DIRECTIONS AND CONCLUDING PERSPECTIVES

Future research on the actin cytoskeleton is likely to emphasize integrative and systems-level approaches. Advances in imaging, single-cell analysis, and computational modeling are enabling more comprehensive mapping of actin dynamics in physiological and pathological contexts. These tools will facilitate the identification of disease-specific cytoskeletal signatures and novel therapeutic targets.

The growing recognition of actin as a central coordinator of mechanical and biochemical signaling underscores its importance beyond structural support. By linking cellular architecture to gene regulation, metabolism, and signaling networks, the actin cytoskeleton emerges as a unifying framework for understanding complex disease phenotypes.

Ultimately, successful therapeutic exploitation of actin regulation will depend on precision—targeting the right pathway, in the right cell type, at the right time. Continued interdisciplinary collaboration among cell biologists, clinicians, and bioengineers will be essential to translate fundamental insights into effective clinical interventions.

Table 4: Therapeutic Strategies Targeting Actin Cytoskeleton Dysregulation.

Therapeutic Approach	Primary Target	Disease Context	Key Challenges
Rho/ROCK inhibitors	Actomyosin signaling	Cancer, fibrosis	Off-target effects
Cofilin modulators	Actin turnover	Neurodegeneration	Delivery to CNS
Gene therapy	Actin regulators	Immunodeficiency	Long-term safety
RNA-based therapies	Regulatory transcripts	Cancer, inflammation	Stability, targeting
Mechanobiological interventions	ECM–actin coupling	Fibrosis, oncology	Clinical translation

CONCLUSION

The actin cytoskeleton is a highly dynamic and tightly regulated cellular system that extends far beyond structural support, playing a central role in cell signaling, mechanics, migration, and gene regulation. Dysregulation of actin dynamics and its associated regulatory networks contributes to the pathogenesis of a wide range of human disorders, including neurodegenerative diseases, cancer, cardiovascular abnormalities, and immune dysfunctions. Rather than arising from isolated defects, these conditions reflect complex, context-dependent disruptions in actin-associated signaling and mechanotransduction pathways. Although direct therapeutic targeting of actin remains challenging due to its essential and ubiquitous nature, growing insights into actin regulatory mechanisms offer promising opportunities for indirect, pathway-specific interventions. Continued integration of molecular, biomechanical, and translational research will be essential for harnessing actin cytoskeleton biology in the development of effective and targeted disease therapies.

REFERENCES

1. Pollard, T. D., Cooper, J. A. (2009). Actin, a central player in cell shape and movement. Science, 326(5957), 1208–1212.
2. Blanchoin, L., Boujemaa-Paterski, R., Sykes, C., Plastino, J. (2014). Actin dynamics, architecture, and mechanics in cell motility. Physiological Reviews, 94(1), 235–263.
3. Dominguez, R., Holmes, K. C. (2011). Actin structure and function. Annual Review of Biophysics, 40, 169–186.
4. Chesarone, M. A., DuPage, A. G., Goode, B. L. (2010). Unleashing formins to remodel the actin and microtubule cytoskeletons. Nature Reviews Molecular Cell Biology, 11(1), 62–74.
5. Campellone, K. G., Welch, M. D. (2010). A nucleator arms race: Cellular control of actin assembly. Nature Reviews Molecular Cell Biology, 11(4), 237–251.
6. Rottner, K., Faix, J., Bogdan, S., Linder, S., Kerkhoff, E. (2017). Actin assembly mechanisms at a glance. Journal of Cell Science, 130(20), 3427–3435.
7. Le Clainche, C., Carlier, M. F. (2008). Regulation of actin assembly associated with protrusion and adhesion in cell migration. Physiological Reviews, 88(2), 489–513.
8. Bugyi, B., Carlier, M. F. (2010). Control of actin filament treadmilling in cell motility. Annual Review of Biophysics, 39, 449–470.
9. Insall, R. H., Machesky, L. M. (2009). Actin dynamics at the leading edge: From simple machinery to complex networks. Developmental Cell, 17(3), 310–322.
10. Ridley, A. J., Schwartz, M. A., Burridge, K., Firtel, R. A., Ginsberg, M. H., Borisy, G., et al. (2003). Cell migration: Integrating signals from front to back. Science, 302(5651), 1704–1709.
11. Hall, A. (2012). Rho family GTPases. Biochemical Society Transactions, 40(6), 1378–1382.
12. Sit, S. T., Manser, E. (2011). Rho GTPases and their role in organizing the actin cytoskeleton. Journal of Cell Science, 124(5), 679–683.
13. Heasman, S. J., Ridley, A. J. (2008). Mammalian Rho GTPases: New insights into their functions from in vivo studies. Nature Reviews Molecular Cell Biology, 9(9), 690–701.
14. Jaffe, A. B., Hall, A. (2005). Rho GTPases: Biochemistry and biology. Annual Review of Cell and Developmental Biology, 21, 247–269.
15. Takenawa, T., Suetsugu, S. (2007). The WASP–WAVE protein network: Connecting the membrane to the actin cytoskeleton. Nature Reviews Molecular Cell Biology, 8(1), 37–48.
16. Ramesh, N., Anton, I. M., Hartwig, J. H., Geha, R. S. (1997). WIP, a protein associated with Wiskott–Aldrich syndrome protein, induces actin polymerization and redistribution in lymphoid cells. Proceedings of the National Academy of Sciences USA, 94(26), 14671–14676.
17. Thrasher, A. J., Burns, S. O. (2010). WASP: A key immunological multitasker. Nature Reviews Immunology, 10(3), 182–192.
18. Feng, Y., Walsh, C. A. (2004). The many faces of filamin: A versatile molecular scaffold for cell motility and signalling. Nature Cell Biology, 6(11), 1034–1038.
19. Stossel, T. P., Condeelis, J., Cooley, L., Hartwig, J. H., Noegel, A., Schleicher, M., et al. (2001). Filamins as integrators of cell mechanics and signalling. Nature Reviews Molecular Cell Biology, 2(2), 138–145.
20. Pollard, T. D., Borisy, G. G. (2003). Cellular motility driven by assembly and disassembly of actin filaments. Cell, 112(4), 453–465.
21. Fletcher, D. A., Mullins, R. D. (2010). Cell mechanics and the cytoskeleton. Nature, 463(7280), 485–492.
22. Jaalouk, D. E., Lammerding, J. (2009). Mechanotransduction gone awry. Nature Reviews Molecular Cell Biology, 10(1), 63–73.
23. Burridge, K., Wittchen, E. S. (2013). The tension mounts: Stress fibers as force-generating mechanotransducers. Journal of Cell Biology, 200(1), 9–19.
24. Olson, M. F., Sahai, E. (2009). The actin cytoskeleton in cancer cell motility. Clinical and Experimental Metastasis, 26(4), 273–287.
25. Yilmaz, M., Christofori, G. (2009). EMT, the cytoskeleton, and cancer cell invasion. Cancer Metastasis Reviews, 28(1–2), 15–33.
26. Machesky, L. M., Li, A. (2010). Invasion and metastasis circuits in cancer: Actin cytoskeleton contributions. Journal of Cell Science, 123(22), 3691–3697.
27. Lambrechts, A., Van Troys, M., Ampe, C. (2004). The actin cytoskeleton in normal and pathological cell motility. International Journal of Biochemistry and Cell Biology, 36(10), 1890–1909.

28. Hotulainen, P., Hoogenraad, C. C. (2010). Actin in dendritic spines: Connecting dynamics to function. Journal of Cell Biology, 189(4), 619–629.

29. Cingolani, L. A., Goda, Y. (2008). Actin in action: The interplay between the actin cytoskeleton and synaptic efficacy. Nature Reviews Neuroscience, 9(5), 344–356.

30. Bamburg, J. R., Bernstein, B. W. (2010). Roles of ADF/cofilin in actin dynamics and disease. Trends in Cell Biology, 20(4), 187–195.

31. Bernstein, B. W., Bamburg, J. R. (2010). ADF/cofilin: A functional node in cell biology. Trends in Cell Biology, 20(4), 187–195.

32. Pak, C. W., Flynn, K. C., Bamburg, J. R. (2008). Actin-binding proteins take the reins in growth cones. Nature Reviews Neuroscience, 9(2), 136–147.

33. Vicente-Manzanares, M., Ma, X., Adelstein, R. S., Horwitz, A. R. (2009). Non-muscle myosin II takes centre stage in cell adhesion and migration. Nature Reviews Molecular Cell Biology, 10(11), 778–790.

34. Murrell, M., Oakes, P. W., Lenz, M., Gardel, M. L. (2015). Forcing cells into shape: The mechanics of actomyosin contractility. Nature Reviews Molecular Cell Biology, 16(8), 486–498.

35. Tojkander, S., Gateva, G., Lappalainen, P. (2012). Actin stress fibers: Assembly, dynamics, and biological roles. Journal of Cell Science, 125(8), 1855–1864.

36. Spudich, J. A. (2014). Hypertrophic and dilated cardiomyopathy: Four decades of basic research on muscle contractility. Circulation Research, 114(4), 751–763.

37. Vang, S., Corydon, T. J., Borglum, A. D., Scott, M. D. (2010). Actin mutations in human disease. Human Mutation, 31(1), 10–19.

38. Clark, A. R., Machesky, L. M. (2016). Moving with purpose: Cancer cell migration in complex microenvironments. Nature Reviews Cancer, 16(12), 825–835.

39. Seetharaman, S., Etienne-Manneville, S. (2020). Actin-based cell polarity in development and disease. Journal of Cell Biology, 219(6), e201908150.

40. Peckham, M. (2011). Engineering the actin cytoskeleton: From nanomachines to therapeutic targets. Biochemical Society Transactions, 39(5), 1140–1145.

41. Stradal, T. E. B., Schelhaas, M. (2018). Actin dynamics in host–pathogen interactions. Annual Review of Cell and Developmental Biology, 34, 65–86.

42. Gouin, E., Welch, M. D., Cossart, P. (2005). Actin-based motility of intracellular pathogens. Current Opinion in Microbiology, 8(1), 35–45.

43. Pizarro-Cerda, J., Cossart, P. (2006). Subversion of cellular functions by Listeria monocytogenes. Journal of Pathology, 208(2), 215–223.

44. Lappalainen, P. (2016). Actin-binding proteins: The long road to understanding the dynamic cytoskeleton. Molecular Biology of the Cell, 27(16), 2519–2522.

45. Pollitt, A. Y., Insall, R. H. (2009). WASP and SCAR/WAVE proteins: The drivers of actin assembly. Journal of Cell Science, 122(15), 2575–2578.

46. Ménasché, G., Fischer, A., de Saint Basile, G. (2009). WASP-related immunodeficiency. Current Opinion in Immunology, 21(5), 595–600.

47. Mullins, R. D., Heuser, J. A., Pollard, T. D. (1998). The interaction of Arp2/3 complex with actin. Proceedings of the National Academy of Sciences USA, 95(11), 6181–6186.

48. Goley, E. D., Welch, M. D. (2006). The ARP2/3 complex: An actin nucleator comes of age. Nature Reviews Molecular Cell Biology, 7(10), 713–726.

49. Rotty, J. D., Wu, C., Bear, J. E. (2013). New insights into the regulation and cellular functions of the ARP2/3 complex. Nature Reviews Molecular Cell Biology, 14(1), 7–12.

50. Schaks, M., Giannone, G., Rottner, K. (2019). Actin dynamics in cell migration. Essays in Biochemistry, 63(5), 483–495.

51. Svitkina, T. (2018). The actin cytoskeleton and actin-based motility. Cold Spring Harbor Perspectives in Biology, 10(1), a018267.

52. Lodish, H., Berk, A., Kaiser, C. A., Krieger, M., Bretscher, A., Ploegh, H., et al. (2021). Molecular Cell Biology (9th ed.). New York, USA: W.H. Freeman and Company.

Citation: Gerlach B (2025) Regulatory Complexity of the Actin Cytoskeleton and Its Contribution to Human Disorders. Appl Cell Biol, 13(3), [65-73]