Beyond cytoskeletal dynamics: Actin-binding proteins as multifaceted regulators in tumour progression and therapy (Review)

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Abstract. Actin-binding proteins (ABPs) have long been recognized as core modulators that control actin filament assembly and disassembly inside eukaryotic cells. Scientific focus has heavily centered on cytoskeleton remodelling associated with tumour cell migration, while overlooking the non-structural regulatory effects of ABPs across oncogenic signalling, epigenetic transcription and drug response. The dual functional phenotypes of classical ABPs, including cofilin, profilin, α-actinin and drebrin, across diverse malignant tumours have been comprehensively investigated, further examining how post-translational modification and subcellular localization switch their oncogenic or tumour-suppressive effects. Notably, the present review highlighted non-canonical ABP signalling crosstalk with the Hippo, Ras homologous (Rho) guanosine triphosphatase (GTPase) and phoshoinositide 3-kinase (PI3K)/protein kinase B (Akt) axes and stratified all ABP-targeted interventions by preclinical maturity: Small-molecule compounds, monoclonal antibodies, RNA interference and clustered regularly short palindromic repeats (CRISPR) gene editing. Unresolved translational barriers, including poor target selectivity, intracellular delivery obstacles and protein functional redundancy were also summarized. Current evidence indicated that ABPs cannot be simply defined as pro-tumour or anti-tumour factors; their biological output strictly depends on tumour subtype, disease stage and the intracellular microenvironment. Addressing the druggability defects of ABP family proteins may provide novel opportunities for developing metastasis-specific anti-cancer therapeutic regimens. Further mechanistic validation of ABP-centred signalling networks will facilitate the future development of isoform-selective anti-metastatic therapeutic strategies for clinical oncology.

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1. Introduction

The actin cytoskeleton constitutes a core dynamic cellular framework that sustains cellular morphology, mediates intracellular cargo transport and drives directional cell motility. Actin-binding proteins (ABPs) act as central modulators governing all actin filament remodelling events, including monomer polymerization, filament disassembly and spatial network arrangement (1). Historically, researchers have defined ABPs primarily as simple structural regulators of cytoskeleton turnover, yet accumulating experimental evidence has proven that their biological effects extend to a much broader range of cellular events. Independent of actin structural rearrangement, ABPs participate in multiple intracellular signalling cascades, control gene transcription programs and reprogram cellular metabolic homeostasis (2). More importantly, extensive clinical and preclinical data indicates that dysregulated ABP activity reshapes core malignant phenotypes, driving tumour growth, distant metastasis and variable drug sensitivity through non-structural regulatory pathways (3,4).

The ABP superfamily contains dozens of distinct subtypes with unique actin-binding domains, variable binding affinities and separate catalytic regulatory modes. Profilin accelerates the loading of G-actin monomers onto elongating filament

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ends, whereas activated cofilin cleaves aged F-actin to recycle free actin monomers. Gelsolin executes calcium-dependent filament severing to alter the filament length, and α-actinin crosslinks parallel actin strands to construct stable stress fibre networks. Tropomyosin stabilizes filament structures and coordinates actomyosin contractile movement. In addition to these well-studied canonical members, additional functional subtypes, such as drebrin, filamin and tropomodulin, together constitute a multilayered regulatory system that finely tunes the dynamic balance of actin (5). The coordinated functional output of these proteins precisely controls cytoskeleton remodelling and ultimately affects all actin-dependent cellular behaviours.

Mounting clinical specimen analyses and cell functional assays validate the close association between abnormal ABP expression and malignant progression across diverse human solid tumours. Distinct ABP expression shifts are consistently associated with tumour advancement and unfavourable patient survival outcomes. For example, elevated cofilin protein abundance was shown to be associated with stronger invasive and migratory capacities in lung, gastric and breast tumour cells; conversely, downregulated α-actinin expression was found to serve as an independent marker for predicting worse overall survival in patients with different types of breast cancer (6). Such divergent phenotypic effects indicate that ABPs exert context-dependent dual roles (either oncogenic or tumour-suppressive), greatly complicating the mechanistic landscape linking actin regulators to malignant transformation.

The regulatory connection between ABPs and tumour development cannot be simplified into a single linear model. A subset of ABPs increases tumour cell migration and extracellular matrix invasion by reconstructing membrane-protrusive structures and rearranging cytoplasmic actin networks. By contrast, certain ABP subtypes suppress oncogenic signal transduction or trigger tumour cell apoptotic cascades to restrain malignant progression. Furthermore, altered ABP expression reshapes tumour cell responses to chemotherapy, targeted agents and immunotherapy, either by increasing treatment efficacy or inducing therapeutic resistance (7,8). Given these dual functional characteristics, comprehensive reviews are urgently needed to clarify the conventional understanding that solely restricts ABPs to cytoskeleton remodelling and summarize their wide-ranging non-structural regulatory functions in cancer.

Recent mechanistic research has revealed complicated cross-talk between ABPs and core oncogenic signalling axes. A study in 2025 hepatocellular carcinoma was recently reported to demonstrate that the drebrin protein binds and dissociates the neurofibromin 2 (NF2)-large tumor suppressor kinase (LATS) kinase complex, thus suppressing Hippo tumour-suppressive signalling and accelerating malignant hepatocellular transformation (9). Notably, these mechanistic findings are derived from a single primary investigation; independent replication data are currently lacking. Additional research has revealed that 14-3-3 scaffold proteins interact with drebrin to modify its subcellular localization and catalytic activity; this regulatory axis, originally identified during neural development, also drives oncogenic transformation in epithelial tumour cells (10). These discoveries demonstrate that ABPs function as key signal transduction hubs independent of cytoskeleton remodelling, linking extracellular stimuli to intracellular kinase cascades and downstream transcriptional programs.

As researchers continue to clarify the multi-layered regulatory functions of ABPs in malignant tissues, targeting these proteins has gradually become a promising therapeutic strategy against metastatic tumours. ABPs lie at the core of tumour cell migratory and proliferative programs, making them attractive druggable targets for anti-cancer intervention. Nevertheless, major translational bottlenecks remain: Most ABPs carry essential physiological functions in normal epithelial and endothelial cells, and broad-spectrum inhibition may disrupt homeostatic actin dynamics and trigger systemic toxicity (11). At present, multiple intervention strategies, including small-molecule selective inhibitors, targeted monoclonal antibodies and gene silencing/editing tools, are undergoing continuous preclinical optimization, with several candidate compounds exhibiting moderate anti-tumour activity in cell and xenograft models (12).

The present narrative review comprehensively summarized current research advances concerning ABPs in tumour progression and translational therapy, with a core innovation focused on their non-canonical functions beyond cytoskeleton control. Their physiological homeostatic roles, pathological mechanisms supporting malignant transformation, multi-layered regulatory networks and translational therapeutic potential were comprehensively organized. By integrating original cutting-edge experimental data and cohort clinical evidence, this review addressed unresolved research contradictions in this field, clarified the complicated dual regulatory phenotypes of ABPs and proposed feasible research directions for subsequent basic mechanistic exploration and clinical translational verification.

The present narrative review aimed to summarize the non-cytoskeletal functions of ABPs in tumour progression, examine the context-dependent dual roles of ABPs, and evaluate preclinical therapeutic strategies targeting ABP family members (Fig. 1).

2. Literature search strategy

The present narrative review synthesized published evidence concerning actin-binding proteins in oncology. Literature retrieval was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com) and Web of Science (https://www.webofscience.com). The search time frame covered articles published between January 2010 and March 2025. The search terms combined the following keywords: ('actin-binding protein' OR cofilin OR drebrin OR profilin OR α-actinin) AND (cancer OR tumour OR metastasis OR targeted therapy). Boolean operators were applied to combine search strings. The inclusion criteria were peer-reviewed original articles and review papers published in English. The exclusion criteria included meeting abstracts, case reports, non-English publications, and papers without full-text availability. In total, ~280 bibliographic records were preliminarily retrieved. After title/abstract screening and full-text assessment, 36 representative references were selected for final synthesis. A PRISMA-compliant flow diagram was not generated because this was not a formal systematic review.

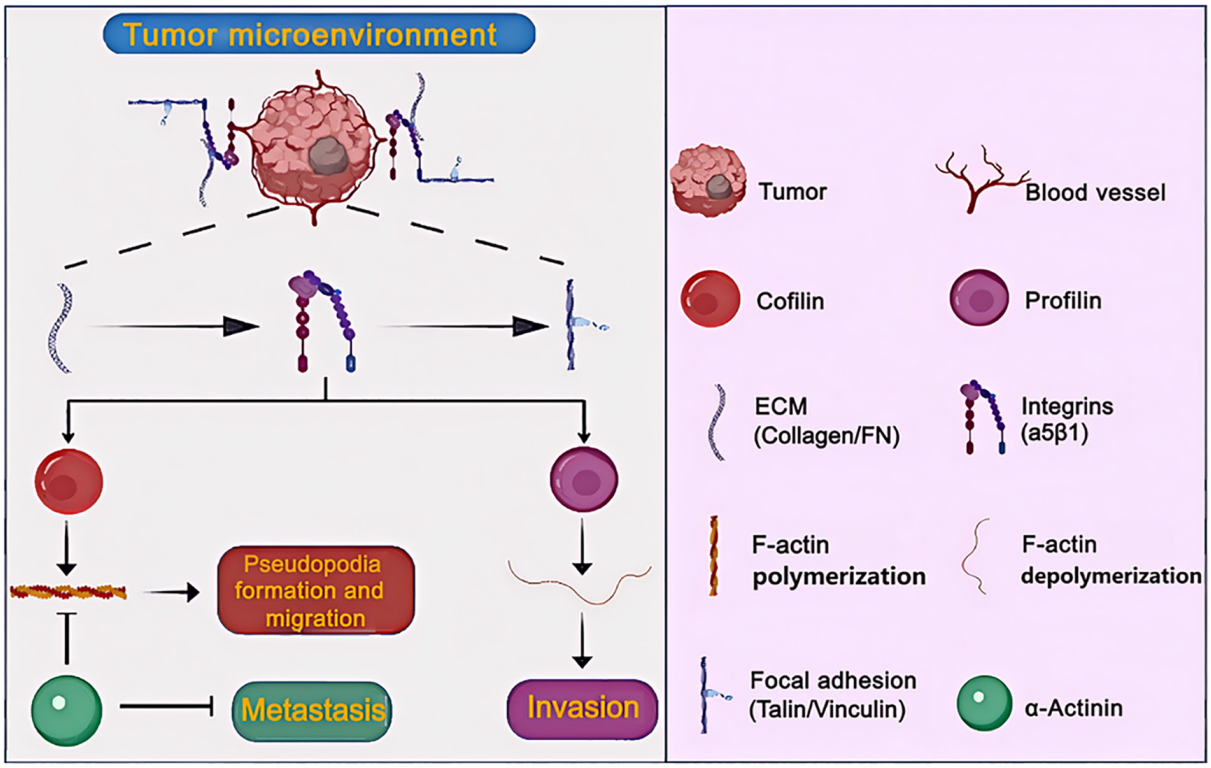


Figure 1. Functional roles and regulatory mechanisms of ABPs in tumour progression. This diagram visually summarizes the multi-dimensional regulatory effects of core ABPs (cofilin, profilin, and α-actinin) on typical malignant cell phenotypes, including cell migration, extracellular matrix invasion and uncontrolled proliferation. ABPs, actin-binding proteins.

3. Physiological functions of ABPs

ABPs constitute a heterogeneous protein superfamily capable of binding to actin monomers or filaments to modulate actin assembly, disassembly and spatial network arrangement. Their physiological bioactivities are far more extensive than merely sustaining cytoskeletal structural balance, covering multiple core biological events required to sustain normal cell operation and organismal homeostasis (13,14). Clarifying these native physiological functions provides a solid theoretical basis for understanding how abnormal ABP activity triggers pathological changes, especially the malignant transformation and therapeutic response variation observed in multiple tumour types.

The core physiological task of ABP members involves balancing actin filament assembly and disassembly cycles. Profilin, one of the most thoroughly characterized actin regulators, accelerates the loading of G-actin monomers onto growing filament ends to increase actin polymerization. This biochemical reaction supports the elongation of actin-rich protrusions at the leading edge of migrating cells, which generates lamellipodia and filopodia to drive forward cell movement. By contrast, activated cofilin breaks aged actin filaments and releases reusable actin monomers to support cytoskeleton remodelling. Gelsolin performs calcium-dependent filament cleavage to alter the length of filaments, thus controlling the pool of free actin monomers and the overall mechanical properties of cytoplasmic actin networks (15). The coordinated functional collaboration of these three proteins maintains a reversible actin turnover equilibrium, which underpins cell migration and all other actin-dependent biological behaviours.

Apart from tuning the actin polymerization balance, ABPs govern the spatial arrangement and mechanical stability of intracellular actin networks (7,13). α-Actinin crosslinks separate actin filaments to construct interconnected stress fibre networks, which endows cells with sufficient mechanical tolerance to withstand external tension; this function is particularly vital for muscle tissues and compact solid organ cells that are constantly under mechanical load (16). Tropomyosin binds along the sides of the actin filament to stabilize the conformation of the filament and coordinates with myosin motor proteins to produce an intracellular contractile force. The orderly spatial arrangement of the actin networks shaped by these ABPs guarantees intact cell morphology, smooth intracellular substance transport and effective resistance against extracellular mechanical stimulation (14).

ABPs also act as vital mediators of intracellular signal transmission and mechanical signal conversion. Multiple ABP subtypes, including α-actinin, can directly bind integrin transmembrane proteins and growth factor receptors, resulting in the construction of physical linkages between the extracellular matrix and cytoplasmic signalling cascades. This structural connection enables cells to perceive mechanical stimulation from the surrounding microenvironment and convert mechanical force into biochemical signalling events, a biological process defined as mechanotransduction (16). By transmitting such mechanical signals, ABPs modulate cell proliferation, differentiation and migratory capacity, and this regulatory mechanism is indispensable for tissues enduring persistent

mechanical stress, such as cardiovascular and musculoskeletal tissues.

The regulatory effects of ABPs on cell migration cannot be simply attributed to structural remodelling of actin. These proteins directly generate pushing and retracting forces that drive whole-cell translocation. At the front protrusive region of migrating cells, profilin and cofilin jointly adjust the rates of actin assembly and disassembly to form lamellipodia and filopodia that push the cell forward. At the trailing edge, α-actinin and gelsolin remodel local actin networks to shrink the cell tail and complete forward translocation. Such coordinated ABP activity supports multiple migration modes, including amoeboid movement, mesenchymal invasion and directional chemotactic movement guided by chemical gradients (17-19).

Beyond driving cell movement, ABPs participate in the assembly and dynamic turnover of cell-matrix adhesion structures termed focal adhesions. Profilin and cofilin remodel actin filaments at the cell leading edge to facilitate the formation of nascent adhesion complexes. Moreover, α-actinin and tropomyosin stabilize actin bundles within the cell body to promote maturation and persistent anchoring of existing focal adhesions (20). Dynamic coordination between ABP activity and focal adhesion assembly maintains stable cell attachment to the extracellular matrix and ensures sustained directional migration.

ABP biofunctions are not limited to cell migration and adhesion regulation; they also participate in the construction and maintenance of diverse intracellular membrane-bound organelles. Certain ABP subtypes organize specialized actin scaffolds surrounding the nuclear envelope to preserve nuclear structural integrity and normal nuclear physiological function (21). Other ABP members shape actin frameworks, supporting vesicle formation and transportation and mediating intracellular cargo trafficking and plasma membrane endocytosis processes (22). Such diverse physiological roles demonstrate that ABPs are indispensable molecular regulators that sustain overall cellular homeostasis.

The biological functions of ABPs extend beyond direct physical binding with actin filaments. Most ABP subtypes interact with other intracellular components, including lipid membranes, microtubule filaments and unrelated cytoskeletal proteins, forming a complex cross-regulatory network that coordinates distinct cellular biological events. For instance, several ABPs serve as molecular bridges that link the actin and microtubule cytoskeletons and enable signal communication between the two major filament systems (23). This inter-cytoskeleton cross-talk is critical for mitotic chromosome segregation, long-distance intracellular transport and stable cell shape maintenance. By connecting independent cellular functional modules, ABPs coordinate the regulation of multiple pathway biological activities (24,25).

4. Pathophysiological significance in tumour progression

Aberrant expression and dysfunction of actin-binding proteins are recognized as key drivers of malignant transformation and are capable of disrupting multiple core cancer hallmarks, including unlimited proliferation, anti-apoptosis, invasive migration and tumour angiogenesis. In contrast to merely reshaping actin filaments, dysregulated ABPs remodel intracellular signalling cascades, alter transcriptional programs and rewire metabolic patterns, and together, promote a malignant phenotype in normal cells (26). Such multi-dimensional regulatory capacity renders ABPs indispensable molecular mediators bridging homeostatic physiology and tumorigenesis.

Cell migration and distant metastasis are the leading causes of cancer-related death, and this lethal biological process largely relies on ABP-mediated cytoskeleton remodelling to enable tumour cells to detach from primary lesions and penetrate adjacent tissues (27). Notably, two representative ABP members, cofilin and gelsolin, support the generation of invadopodia, actin-rich membrane protrusions that degrade extracellular matrix barriers and accelerate tumour infiltration (5). Clinical cohort data demonstrated that elevated cofilin expression is associated with increased invasive capacity in patients with breast, lung and gastric malignancies. By contrast, low α-actinin abundance serves as an adverse prognostic marker for patients with breast cancer; notably, α-actinin includes multiple isoforms. Reduced ACTN1 expression was shown to be associated with poor survival in breast cancer cohorts, whereas overexpression of the ACTN4 isoform was found to drive tumour metastasis (28,29). Deubiquitinating-enzyme regulation for various ABP isoforms and prognostic associations for ACTN1, which is functionally distinct from oncogenic ACTN4 are described (4). This discrepancy reveals that individual ABPs exert opposing pro- or anti-tumour effects determined by protein features and tumour microenvironment context (30).

The regulatory link between ABPs and tumour movement cannot be generalized with a unified rule, as their functional output varies greatly under distinct cellular contexts. In numerous malignant cell lines, it has been shown that profilin increases actin polymerization at the cell leading edge to generate lamellipodia and filopodia, facilitating directional forward migration. Under other conditions, including specific tumor-cell backgrounds, moderate profilin-1 overexpression, nuclear subcellular localization, and different stages of metastatic progression, profilin stabilizes filament networks and restricts membrane protrusion, thus suppressing cell mobility (31). This context-dependent duality requires researchers to conduct layered, refined mechanistic research rather than draw simplistic conclusions; protein identity, tumour subtype and disease stage all jointly determine whether an ABP promotes or inhibits metastasis.

Beyond driving tumour invasion, abnormal ABP activity disturbs mitotic progression and survival signals to sustain malignant proliferation. During cell division, properly organized actin networks controlled by ABPs guarantee accurate chromosome segregation and smooth cytokinesis; disrupted ABP balance breaks this process and triggers uncontrolled tumour cell multiplication (32). Moreover, ABPs maintain cellular structural integrity and participate in apoptotic signalling cascades, whose dysfunction allows cancer cells to evade programmed cell death. Additionally, ABP-mediated actin remodelling modulates endothelial and vascular smooth cell behaviours, supporting the formation of new blood vessels that deliver nutrients to expanding tumour masses (33).

ABPs exert profound tumour-modulating effects through crosstalk with classic tumour-suppressive signalling axes,

among which the Hippo pathway has been widely validated. This pathway governs organ size and restrains oncogenic transformation via the NF2-LATS kinase complex (34). Recent hepatocellular carcinoma research has confirmed that drebrin physically dissociates NF2-LATS complexes, inactivating Hippo tumour-suppressive signalling and accelerating malignant liver transformation (9). Notably, this observation is derived from a single preclinical study and awaits further independent experimental validation. This evidence directly shows that ABPs can trigger tumorigenesis through non-structural signal regulation independent of cytoskeleton rearrangement.

Apart from Hippo signalling, ABPs dynamically interact with three major oncogenic pathways that are frequently hyperactivated in human tumours: The Ras homologous (Rho) guanosine triphosphatase (GTPase) family, sarcoma (Src) kinases and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) cascades. These binding interactions alter the activation status and subcellular localization of core signalling molecules, reshaping tumour cell morphology, adhesion state, proliferation rate and invasive potential (35). For instance, multiple ABP subtypes directly bind Rho GTPases to tune actin network dynamics, resulting in the construction of complicated feedback circuits that tumour cells hijack to sustain unlimited growth and distant dissemination (36).

Wide-ranging expression shifts of ABP families are commonly observed across clinical tumour specimens, directly shaping malignant biological traits. In a variety of epithelial cancers, the overexpression of ABPs that accelerate actin disassembly or filament elongation was shown to be associated with advanced tumour stage and poor patient survival (37). By contrast, the downregulation of actin-stabilizing ABPs was found to remove natural barriers against cell invasion, also driving tumour progression (38). Such transcriptional and post-translational expression fluctuations originate from gene mutation, epigenetic silencing and modified protein modification cycles (39), all of which must be clarified to design ABP-targeted anti-tumour interventions.

The biological roles of ABPs in tumour development become even more complicated due to their latent tumour-suppressive functions. A subset of ABP proteins can bind and neutralize oncogenic molecules, blocking aberrant proliferative signalling and triggering cancer apoptosis. Once these protective ABPs are silenced or functionally impaired, oncogenic pathways lose natural inhibitory checkpoints and run continuously to fuel tumour outgrowth (40). This dual identity, acting as either a metastasis promoter or a tumour suppressor, adds significant complexity to the mechanistic landscape of ABP-related cancer research.

ABP expression profiles also determine tumour sensitivity to clinical anti-cancer regimens, governing therapeutic efficacy and the emergence of drug resistance. Actin networks modulated by ABPs control the transmembrane uptake, intracellular trafficking and apoptosis-triggering capacity of chemotherapeutic agents; altered ABP levels can either amplify drug cytotoxicity or shield tumour cells from treatment damage (41). Moreover, ABPs remodel cellular signalling, metabolic status and surface antigen presentation to interfere with targeted therapy and immunotherapy responses (42). These properties grant ABPs dual clinical value: They can act as predictive biomarkers for treatment stratification and as promising druggable targets for novel combination regimens.

5. Regulation of ABPs

Multiple-layered regulatory systems tightly govern the activity and biological functions of actin-binding proteins, enabling cells to fine-tune actin network remodelling upon diverse extracellular stimuli and intracellular metabolic shifts. Such multi-level control has gained particular research value in oncology: Disrupted ABP regulatory circuits directly drive the formation of malignant cell phenotypes (43). Unravelling the full spectrum of ABP regulatory mechanisms provides essential theoretical support for designing targeted therapeutic interventions against these actin regulators or their upstream signalling cascades.

Post-translational modification is the most extensively studied mode for modulating ABP catalytic capacity and subcellular distribution. Phosphorylation events exert dominant regulatory effects by reshaping actin-binding affinity and protein conformation. Cofilin, a core actin depolymerizer, undergoes serine-3 phosphorylation catalysed by the LIM domain kinase (LIMK)1/2 and testis specific kinase (TESK)1/2 kinase families; this chemical modification was shown to completely suppress its filament-cutting activity and stabilize static actin bundles (44). Cellular slingshot phosphatases have been found to reverse this inhibitory phosphorylation state, restoring the ability of cofilin to recycle actin monomers and support dynamic cytoskeleton reshaping during migration and mitosis (45). The reversible phosphorylation cycle of cofilin acts as a core molecular switch that governs all actin-dependent cellular behaviours (46).

Beyond phosphate group attachment, three additional post-translational labels, ubiquitination, acetylation and sumoylation, jointly expand the regulatory repertoire of ABPs. Ubiquitin tagging results in abnormal or redundant ABP isoforms for proteasomal degradation, decreasing their intracellular protein abundance. Acetylation alters the surface charge of actin-binding domains, weakening or strengthening physical contact between ABPs and actin filaments to alter their functional output (47). Collectively, these diverse modification types result in an intricate tuning system that rapidly reprograms ABP activity in response to fluctuating intracellular signalling cues (48).

Protein-protein binding interactions represent another indispensable regulatory layer that is independent of chemical modification. Partner protein binding reshapes ABP conformation, redirects its subcellular localization or blocks its actin-binding pockets to modulate biological activity. Profilin is physically associated with the actin-related protein (Arp)2/3 complex, accelerating *de novo* actin branch generation and expanding branched filament networks at cell protrusive fronts (49). Moreover, α-actinin forms stable complexes with myosin II to modulate the intracellular contractile force output during cell translocation (50). All these intermolecular linkages integrate ABP-mediated actin remodelling with other core cellular functional modules.

Spatial compartmentalization inside cells also imposes strict functional restrictions on each ABP subtype, resulting in the formation of a spatial regulatory mechanism. Distinct

ABPs accumulate in specialized subcellular zones to execute compartment-specific tasks. Certain variants concentrate at the leading edge of motile cells to drive actin polymerization and membrane protrusion, whereas others reside within the cell body to assemble stable stress fibres and maintain cell morphology. Membrane anchoring, intermolecular binding partners and reversible post-translational marks jointly determine ABP subcellular positioning, ensuring that each protein performs its designated function in the proper microenvironment (51,52).

Transcriptional and translational regulation controls total intracellular ABP abundance, serving as a long-term regulatory layer distinct from rapid post-translational tuning. Malignant tissues universally display disordered ABP expression profiles, with some family members being overexpressed and others being significantly downregulated across different tumour subtypes. Such expression shifts stem from somatic gene mutations, epigenetic silencing or hyperactivated upstream transcription factors. Classic oncogenic transcription regulators, including nuclear factor (NF)-κB, signal transducer and activator of transcription (STAT) and hypoxia inducible factor (HIF)-1, directly bind the promoter regions of multiple ABP genes to alter their transcription efficiency in hypoxic or inflammatory tumour microenvironments (53). Decoding the transcriptional regulatory axes of ABPs facilitates gene-level intervention strategies for tumour suppression.

Intracellular biochemical and mechanical microenvironments further tune ABP functional output in a context-dependent manner. Lipid molecules, free ion concentrations and small signalling metabolites can alter ABP-actin binding efficiency. Additionally, intracellular cytoskeletal tension and overall cellular stiffness dynamically alter ABP catalytic activity to match environmental mechanical cues (54). This environment-sensitive regulatory mode ensures that the actin remodelling speed and scale perfectly match cellular functional demands under variable external conditions (55).

In malignant tissues, the multi-layered regulatory network of ABPs frequently falls out of balance, sustaining invasive tumour phenotypes. In some tumour subtypes, hyperactivated or overexpressed ABPs that disassemble actin filaments accelerate extracellular matrix penetration and are associated with poor patient survival. In other malignancies, the loss of actin-stabilizing ABP subtypes removes natural barriers against tumour cell detachment and metastasis (56,57). Such regulatory breakdowns originate from combined defects in gene transcription, epigenetic labelling, kinase/phosphatase balance and protein degradation pathways (58).

The multi-dimensional, interwoven regulatory modes of ABPs create substantial obstacles for anti-tumour drug design. Therapeutic agents targeting these proteins must precisely distinguish tumour-specific abnormal ABP activity from their essential homeostatic functions in normal somatic cells to avoid severe systemic toxicity. The successful development of selective modulators requires full clarification of context-specific ABP signalling circuits in cancer. Even with such translational hurdles, ABPs remain high-value druggable targets, as single compounds targeting these regulators can simultaneously interfere with multiple core malignant hallmarks.

To summarize, ABP function is governed by a multi-layered regulatory network that includes post-translational modification, intermolecular binding partners, spatial compartmentalization and transcription control. These coordinated regulatory modules enable cells to fine-tune actin remodelling in response to diverse internal and external stimuli. In tumour tissues, breakdown of any single regulatory layer disturbs ABP homeostasis and promotes malignant progression, highlighting the need for systematic research on ABP regulatory mechanisms to develop precise anti-cancer therapeutics.

6. Clinical therapeutic targets

Owing to their comprehensive control of malignant proliferation, invasion and angiogenic remodelling, actin-binding proteins have drawn extensive attention as candidate anti-tumour therapeutic targets. These regulators take part in nearly all core malignant phenotypes, making them ideal intervention nodes to restrain tumour progression. Nevertheless, researchers face prominent translational barriers: Any ABP inhibitor must selectively block abnormal tumour-related activity while preserving indispensable cytoskeletal functions in healthy tissues. In this section, existing intervention modalities targeting ABPs, as well as their clinical application prospects and unresolved developmental bottlenecks, were comprehensively examined.

Small-molecule compounds constitute the most mature research direction for ABP intervention. Such chemical agents can be structurally optimized to bind specific ABP functional domains and block their catalytic activity. Cofilin-targeted inhibitors are typical representatives. These molecules have been shown to suppress cofilin-mediated actin disassembly, stabilize cytoplasmic filament networks and effectively restrict the invasive capacity of malignant cells (59). Corresponding chemical modulators targeting profilin, gelsolin and α-actinin are also undergoing continuous structural optimization in preclinical laboratories. Small-molecule drugs possess unique strengths, including oral bioavailability and efficient transmembrane penetration, yet three core defects hinder clinical transformation: Insufficient subtype selectivity, widespread off-target toxic reactions, and difficulty in the accumulation of effective drug concentrations inside solid tumour lesions (60).

Unlike broad-spectrum ABP inhibitors, subtype-specific antagonists tailored to tumour-dysregulated ABPs have safer and more precise therapeutic effects. As validated by hepatocellular carcinoma mechanistic studies, drebrin overactivates the oncogenic Hippo-Yes-associated protein (YAP) axis by disrupting NF2-LATS complex assembly (9). The small-molecule agent BTP2 was designed to specifically bind drebrin, block YAP nuclear translocation and restrain liver tumour proliferation in hepatocellular-carcinoma xenograft models (pre-clinical stage, for which no human clinical data are available) (9). The development of such exclusive inhibitors requires thorough structural biology analysis of target ABPs and comprehensive verification of their tissue-specific pathogenic functions in corresponding tumour subtypes.

Monoclonal antibody therapy provides another intervention route for ABP regulation. Antibody reagents can be engineered to bind ABPs or their interaction partners to interfere with downstream signalling cascades, a mature technical system widely applied in clinical anti-tumour treatment. However, most functional ABPs are located inside cells rather than on

Table I. Current therapeutic strategies targeting ABPs in cancer.

Therapy class	Target ABP	Example drug	Mechanism	Stage	Challenges
Small molecule inhibitors	Drebrin	BTP2	Inhibits YAP nuclear translocation	Preclinical (xenograft model) (5)	Limited tissue penetration
	Cofilin	CCG-1423	Blocks Rho/MRTF-SRF signalling	Preclinical tool compound (33)	Off-target effects
Gene therapy	α-Actinin (ACTN4)	siRNA-ACTN4	Silences ACTN4 to suppress metastasis	Preclinical	Off-target editing

α-Actinin isoforms exert divergent functions: Low ACTN1 expression is a predictor of poor prognosis in patients with breast cancer, whereas ACTN4 overexpression promotes metastasis. ABPs, actin-binding proteins; YAP, yes-associated protein; Rho, Ras homologous; MRTF, myocardin-related transcription factor; SRF, serum response factor; ACTN4, α-actinin 4; ACTN1, α-actinin 1.

membrane surfaces, constituting a major delivery obstacle for large antibody molecules. Additional risks include *in vivo* immunogenicity and poor penetration into dense tumour stroma (61). Even with these limitations, antibody drugs still stand out because of their ultrahigh binding specificity and mild systemic toxicity and are worthy of further delivery system optimization.

RNA interference and clustered regularly short palindromic repeats (CRISPR) gene editing technologies achieve gene-level suppression or knockout of pathogenic ABPs. Small interfering (si)RNA and short hairpin (sh)RNA molecules degrade ABP transcripts to reduce the abundance of intracellular proteins, while CRISPR-CRISPR-associated protein 9 (Cas9) permanently inactivates target gene loci (62). These genetic tools exhibit absolute targeting precision for specific ABP subtypes that are overexpressed in tumours. Their translational bottlenecks focus mainly on stable tumour-specific delivery, nonspecific gene silencing side effects, and compensatory upregulation of homologous ABPs after single-gene knockout. Despite current technical restrictions, gene modulation tools remain powerful experimental research platforms and hold long-term clinical transformation potential.

Therapeutic strategies are not limited to direct binding of ABPs; indirect intervention against their upstream regulatory enzymes represents another feasible solution. The phosphorylation status of ABP plays a dominant role in functional switching; thus, kinase or phosphatase inhibitors can indirectly alter ABP activity without directly targeting actin-binding domains. Similarly, chemical modulators that correct ubiquitination and acetylation cycles also reshape ABP intracellular abundance and function. This indirect intervention method avoids the sequence homology issue of ABP family proteins and decreases the risk of drug resistance caused by ABP gene mutations (63).

At present, nearly all ABP-targeted intervention schemes remain within the cell and animal preclinical research phases, with only a few lead compounds entering preliminary efficacy verification. Multiple candidate molecules targeting other ABP subtypes are under structural modification and efficacy screening. With deeper clarification of ABP regulatory networks and continuous innovation in pharmaceutical synthesis technology, ABP-centred treatment regimens will constitute a larger proportion of clinical anti-tumour protocols.

Before advancing ABP modulators to clinical trials, researchers must compare protein expression and functional differences between tumour lesions and normal tissues. Optimal druggable targets feature high abundance or constitutive abnormal activation in tumours while maintaining negligible physiological influence in healthy organs. Comparative cross-tumour analysis of ABP expression profiles helps filter the most valuable intervention objects; moreover, comprehensive research on the physiological functions of native ABPs accurately predicts possible *in vivo* toxic side effects, guiding rational drug structural design.

Single-target ABP monotherapy rarely achieves complete tumour suppression due to the high heterogeneity and multi-pathway crosstalk of malignant diseases. Combination regimens pairing ABP modulators with conventional treatments generate synergistic anti-tumour effects. For instance, cofilin inhibitors combined with chemotherapy simultaneously eliminate primary tumour cells and block distant metastasis. Co-administration with immunotherapy remodels both the intrinsic malignant phenotype of tumour cells and the immune cell composition within the tumour microenvironment, increasing overall therapeutic response rates (64).

Biomarker screening and validation are indispensable links supporting personalized ABP-targeted treatment. Specific molecular markers associated with ABP expression can assist clinicians in screening sensitive patient subgroups, predicting individual treatment response, and dynamically monitoring therapeutic efficacy and drug resistance emergence. Timely adjustment of medication plans based on biomarker signals can maximize treatment benefits and prevent ineffective drug administration. As summarized in Table I, multiple pre-clinical intervention modalities targeting ABPs have been reported.

7. Future directions and challenges

Further in-depth mechanistic research on actin-binding proteins in malignant models will open multiple innovative research branches and lay the groundwork for novel anti-tumour drug design. Nevertheless, multiple technical and translational barriers stand between current laboratory discoveries and clinically usable ABP-targeted regimens. In this section, forward-looking research focuses were outlined, and unresolved bottlenecks restricting the clinical transformation

of ABP-related basic findings were comprehensively summarized.

Several intrinsic limitations should be acknowledged for the present narrative review. Most of the included experimental evidence originates from pre-cellular and xenograft animal studies, while clinical-trial data remain scarce. Potential publication bias may exist among original primary reports. Moreover, literature inclusion depended on expert-driven selection rather than formal systematic-review protocols.

A core emerging research trend focuses on multi-layered crosstalk between ABPs and other intracellular functional assemblies beyond single actin filaments. Existing studies mostly isolate ABPs as independent actin regulators, ignoring their physical linkage with microtubule skeletons and membrane lipid components. Exploring such intermolecular interactions enables researchers to construct a holistic panoramic regulatory network of intracellular signalling and uncover untapped intervention targets hidden in multi-cytoskeleton cross-talk. For instance, recent experiments have verified that certain ABP subtypes act as molecular bridges connecting the actin and microtubule systems, jointly controlling tumour cell mitosis and invasive migration through coordinated cytoskeleton remodelling (65).

Cutting-edge imaging and mass spectrometry proteomics tools have become indispensable technical support for dissecting dynamic ABP behaviours in living cells and intact animal tissues. Traditional static biochemical assays fail to capture the time-varying subcellular distribution and transient binding partners of ABPs, whereas modern analytical platforms effectively fill this gap. Nanoscale super-resolution microscopy visualizes the precise positioning of ABPs at membrane protrusion structures, and quantitative proteomics screens unreported interacting proteins and novel post-translational modification sites of actin regulators (66). Such high-resolution technical platforms will continuously uncover unknown regulatory cascades and provide fresh molecular targets for subsequent drug development.

Systems biology combined with computational simulation has gradually become an auxiliary research tool for ABP functional exploration. Mathematical modelling was used to quantify the dynamic variation in ABP expression and activity and predict how single or combined ABP disturbances reshape tumour cell proliferation and invasion phenotypes (67). These predictive simulations guide targeted experimental design, simplify redundant laboratory verification, and lead to the interpretation of complex multiomics datasets acquired from tumour specimens. With the increase in computing power and the accumulation of multi-dimensional biological data, computational prediction will become more important for early-stage compound screening and mechanism exploration in ABP research.

Despite the abundance of promising research directions, researchers still face prominent obstacles in the development of safe and effective ABP modulators. The most critical difficulty lies in achieving high-selectivity candidate compounds. All ABP subtypes perform essential housekeeping tasks in normal somatic cells; nonspecific global inhibition of these proteins triggers severe systemic organ toxicity. Thus, ideal therapeutic agents block only tumour-specific abnormal ABP signalling without interfering with physiological homeostatic functions in healthy tissues. This goal requires a comprehensive comparative analysis of ABP regulatory differences between normal and malignant cells and rational structural modification of small molecules to recognize tumour-unique conformational variants of ABPs.

Intracellular delivery efficiency creates another major translational barrier for ABP-targeted drugs. Most functional ABPs are distributed inside the cytoplasm rather than on cell membrane surfaces, making it difficult for macromolecular agents such as antibodies to cross lipid bilayers and reach target sites. Numerous small-molecule candidates also suffer poor tissue enrichment and rapid metabolic clearance *in vivo*. Multiple delivery strategies are being optimized to resolve this defect, including liposomal encapsulation and tumour-targeted nanoparticle carriers that shield therapeutic cargos and guide them to lesion regions (68). The use of tumour-specific prodrugs activated by enzymes overexpressed in malignant tissues is another viable scheme to restrict drug activity within tumour masses and reduce off-tissue exposure.

Acquired drug resistance severely limits the long-term efficacy of any single ABP-targeted intervention. Malignant cells evolve multiple escape mechanisms under sustained drug pressure: Target gene mutations that disrupt compound binding pockets, compensatory upregulation of functionally redundant ABP paralogues, and rewiring of upstream kinase cascades to bypass inhibited actin regulators (69). Fully decoding these resistance pathways is a prerequisite for designing countermeasures, such as multi-agent combined regimens and sequential switching of different ABP modulators, to delay or reverse therapeutic failure in patients.

Multiple practical obstacles exist during the transition from basic laboratory data to standardized clinical application. Reliable predictive and monitoring biomarkers matching ABP signalling need to be screened and validated in large clinical cohorts to distinguish patient subgroups responsive to ABP therapies. Standardized clinical trial protocols must be formulated to objectively evaluate drug safety and anti-tumour efficacy and meet strict regulatory approval criteria. In addition, the large-scale production costs and technical limitations of biologic drugs such as monoclonal antibodies restrict their popularization in routine clinical practice.

Despite these unresolved limitations, ABPs still retain great translational value as anti-tumour intervention nodes. These proteins participate in nearly all core malignant biological traits, and the continuous accumulation of mechanistic evidence plus iterative optimization of pharmaceutical technologies steadily removes transformation barriers. With ongoing technical breakthroughs, researchers will develop more mature selective ABP modulators for clinical anti-tumour treatment.

8. Conclusion

ABPs perform central regulatory functions far beyond canonical actin cytoskeleton remodelling during tumorigenesis. By forming elaborate binding complexes with actin filaments and diverse oncogenic signalling axes, ABPs dominate core malignant characteristics, including uncontrolled proliferation, apoptotic evasion, invasive migration and tumour angiogenesis; clinical evidence consistently links aberrant

ABP expression or hyperactivation to advanced tumour stages and poor patient prognosis. Notably, four interconnected regulatory tiers shape ABP functionality, post-translational modification, protein-protein binding, dynamic subcellular localization and transcriptional regulation, and decoding these layered networks enables the identification of tumour-specific therapeutic targets, facilitating the design of selective interventions that block oncogenic ABP activity while preserving indispensable cytoskeletal homeostasis in normal tissues. In addition, four primary therapeutic modalities have been established to modulate ABPs: Specific small-molecule inhibitors, targeted monoclonal antibodies, RNA silencing and CRISPR gene editing. However, clinical translation is hindered by three persistent obstacles: Poor target specificity, limited intracellular drug delivery and readily acquired treatment resistance.

Targeting ABP signalling represents a groundbreaking, transformative strategy for anti-cancer drug development. Accumulating mechanistic findings and advances in pharmaceutical technologies continue to mitigate the above translational barriers, building robust theoretical and engineering foundations for future ABP-targeted agents. Persistent in-depth investigations into the multi-faceted biological roles, multilayered regulatory circuits and clinical translational potential of ABPs remain critical to convert basic laboratory discoveries into safe, standardized clinical regimens and improve long-term survival outcomes for cancer patients.

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Authors' contributions

ML and YW conceived the overall framework of this review. ML, YW, CD, QL, RH and JY jointly completed the original manuscript draft. WZ revised, polished and edited the full text throughout the writing process. All authors read and approved the final submitted version of the manuscript. Data authentication is not applicable.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an artificial intelligence tool (Doubao) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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