Functions of nuclear actin-binding proteins in human cancer (Review)

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Abstract. Nuclear actin-binding proteins (ABPs) perform distinguishable functions compared with their cytoplasmic counterparts in extensive activities of living cells. In addition to the ability to regulate actin cytoskeleton dynamics, nuclear ABPs are associated with multiple nuclear biological processes, including chromatin remodeling, gene transcriptional regulation, DNA damage response, nucleocytoplasmic trafficking and nuclear structure maintenance. The nuclear translocation of ABPs is affected by numerous intracellular or extracellular stimuli, which may lead to developmental malformation, tumor initiation, tumor progression and metastasis. Abnormal expression of certain ABPs have been reported in different types of cancer. This review focuses on the newly identified roles of nuclear ABPs in the pathological processes associated with cancer.

Contents

1. Introduction

Actin is one of the most abundant proteins identified in almost all eukaryotic cells, and it is a highly conserved protein during evolution (1). Actin-binding proteins (ABPs) refer to proteins that contain actin-binding domains that interact with actin. They can bind to actin monomers, actin polymers or both (2).

Early studies have focused on the biological features and physiological mechanisms of cytoplasmic actin. Therefore, ABPs were considered to be distributed only in the cytoplasm and associated with the organization of actin cytoskeleton (3). In the cytoplasm, actin is associated with numerous cellular activities, including sustaining cellular morphology, determining cellular organelle distribution, mediating intracellular transfer, endocytosis and exocytosis, cell division, cell migration and adhesion (4-8). Meanwhile, ABPs regulate actin cytoskeletal structure by modulating actin filament cross-linking into networks or depolymerizing into monomers, allowing actin to switch between the polymeric (F-actin form, filamentous actin) and monomeric state (G-actin form, globular actin) (2,9).

However, recent studies (10,11) indicate that a great number of actin and ABPs exist in the nucleus. Nuclear actin and nuclear ABPs exhibit nuclear-specific functions that are different from those in the cytoplasm. Although the precise biological mechanisms remain elusive, we are fortunate to uncover several observations (12). This review aims to present up-to-date discoveries of nuclear actin and nuclear ABPs in the field of cancer research.

2. Actin and actin-binding proteins (ABPs) in the nucleus

Studies in the recent decades provide a plethora of evidence that has broadened our horizon on the functions of nuclear actin and nuclear ABPs in the eukaryotic cell life (12-14). Since the existence of nuclear actin was confirmed, subsequent studies also established the presence of ABPs in the nucleus (12,14,15). The very first nuclear ABP was reported as early as 1987, henceforth, the rest of the ABP family in the nucleus has come to light comprising of profilin, anillin, flightless I (Fli I), filamin α (FLNα), α-actinins, myosins, gelsolin and ezrin-radixin-moesin proteins (12,13,16,17). Although these ABPs are primarily in the cytoplasm, they can translocate into the nucleus under certain circumstances, for example, extracellular stimuli (stress), hormone stimulation and intracellular signaling (16).

In the nucleus, actin is associated with chromatin remodeling, DNA replication, DNA repair, gene transcriptional regulation, RNA processing, nuclear protein transportation and maintenance of nuclear structure, for instance, the nuclear

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envelope assembly (12,18-20). Nuclear ABPs are closely associated to nuclear actin and implicated in various nuclear activities. ABPs promote actin filament nucleation or sequestering, manipulate nuclear actin dynamics and determine the ratio of nuclear to cytoplasmic actin (13). Therefore, ABPs directly or indirectly associate with chromatin remodeling, DNA replication, transcription, DNA repair, nucleocytoplasmic transport and maintenance of nuclear structure integrity (12,13,21). Furthermore, nuclear actin is required by all three RNA polymerases in transcriptional activation (22-24). The study by Miyamoto and Gurdon (25) mentions the major function of nuclear actin and ABPs in transcriptional regulation and nuclear reprogramming.

In eukaryotic cells, the cytoplasm and nucleus are separated by the nuclear envelope, which is a double membrane barrier. Trafficking of proteins and other molecules between these two compartments occurs by passing through the nuclear pore complex. Additionally, cytoplasmic ABPs can interact with the nuclear receptor in the cytoplasm, form complexes and facilitate nuclear translocation. Therefore, ABPs mediate transcriptional activation of nuclear receptors. These nuclear receptors include the glucocorticoid and estrogen receptor, androgen receptor (AR), thyroid receptor and peroxisome proliferator-activated receptor-c (26-28). Furthermore, they are associated with transcriptional activation of multiple genes and are involved in a spectrum of functions, including cell proliferation, differentiation and apoptosis (21,29,30).

3. Nuclear ABPs in cancer cells

Numerous ABPs demonstrate the ability to shuttle between the cytoplasm and nucleus via different mechanisms. The question remains whether it is the shuttling of ABPs between different cellular compartments that is linked to pathological behaviors, including abnormal cell development and differentiation, carcinogenesis and metastasis. However, this needs to be clarified. The theory that ABPs in the nucleus affect the aforementioned pathological processes is intriguing. In the sections, the nuclear ABPs that are associated with chromatin remodeling, transcriptional regulation, DNA damage repair, protein nucleocytoplasmic shuttling and nuclear structure maintenance in human cancer cells are summarized in Table I and Fig. 1.

Fli I homolog (FLII), with a C-terminal gelsolin-like actin-binding domain, is a member of the gelsolin protein superfamily. FLII interacts with BAF53, a subunit of the SWItch/Sucrose Non-Fermentable chromatin-remodeling complex, and recruits the latter to the promoter and enhancer regions of the trefoil factor 1 gene, an estrogen receptor (ERα) target gene (31) (Fig. 1). FLII also regulates chromatin accessibility for the binding of RNA polymerase II and other transcriptional coactivators to the promoter and enhancer of other ERα target genes, including growth regulation by estrogen in breast cancer 1, continuous traumatic stress disorder and MYC in MCF-7 breast cancer cells. In addition, FLII promotes the hormone-dependent growth of breast cancer cells (32).

Villin is a tissue-specific ABP predominantly expressed in the epithelium, including the gastrointestinal tract and digestive organs. Overexpression of villin is reported in tissues of Barrett's metaplasia, gastric and colorectal adenocarcinoma (33,34). Furthermore, villin is distributed in the cytoplasm and nucleus and cytoplamic-nuclear transport of villin keeps the system dynamically stable. It migrates to the nucleus upon stimulation, including hypoxia and injury. Another postulation is that tyrosine phosphorylation of villin may prompt its gathering in the nucleus. A study reveals that villin in the nucleus can interact with ZBRK1 [also called zinc finger and breast cancer type 1 (BRCA1)-interaction protein], a transcriptional corepressor and also a ligand of the human Slug promoter, thus regulating the activity of Slug and gene expression (34).

The villin-ZBRK1 complex eliminates the corepressor effect of ZBRK1 and upregulates Slug expression. Slug is a crucial transcriptional regulator of epithelial-mesenchymal transition (EMT). Therefore, nuclear villin performs an important role in inducing EMT, which is considered essential in tumorigenesis (34), invasiveness and metastasis. A previous study demonstrates that severe combined immunodeficiency mice injected with xenografts derived from five colon cancer cell lines developed tumors in 21 days at a 100% frequency, and by staining with villin antibodies, the xenografts reveal strong nuclear accumulation of villin (34). Furthermore, villin expression is observed in gastric, colorectal, pancreatic, biliary, liver, renal, cervical, endometrioid, lung and other types of cancer (34-36), particularly with propensity for metastasis and poor prognosis.

α-actinin 4 (ACTN4), a member of the ABP family, is a regulator of gene transcription that is presumably mediated by nuclear hormone receptors. Although the majority of ACTN4 is located in the cytoplasm, the proportion of ACTN4 in the nucleus is unneglectable. ACTN4 binds to the nuclear receptors in a hormone-dependent manner. Furthermore, ACTN4 is a coactivator of the estrogen receptor α (ER-α) that regulates target gene transcription in MCF-7 breast cancer cells, subsequently promoting tumor cell proliferation (37). Overexpression of ACTN4 in the nucleus increases the expression of progesterone receptors and antigen related to ER (pS2), and target genes of ER-α (Fig. 1). Furthermore, it can interact with the pS2 promoter and potentiate estradiol (E2)-induced transcription. Additionally, it interacts with the AR and functions as a co-regulator of AR-mediated transcription (38).

Nuclear ACTN4 serves as a transcriptional coactivator for nuclear factor κ-light-chain enhancer of activated B-cell (NF-κB) (39). NF-κB activation in ERα-negative breast cancer promotes cancer cell proliferation (40). Furthermore, ACTN4 also interacts with histone deacetylase 7 (HDAC7), a transcriptional corepressor of myocyte enhancer factor 2 (MEF2), competitively inhibiting the repressing effect of HDAC7 and potentiating MEF2 transcription activity (41). ACTN4 interacts with HDAC7 by its C-terminal calmodulin (CaM) -like domain, and activates ERα transcription, which contributes to tumorigenesis in breast cancer (42). In addition, elevated levels of ACTN4 are widely identified in other malignancies, including colorectal, pancreatic, prostate and ovarian cancer, salivary gland carcinoma and esophageal cancer (38,42-46).

FLNα, also called ABP-280, is a scaffold protein. Filamin deficit is prevalent among carcinomas, including colon, prostate and breast cancer. It is verified that FLNα acts as a promoter in cancer metastasis and invasion in the cytoplasm,

Table I. Summary of nuclear functions of actin-binding proteins in human cancer.

Nuclear function	ABP	Mechanism	Tumor	(Refs.)
Chromatin remodeling	Flightless I homolog	Recruits chromatin remodeling complex	Breast cancer	(31,32)
Transcriptional regulation	Villin	Interacts with transcriptional corepressor	Lung, gastric, colorectal, pancreatic, biliary, liver, renal, cervical and endometrioid cancer	(33-36)
	α-actinin 4	Interacts with nuclear receptor (act as a coactivator); interacts with transcriptional corepressor	Breast, prostate, ovarian, colorectal, pancreatic and esophageal cancer, and salivary gland carcinoma	(37-39,41-46)
	Filamin α	Interact with transcription factors	Colon, breast and prostate cancer	(47-49)
	Transgelin	Speculated to act as a transcriptional regulator	Colorectal cancer	(57,58)
DNA damage response	Filamin α	Participates in double strand break repair (DSBR)	Breast cancer, certain melanomas	(61,63)
	Nesprin-1	Participates in the DNA damage response (DDR), DNA mismatch repair (MMR)	Liver cancer	(64)
Protein nuclear translocation	Nesprin-2	Participates in protein nuclear localization	Breast cancer	(65-67)
Nuclear structure maintenance	Nesprin-1	Constitutes the linker of nucleoskeleton and cytoskeleton (LINC) complex	Lung and pancreatic cancer	(69)
	Nesprin-2	Constitutes LINC complex	Breast and colorectal cancer, head and neck squamous cell carcinoma	(70-72)

ABP, actin-binding protein.

while it functions as a tumor suppressor in the nucleus (47). Furthermore, cytoplasmic FLNα interacts with a number of proteins, for example, β1-integrin, phosphatidylinositols and small GTPases, which facilitate cell adhesion and migration. Furthermore, nuclear FLNα interacts with transcription factors and the associate transcription machinery subsequently restrains cell migration and represses cell growth. A previous study demonstrates that nuclear FLNα prohibits ribosome RNA transcription by interacting with RNA polymerase I (48). In addition, nuclear FLNα binds to the AR and modulates the nuclear translocation of the latter, thus regulates AR-induced gene expression. AR is a steroid nuclear receptor and closely associated with prostate cancer. Nuclear FLNα inhibits AR target gene transcription, thus negatively regulating cancer development (49).

Transgelin is an ABP mostly distributed in the cytoplasm of fibroblasts and several epithelial cells (50). Its expression is often altered in human types of cancer (51-55). Previous research by this group (56) revealed that activated AKT and c-jun NH2-terminal kinases promote the expression of transgelin in the cytoplasm and contribute to colorectal cancer progression. Additionally, it is revealed that transgelin was located in the cytoplasm and nucleus of colorectal cancer cells (57). Overexpression of transgelin in human colon cancer cells affects the expression of ~250 other transcripts and enhances the metastatic behavior (58). Thus, it is speculated that transgelin is another transcriptional regulator within the ABP family.

The recovery of DNA damage is essential in the maintenance of genome integrity. The nuclear FLNα is associated with DNA damage repair (59). By contacting BRCA1 and breast cancer type 2 (BRCA2), nuclear FLNα is involved in the process of homologous recombinational and non-homologous DNA repair (60). Furthermore, FLNα interacts with BRCA1 with its extreme C-terminus and mediates BRCA1 and Rad51 foci formation following DNA damage (Fig. 1). In addition, the lack of FLNα may contribute to predisposition to breast cancer (61). In double strand break repair (DSBR), FLNα interacts with BRCA2 and subsequently forms the repair complex (Fig. 1). The deficiency in FLNα makes the cells susceptible to ionizing radiation and delays the recovery from G2/M arrest, which may trigger the incidence of cancer (60-63). Measurement of FLNα expression reveals that FLNα is negative in several melanomas (63). In the absence of FLNα, cells

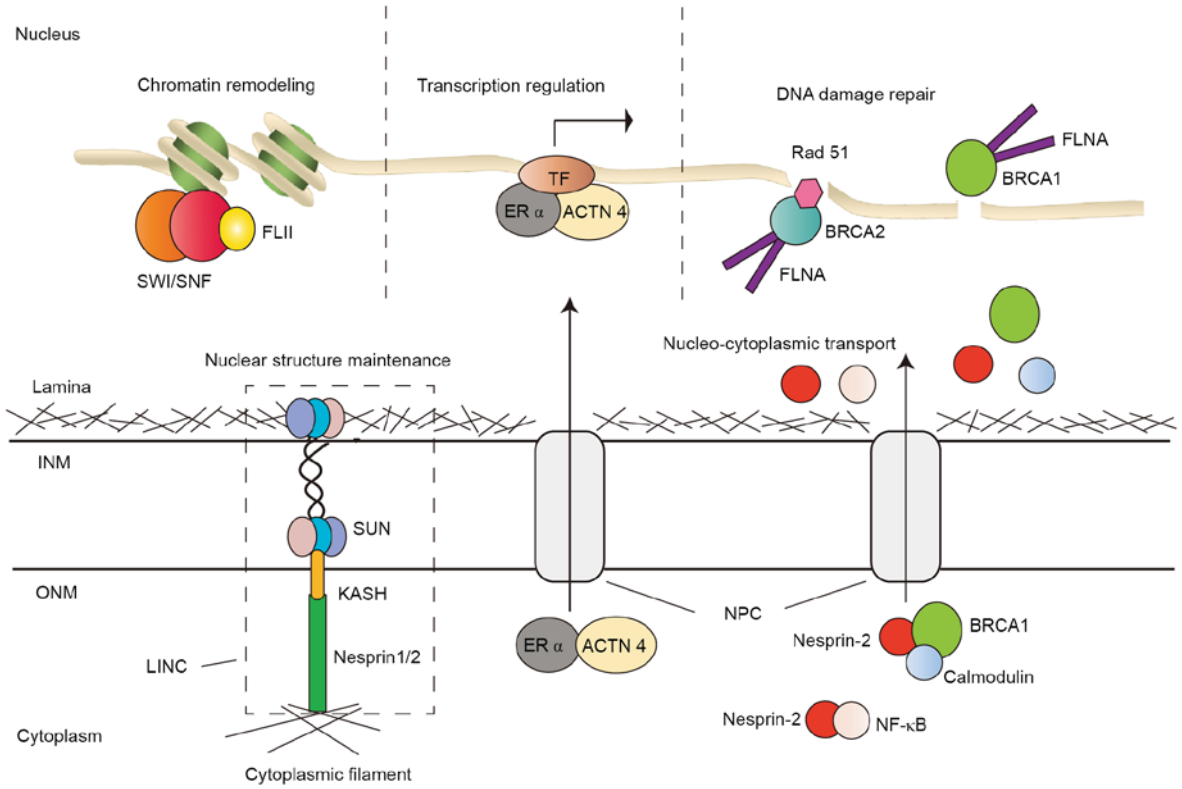

Figure 1. Illustrations of ABPs in the nucleus. ABPs are involved in chromatin remodeling, gene transcriptional regulation, DNA damage repair, nucleocytoplasmic transport and nuclear structure maintenance. ABP, actin-binding protein; INM, inner nuclear membrane; ONM, outer nuclear membrane; NPC, nuclear pore complex; LINC, linker of nucleoskeleton and cytoskeleton complex; SUN, SUN domain proteins; KASH, KASH domain; FLII, flightless I homolog; SWI/SNF, SWItch/Sucrose Non-Fermentable chromatin remodeling complex; ACTN 4, α-actinin 4; ERα, estrogen receptor α; TF, transcription factor; FLNα, filamin α; NF-κB, nuclear factor κ-light-chain enhancer of activated B-cells; BRCA2, breast cancer type 2; BRCA1, breast cancer type 1.

impair to recover from DNA damage and incline to accumulate genetic mutations and initiate tumorigenesis.

Nesprin-1, also known as Enaptin, is a nuclear envelope protein, consisting of a C-terminal KASH domain, a long spectrin repeat region and an N-terminal F-actin binding domain. Novel observations indicate that Nesprin-1 is involved in the DNA damage response and DNA mismatch repair (MMR), thus maintaining genetic stability (64). The study indicates that Nesprin-1 interacts with the DNA MMR proteins, MSH2 and MSH6, and regulates the expression level and function of these proteins, which are associated to DSBR. Reduction of Nesprin-1 may lead to deficiency in correcting DNA damage, therefore triggering tumorigenesis and accelerating tumor progression. Consistent with this, Nesprin-1 expression significantly decreases in liver cancer and numerous other types of human cancer (64). Nesprin-2 is a nuclear membrane protein of the nuclear envelope spectrin-repeat (nesprin) family, which contains an actin-binding domain. Loss of Nesprin-2 is associated with less nuclear accumulation of c-Fos, mothers against decapentaplegic homolog (SMAD) 2, 3 and 4, holding back the course of nuclear translocation (65,66). Furthermore, the latest studies imply that Nesprin-2 is a prerequisite for the nuclear transport of certain proteins, for example, BRCA1 and NF-κB (Fig. 1). The nuclear localization of BRCA1 is regulated by a RAN-independent Ca^{2+}/CaM mediated machinery in which Nesprin-2 is necessary (66). Additionally, abnormality in Nesprin-2 nuclear trafficking results in impaired nuclear translocation and mislocalization of BRCA1. Downregulation of Nesprin-2 is revealed in breast cancer tissue (67). Therefore, disturbance of nuclear translocation of certain proteins by the ABPs may be associated to a number of diseases, including cancer (66).

Nesprins, a family of nuclear envelope proteins, together with SUN domain proteins, form the core of the linker of nucleoskeleton and cytoskeleton (LINC) complex. As a key component of the LINC complex, nesprins tether nuclei to the cytoskeleton and are essential in the maintenance of the nuclear architecture (Fig. 1). Loss of nesprins leads to risk of nuclear structural instability, including nuclear shape, size and chromatin organization, which is implicated in tumorigenesis (68). Furthermore, nesprin-1 downregulation is reported in lung cancer, and synaptic nuclear envelope protein 1 gene mutation is observed in pancreatic cancer with metastasis (69).

Spectrin repeat containing, nuclear envelope protein 2 abnormality is revealed in breast and colorectal cancer, and head and neck squamous cell carcinoma (70-72). One possible mechanism is that nesprin downregulation modulates nuclear stiffness via the LINC complex, and increases nuclear malleability for cells to migrate through restricted tissue spaces (69).

4. Conclusion and perspectives

ABPs have been revealed in both the cytoplasm and nucleus of eukaryotic cells. These proteins share an actin-binding

calponin homology domain, exhibit different functions and are involved in diverse activities in the two cellular compartments. Numerous studies observe a significant proportion of ABP shuttle between the cytoplasm and the nucleus. Cytoplasmic ABPs may translocate into the nucleus in response to the alternation of the extracellular microenvironment, including hypoxia, inflammation and injury. The subcellular localization of ABPs is associated with the onset and development of various pathogenesis and carcinogenesis processes. Recent observations (73-75) demonstrate that nuclear ABPs may be involved in chromatin remodeling, function as transcriptional regulators, are involved in the DNA damage response and DNA mismatch repair, mediate protein nuclear translocation and maintain nuclear structural stability. Altogether, the nuclear ABPs maintain the genomic integrity and reduce cellular oncogenic potential; whereas mutations and deficiencies of nuclear ABPs contribute to tumorigenesis and metastasis.

Although the comprehensive molecular mechanism of specific nuclear ABPs remains elusive, the understanding of the association between nuclear ABPs and relevant diseases is extended. The investigation of ABPs' nuclear function and their effects on cancer remains underway and lots of questions remain to be answered. These studies will help to identify novel therapeutic targets in fighting against cancer in the near future.

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