Role of cellular cytoskeleton in epithelial-mesenchymal transition process during cancer progression (Review)

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Received December 17, 2014; Accepted February 20, 2015

DOI: 10.3892/br.2015.494

Abstract. Currently, cancer metastases remain a major clinical problem that highlights the importance of recognition of the metastatic process in cancer diagnosis and treatment. A critical process associated with the metastasis process is the transformation of epithelial cells toward the motile mesenchymal state, a process called epithelial-mesenchymal transition (EMT). Increasing evidence suggests the crucial role of the cytoskeleton in the EMT process. The cytoskeleton is composed of the actin cytoskeleton, the microtubule network and the intermediate filaments that provide structural design and mechanical strength that is necessary for the EMT. The dynamic reorganization of the actin cytoskeleton is a prerequisite for the morphology, migration and invasion of cancer cells. The microtubule network is the cytoskeleton that provides the driving force during cell migration. Intermediate filaments are significantly rearranged, typically switching from cytokeratin-rich to vimentin-rich networks during the EMT process, accompanied by a greatly enhanced cell motility capacity. In the present review, the recent novel insights into the different cytoskeleton underlying EMT are summarized. There are numerous advances in our understanding of the fundamental role of the cytoskeleton in cancer cell invasion and migration.

Contents

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Key words: cytoskeleton, epithelial-mesenchymal transition, cancer progression

1. Introduction

Despite considerable advances, cancer metastases, the spreading of cancer cells to another part of the body causing secondary cancer, remains a major clinical problem that highlights the importance of recognition of the metastatic process of carcinoma in cancer diagnosis and treatment. A critical process associated with the metastasis process is the transformation of epithelial cells toward a motile mesenchymal state, a process called epithelial-mesenchymal transition (EMT) (1). During this transfer, in addition to modifying their adhesive repertoire, cancer cells involve morphological changes from epithelial cells with an apical-basal polarity to spindle-like mesenchymal phenotypes with various migratory protrusions that are required for cell invasion and migration (2). Various types of migratory organelles have been reported such as podosomes, invadopodia, filopodia and lamellipodia. Although the specific shapes of these organelles are different, they are evolved from dynamic actin cytoskeleton remodeling (3-5). Shankar *et al* (4) first proposed the important role of actin dynamics and therefore, membrane protrusions on the induction of transforming growth factor-β (TGF-β)-induced EMT. The study identified 19 pseudopod-enriched proteins from various cancer metastatic cells, such as AHNAK, septin-9, eukaryotic translation initiation factor 4E and S100A11, which have been associated with malignant tumors. Inhibition of one of these proteins leads to reduction of actin cytoskeleton dynamics, inhibition of cell migration and invasion, as well as reversion of EMT that could be restrained by the steadiness of the actin cytoskeleton. This study indicated a direct link between EMT and actin dynamics demonstrating a significant role of the actin cytoskeleton in the generation and development of tumor. In recent years, investigators have also begun to pay attention to the effect of the reorganization of the actin cytoskeleton on cell polarity, cell proliferation and cell cycle progression (6,7). In the present review, the current available insights into the cytoskeleton underlying EMT are summarized.

2. Actin cytoskeleton

The cytoskeleton, composed of the actin cytoskeleton, the microtubule network and the intermediate filaments provide structural design and mechanical strength that is necessary to mold cell shape (8). Although these cytoskeletal components

act synergistically, it is the actin cytoskeleton that provides the driving force required for cell migration (9). Thus far, two isoforms, the β- and γ-actins, have been discovered and confirmed to exist in non-muscle cells. Numerous studies have indicated different distributions and roles between the two actin isoforms (10). β-actin, responsible for cell connection and contraction, is distributed mainly in circular bundles, ventral stress fibers, intercellular junctions and contractile mitotic rings. γ-actin is predominantly located in dorsal stress fibers in stationary cells, while in motile cells it participates in the formation of lamellar, cortical and lamellipodia structures. In cells lacking β-actin, the number of stress fibers are reduced and wide protrusions are formed, while cells lacking γ-actin tend to the formation of thick actin bundles and the reduction of lamellar and lamellipodia structures. In neoplastically transformed cells, β-actin is downregulated and transformed to a dispersed state with increased cell transformation, as it is found diffusely located in the cytoplasm and distributed in the regions of lamellar activity in ruffles along the whole cell perimeter, instead of contributing to intercellular junctions (10). No difference in γ-actin distribution is found between neoplastically-transformed cells and normal keratinocytes, but the amount of γ-actin is increased. In SiHa and CaSki cells underlying EMT, the number of β-actin fibers are further reduced and the distribution of β-actin is more diffused. The location of γ-actin is not significantly changed. These results demonstrated that the degree of cell transformation was closely associated with changes in the distribution and amount of cytoplasmic actin isoforms (11).

The actin network is a dynamic structure with continuous directional polymerization and disassembly (12). The monomers of actin are regarded as globular-actin (G-actin), while the polymers are known as filamentous-actin (F-actin). G-actin commonly tends to polymerize into actin filaments in physiological salt circumstances. The actual equilibrium between G-actin and F-actin depends on the actin critical concentration. When the actin concentration is above the set point, the process of actin polymerization starts (13). In cancer cells undergoing an EMT process, G-actin polymerizes to form actin filaments to initiate the formation of a leading edge. Newly formed actin filaments subsequently interacted with binding proteins and contractile proteins, such as myosin II, leading to the movement of actin fibers on the substrate toward the leading edge (14). Thus, dynamic reorganization of the actin is a prerequisite for the morphology, migration and invasion of cancer cells (15,16).

The actin-depolymerizing factor (ADF)/cofilin family of proteins, which is composed of cofilin-1, cofilin-2 and ADF, are regarded as the most important regulators of dynamic actin reorganization (17). The LIM domain kinases (LIMKs) function through directly inactivating the ADF/cofilin family of proteins to rearrange the actin cytoskeleton (18). The LIMK/cofilin pathway is directly under the management of the integrin-linked kinase (ILK)/b-parvin/bPIX/cell division control protein 42 (Cdc42)/p21-activated kinase (PAK) signaling axis, which participates in supporting abundant filopodium-like protrusions display. The ILK/b-parvin/bPIX/Cdc42/PAK/LIMK/cofilin signaling pathway suppresses the cleavage of actin fibers, resulting in the stabilization of filopodium-like protrusions during the EMT process. This pathway also plays a vital role in governing cell proliferation, tumor-initiating potential and metastatic aggressiveness (4). P120-catenin, a fundamental regulator of anchorage-independent growth, is identified to cause the suppression of the ras homolog (Rho)/Rho-associated protein kinase/LIMK/cofilin signaling pathway that act synergistically with the p190RhoGAP signaling and the mitogen-activated protein kinase kinase/mitogen-activated protein kinase signaling to regulate the actin reorganization (19).

Shibue *et al* (20) also identified Rho in filopodia (Rif)/mouse diaphanous 2 (mDia2) signaling as polymerizing machinery of actin to stimulate the formation of filopodium-like protrusions. Mellor (21) uncovered the essential combined efforts of Rif and mDia2 on the induction of actin nucleation and subsequent extension of actin filaments. The Rif/mDia2 signaling and the ILK/b-parvin/bPIX/Cdc42/PAK/LIMK/cofilin signaling cooperate to induce and maintain the filopodium-like protrusions involved in the EMT program (22). As an immediately early effector downstream of the TGF-β-Smads signaling through transcription repressor activating transcription factor 3 (23), JunB plays significant roles in the EMT process (24). It induces the organization of actin stress fibers and focal adhesions, including integrins and palladin, through the regulation of tropomyosin α-1, which belongs to the tropomyosin family (25).

Certain regulators of local actin reorganization were also identified to have significant roles in tumor cell migration and invasion, such as the actin-related protein2/3 (Arp2/3) complex, cortactin, fascin, epidermal growth factor receptor kinase substrate 8, α-actinin, filamin and LIMK/cofilin belonging to the Wiskott-Aldrich syndrome protein (WASP) family (4). Arp2/3 is a protein complex, involved in the initiation of actin filament polymerization. Arp2/3 is frequently overexpressed in malignant tumors, such as breast and liver carcinomas, suggesting a strong correlation between dynamic actin reorganization and cancer progression (26-28). Cortactin, an actin-binding protein, is thought to activate Arp2/3, which promotes actin filament polymerization at the leading edge. The overexpression and phosphorylation of cortactin is closely correlated with cell migration and metastasis (29,30). Fascin is significantly associated with time to recurrence, metastatic spread, tumor seeding and cancer prognosis (31). It is an actin-bundling protein mainly located in the invadopodia and filopodia, involved in the regulation of cell assembly and turnover. The upregulation of fascin promotes cell migration by stimulating the formation of protrusion and increasing the activity of cell migration (32).

Gay *et al* (33) first revealed the refilin proteins, including RefilinA and RefilinB, as a novel family of actin regulators. RefilinA dimer promotes the actin-binding filamin A (FLNA) to form a polymolecular complex on filamentous actin (F-actin) and functions to convert FLNA from an actin-branching protein into an F-actin bundler. RefilinB combined with FLNA organize a unique perinuclear actin network at the apical surface during the EMT. The refilin proteins perform their function through the downstream effector, FLNA to regulate the dynamic actin cytoskeleton reorganization (34).

Another family of actin-binding proteins is the tropomyosins, including over 40 isoforms (35). Altered tropomyosin isoforms stabilize actin filament bundles in different degrees and show certain correlation with different focal adhesion morphology based on their ability to affect size and signaling of focal adhesion (36). The synchronous effects of various tropomyosins on the actin cytoskeleton and the adhesion-cytoskeleton linkage are critical for precise control of the initiation and arresting of cell invasion and metastasis (37). Bach *et al* (38) identified the tropomyosin isoform Tm5NM1 that stabilizes focal adhesions and actin filaments concurrently to affect cell migration in 2D and 3D cultures. The modulation of the actin cytoskeleton by tropomyosins is also thought to have a large impact on anchorage-independent growth (39).

The WASP/WASP family verprolin-homologous protein (WAVE) is a family of actin-binding proteins composed of five members; WASP, NWASP, WAVE1, 2 and 3 (40). Taylor *et al* (5) demonstrated that WAVE3 is required for the initiation of EMT through the involvement of DNA synthesis, the cell cycle progression, the migration and the formation of protrusions in triple-negative breast cancer cells. In response to the Rho GTPases, the WASP/WAVE proteins increase the activities of Arp2/3 able to promote assembly of actin filaments and remodeling of actin cytoskeleton dependent upon the involvement of nucleation-promoting factors (NPFs). Notably, the WASP and WAVE subfamilies are part of the NPFs, indicating the persistence of an extremely positive feed-forward mechanism during the actin cytoskeleton reorganization process (41,42). The activity of NPFs is also regulated by Cdc42 and ras-related C3 botulinum toxin substrate (Rac) that are required for the activities of the WASP/WAVE family (43,44). Rac1 and Cdc42 are localized in the front edge toward the direction of migration (45). Cdc42 stimulates long unbranched bundles of actin for the formation of filopodia, which receive outward stimulation (46). Rac1 regulate branched actin polymerization for the formation of protrusion, which are thought to drive the cell forward (47). Interferon regulatory factor 4 binding protein (IBP) has been identified to mediate the activities of Cdc42, Rac1 and ras homolog gene family, member A (RhoA) in breast cancer. It can induce the actin cytoskeleton remodeling, stimulate the formation of filipodium and lamellipodia and regulate cell morphology. Zhang *et al* (48) identified IBP in the involvement of epithelial mesenchymal transition induced by epidermal growth factor.

Formins are conserved members of actin nucleating proteins that can enhance actin nucleation at the F-actin end (49). Due to the ability to profoundly change the actin cytoskeleton, formins have been regarded as important regulators of cell movement, development and organization. The activity of formins is modulated by Rho GTPases, which control the assembly of stress fiber, the formation of protrusions and the mode of cell motility (50,51). Formins have a crucial role in EMT as molecular switches to remodel the actin cytoskeleton and spindle-shaped morphology. Formin homology domain protein (FHOD1) is mainly found in mesenchymal cells in human tissues and is proposed to induce the formation of actin filaments directly (52). Gardberg *et al* (49) reported that FHOD1 is upregulated at the leading edge in mesenchymally-transformed cells upon EMT. This poorly studied formin promotes the actin cytoskeleton reorganization and stress fiber formation, which are essential for cancer cell invasion and migration. The knockdown of FHOD1 inhibits the formation of protrusions to prevent the EMT process. FHOD1 can also increase the expression of myosin light chain 2 (MLC2) and affect MLC2 phoshorylation at Thr18 and Ser19. The phosphorylated MLC2 is required for the formation of stress fibers and myosin filaments, which provide contractile activity to enhance migration of cancer cells (53).

Several proteins once identified to have specific functions are now designated to have a close association with the actin cytoskeleton. The metaderin (MTDH) complex, which was first identified as a component section of the tight junction, is now regarded as an actin cytoskeleton regulator by Yao *et al* (54). MTDH protein is dominantly co-localized with occludins and zonula occludens-1 in the cytoplasm of the polarized epithelial cells. Overexpression of MTDH significantly decreases the F-actin-enriched filopodia, increases the cell size and weakens the mesenchymal feature. MTDH overexpression inhibits the ability of cell migration and invasion, while MTDH suppression induces the epithelial mesenchymal transition analogous to the TGF-β stimulation 24918821. Cytokines may regulate the actin cytoskeleton remodeling at the polarized edge through specific intracellular signaling pathways to form protrusions (55,56). Cyclin A2 plays a novel and critical role in regulating basic cell division as it mediates the switch between S phase and G_2/M transition. It triggers DNA synthesis in association with cyclin-dependent kinase 2 during S phase and it initiates the activation of cyclin B1-CDK1 at G_2/M transition (57). Bendris *et al* (58) found that cyclin A2 is a novel regulator of the actin cytoskeleton. In cells deficient of cyclin A2, the cytoskeleton is evidently deranged and the localization of focal adhesions is markedly changed, which may be rectified by cyclin A2 based on the RhoA-ROCK signaling pathway.

3. Microtubule network

The microtubule network is another type of cytoskeleton that provides the driving force during cell migration (59). The microtubule is a polymer form of tubulin dimers. α-tubulin modifications are regulated at a posttranslational level to affect cell motility (60). During the EMT program, the tubulin tyrosine ligase enzyme is downregulated, leading to the detyrosination of α-tubulin at the invasive side. The accumulation of detyrosinated α-tubulin is essential for the formation of microtentacle, which is a microtubule-based membrane extension. Glu-tubulin and Twist expression levels exhibit good concordance *in vivo* and *in vitro*, particularly at the earliest stages of tumor migration and invasion (61).

In the monolayer culture, stress fibers and microtubules act in concert to support the certain cell shape (59). In the 3D culture, actin filaments were distributed mainly at the surface of the cell body and few stress fibers were observed in the center of the protrusions in the EMT-induced cells; by comparison, microtubules were mainly detected in the protrusions. In cells without EMT induction, microtubules exhibit uniform distribution in the cytoplasm. The morphology of protrusions in the 3D collagen gel culture also appear to be markedly different from that in the 2D culture, demonstrating that the living environment of cells has an affect on the protrusion formation. The result that colchicine, rather that

cytochalasin B, efficiently prohibited the formation of invasive protrusions demonstrates that the invasive protrusions are microtubule-based structures. The cell protrusions cannot be blocked by inhibitors for membrane type 1 matrix metalloproteinase 1, proto-oncogene tyrosine-protein kinase and phosphoinositide-3 (PI3) kinase. This result further demonstrates that the invasive protrusions in 3D collagen gel are not supported by the actin cytoskeleton (62).

The microtubule-associated protein tau plays a fundamental role in the regulation of tubulin assembly required for the formation of membrane protrusions (63). Protein phosphatase 2 and heat-shock protein 90 act on tau to regulate the microtubule stability, which are required for the protrusion formation (64,65). Certain actin cytoskeleton regulators, such as PI3K-Akt signal and Rho GTPases, were newly recognized essential regulators of the microtubule stability (66,67). Further investigations are required to prove the specific regulatory mechanism for the actin cytoskeleton and the microtubule network.

Tian *et al* (68) reported a novel mechanism of microtubule regulation via hepatocyte growth factor (HGF)/Rac1/PAK1/stathmin signaling pathway. HGF stimulates the phosphorylation of the stathmin through the Rac1 activation to regulate the microtubule dynamics (69). HGF also increases the peripheral microtubule and stimulates the growth of acetylated tubulin (70). Stathmin is involved in regulating cell migration and cell cycle and a recent study has provided evidence indicating that stathmin has a significant role in regulating microtubule dynamics (71). Stathmin has been indicated in regulating the destabilization of the microtubule network by disassembling the microtubule polymer into α/β-tubulin heterodimers and by raising the catastrophe frequency (72). The phosphorylation of the stathmin at its four serine residues is closely associated with its activity to destabilize microtubules (73). The interaction between stathmin and the α/β-tubulin heterodimers also modulates the activity of stathmin. Li *et al* (74) reported that Siva1 restrained the activity of the stathmin through the Siva1-CaMKII-stathmin signaling to promote the microtubule formation and inhibit the EMT and tumor metastasis. Siva1 functions to stabilize the microtubule network to suppress EMT.

Anaphase-promoting complex (APC)/β-catenin-rich complexes are mainly distributed among membrane extensions and they have a robust impact on tumor cell behavior (75,76). The APC is generally localized at protrusion tips depending on the microtubule network but not the actin cytoskeleton (77). β-catenin was also concentrated at the protrusion ends (78). The APC/β-catenin-rich complex activation, which is adjusted by the phosphorylation level, controls cytoskeletal dynamics that regulate tumor cell morphology and the migratory potential. Odenwald *et al* (79) identified that these complexes were dependent on an intact microtubule network to be fully functioning. The suppression of the protrusion-associated APC/β-catenin complex would intensely prevent the invasion and migration of tumor cells, but does not have a profound effect on cell proliferation.

Certain antitumor drugs have been reported to function through impact on microtubule dynamics, resulting in abnormal apoptosis and mitosis. Taxol was the first drug known to promote tubulin assembly and inhibit microtubule disassembly to interrupt the mitosis. It can then steadily fix the cancer cells in the mitotic phase from rapid reproduction (80). ABT-751, a type of orally-active anticancer compound, works through binding firmly to the tubulin dimers to stabilize them (81). Vinca alkaloids, an anticancer drug, increase the tubulin expression and change the mitotic spindle microtubule dynamics, inhibiting cell mitosis (82). As microtubules have a significant effect on tumor migration and invasion during EMT, the mechanism of these antitumor drugs may function not only through inhibiting cell division, but also through inhibiting the formation of the microtubule network-based membrane protrusions that provide the driving force during cell migration and cell invasion (83-85).

4. Intermediate filaments

Intermediate filaments are essential constituents of cytoskeletal proteins, ubiquitous in eukaryotic cells, and are ~10 nm in diameter (86). Helfand *et al* (87) reported that the largest genes family of the human genome encodes the intermediate filaments, which are one of the most rubbery and insoluble structures in cells. This family has six isoforms with different amino acid sequences, including type I-VI, of which vimentin and nestin attract the most attention (88). Although different isoforms have different structures, they are organized with similar structural domains (89).

Intermediate filaments function in supporting the plasma membrane and maintaining the cell shape (90). As they are localized to the plasma membrane through transmembrane proteins, they are involved in maintaining the traction forces between cells and protecting cells from disruption. Unlike the actin cytoskeleton and the microtubule cytoskeleton, intermediate filaments show distinct patterns of tissue expression (91).

A type I intermediate filament, keratin, is specifically expressed in epithelial cells, while type III intermediate filaments are mostly expressed in the endothelial, mesenchymal and hematopoietic cells (92-94). During the EMT process, intermediate filaments are significantly rearranged, typically switching from cytokeratin-rich to vimentin-rich networks (95). Cell motility capacity is significantly enhanced due to the intermediate filament change. Under the stress stimulation, intermediate filaments are also significantly upregulated to induce the rearrangement of the cytoskeleton (96,97).

A type III intermediate filament, vimentin, is a typical marker for the mesenchymal cell (91), which is attracting increasing attention as a classical EMT biomarker. Vimentin maintains the cell shape in a quiescent cell; however, it is involved in the highly dynamic remodeling of the cytoskeleton in a motile cell (98). Vimentin has previously been indicated to be upregulated during EMT in epithelial cells, resulting in a more mesenchymal phenotype and motile behavior (99). Liu *et al* (100) used time-lapse video microscopy to indicate that vimentin is closely associated with the metastatic potential of epithelial cells measured by the wound healing assay. Silencing of vimentin may inhibit the invasion and migration of renal cell carcinoma (RCC) cells. As it is found that silencing vimentin would switch mesenchymal cells into epithelial phenotype and that the transfection of vimentin would change epithelial cells into mesenchymal phenotype, the level of vimentin expression

is strongly linked to mesenchymal phenotype. The level of vimentin expression was significantly upregulated in clinical RCC specimens, as compared to normal tissues by immunohistochemistry assay. Vimentin is regulated by *miR-138* and *miR-141,* which participates in cell migration, adhesion and signaling processes (101).

A type VI intermediate filament, nestin, was initially characterized as a biomarker of functional stem cells, such as central nervous system stem cells, but now it is described as a biomarker of various cancer stem cells, including ovarian, head and neck, prostate and brain tumors, based on the phenomenon that nestin are found abundant in the invasive edge of cancer stem cells (102). Nestin reportedly interacts with vimentin or desmin to form heterodimers or polymers; these structures provide cellular mechanostructural support, maintain cellular membranes and restrict organelles to a limited area (103).

Nestin has also been found to function through interaction with other intermediate filaments, such as vimentin and desmin, to regulate apoptosis-related factors, to support cellular mechanostructure and to coordinate cytoskeleton reorganization during mitosis (104).

Kawamoto *et al* (105) indicated that nestin played a significant role in stromal and nerve invasion. Matsuda *et al* (106) suggested that nestin is involved in the process of cell invasion and migration through impacting on the actin cytoskeleton and cell adhesion behaviors. Nestin not only takes part in the EMT process, but it also participates in a positive feed-forward loop that regulates the tumor metastasis. TGF-β1 was found to upregulate nestin expression predominantly by the Smad4-dependent pathway, while nestin overexpression was shown to increase the expression of TGF-β1 and its downstream signals at the gene and protein levels through the same signal. The autocrine positive feedback regulatory loop between nestin and TGF-β1 is decisive to the tumor metastatic network, which provides novel ideas for the cancer treatment. Nestin overexpression was also demonstrated to provide tumor cells with a high metastatic motility, promoted cancer cell growth by degrading extracellular matrix and suppressed immune responses by nullifying interleukin 2, cytotoxic T lymphocyte and Toll-like receptors, which are all crucial molecules for host immune surveillance (107).

5. Future directions

The cytoskeleton is a dynamic network of three intracellular filaments that play a fundamental role in the management of cell shape and behaviors. It is an attractive potential therapeutic target for cancer metastasis due to its close association with EMT. However, there is an accumulation of evidence in the literature demonstrating that several metastatic and invasive cancers have not undergone a thorough EMT. These cancers may even lack signs of EMT, including the loss of epithelial features, the reduction of the epithelial marker E-cadherin and the increase of mesenchymal proteins (108). The TGF-induced EMT is also found to restrain cell invasion, which may be alleviated by overexpression of hyperactivated Ras (109). Thus, more research is required to understand the intricate association between cellular dynamic cytoskeleton and cancer invasion. Further study in more depth is also required to depict the features of the dynamic expression and arrangement of intracellular filaments during cancer invasion and migration. In anticancer research, the main difficulty lies in specifically inhibiting the dynamic cytoskeleton reorganization associated with cancer progression.

Acknowledgements

The present study was supported by a grant from the Shanghai Science and Technology Department of Medicine for guiding biomedical projects (no. 134119a1400) and a grant from the Research Fund for the Doctoral Program of Higher Education (New Teacher) (no. 20130071120048).

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