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Chapter 15

Novel Insights into the Role of the Cytoskeleton in Cancer

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Abstract

The cytoskeleton is a complex network of highly ordered intracellular filaments that plays a central role in controlling cell shape, division, functions, and interactions in human organs and tissues, but dysregulation of this network can contribute to numerous human diseases, including cancer. To clarify the various functions of the cytoskeleton and its role in cancer progression, in this chapter, we will discuss the microfilament (actin cytoskeleton), microtubule (β-tubulin), and intermediate filament (keratins, cytokeratins, vimentin, and lamins) cytoskeletal structures; analyze the physiological functions of the cytoskeleton and its regulation of cell differentiation; and investigate the roles of the cytoskeleton in cancer progression, the epithelial-mesenchymal transition process (EMT), and the mechanisms of multidrug resistance (MDR) in relation to the cytoskeleton. Importantly, the cytoskeleton, as a key regulator of the transcription and expression of many genes, is known to be involved in various physiological and pathological processes, which makes the cytoskeleton a novel and highly effective target for assessing the response to antitumor therapy in cancer.

Keywords: Cytoskeleton, Regulator, cell differentiation, drug resistance, EMT

1. Introduction

The cytoskeleton is a structure similar to a bird's nest; it can be tightly packed or sparse and is found in both prokaryotes and eukaryotes [1]. The main component of the cytoskeleton is protein, and the specific differences in structure never affect the type of proteins incorporated [2]. The cytoskeletons of prokaryotes display apparent plasticity in composition, without conservation of the core filament-forming proteins. However, the eukaryotic cytoskeleton has evolved in a variety of functions through the addition of accessory proteins and extensive

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gene duplication. The distribution of cytoskeletal filaments puts constraints on the likely prokaryotic line that made the leap into eukaryogenesis [3].

There are three main cytoskeletal structures in eukaryotes, microfilaments (MFs, ≈7 nm diameter), microtubules (MTs, ≈25 nm diameter), and intermediate filaments (IFs, ≈10 nm diameter) [1]. MFs are responsible for cell contraction and reinforcement of the cell surface and allow changes in cell morphology. Actin and tubulin are the main globular proteins that form MFs and MTs, respectively. Actin is a ubiquitous eukaryotic filament-forming protein. Actin filaments (also called microfilaments or F-actin) consist of two proto filament polymers wound together in a right-handed helix [3]. Eukaryotic actin is a member of a large and diverse superfamily of ATPases that includes Hsp70 chaperones and several classes of sugar/sugar alcohol kinases [4, 5] as well as eukaryotic actin-related proteins (ARPs) [6, 7]. The actin cytoskeleton is involved in actin-based cytoskeletal structures, including various functionally distinct structures of actin organization, and can be regulated by actin regulatory proteins. It is well known that the actin cortex consists of a dense mesh-like array of F-actin anchored to the cell membranes [8, 9]. This structure provides the core "skeleton" of the cell, functioning to define cell shape and provide resistance to mechanical stress. Reorganization of the actin cytoskeleton describes a process where cells actively alter the architecture of actin filaments to adjust cell shape in response to environmental requirements. Globular- (G-) actin is a highly conserved, polar protein with a molecular weight of 42 kDa that forms dimers and trimers in a process called actin nucleation; these structures then assemble into a double-stranded helical filament (F-actin) with a diameter of 7–9 nm (actin polymerization) [10–15]. Filopodia are thin, hair-like cellular protrusions that consist of parallel actin bundles cross-linked by interacting protein partners such as fascin, α-actinin, fimbrin, and formins [16]. Filopodia sense changes in the cellular microenvironment, such as growth factor concentrations, to guide cellular movement through the surrounding matrix [10–12]. Fascin is a highly conserved actin-bundling protein with three isoforms. While Fascin-1 is ubiquitously expressed during embryogenesis, its expression is later restricted to the endothelium, neuronal tissue, and testis [16]. Fascin-2 and Fascin-3 are expressed in the retinal epithelium and testis only [17]. Fascin is phosphorylated by protein kinase C (PKC), which regulates its actin bundling activity in accordance with the current microenvironmental conditions, which are communicated via surface integrins [16].

Microtubules are responsible for structural strength and cell shape. They allow organelles to move within cells. These structures act like rails on which kinesin and dynein can pull organelles. Most microtubules consist of 13 protofilaments that interact laterally to form a hollow tube and arise from the polymerization of heterodimers of a- and ß-tubulin, which are added to the plus-end of microtubules containing GTP in both subunits [3, 18].

As the major components of the cytoskeleton, intermediate filaments (IFs) are ubiquitous cytoskeletal elements that are encoded by about 70 genes in the human genome [19–21] and are divided into six groups based on their structure. These groups include the keratins, cytokeratins, mesoderm-specific intermediate filaments, neurofilaments and related proteins, lamins, and beaded filament proteins of the eye lens [21–24]. Although these IF proteins have very different amino acid sequences, the organization of the structural domain is similar [24]. The keratin group is defined as the group of intermediate filaments within epithelial cells, forming particles from 44 kDa to approximately 66 kDa that are characterized by high stability and

chemical resistance [25]. As the major structural proteins of the nuclear lamina, the lamins are subdivided into A- and B-types, both of which belong to the type V intermediate filament protein family [26].

On the other hand, prokaryotes also have homologs of the eukaryotic microfilaments (actin), microtubules (tubulin), and intermediate filament proteins [27]. FtsZ was first found in the prokaryote as the cytoskeleton and forms filaments but not tubules [28]. The MreB and ParM proteins in prokaryotic cells function like actin in eukaryotic cells [29]. The third type of cytoskeleton in prokaryotes is crescentin, which is responsible for the shape of cells [30].

2. The physiological functions of the cytoskeleton and the regulation of cell differentiation

The cytoskeleton is the frame around or within the cell, and a system of intracellular filaments is crucial for cell shape, division, and function in all three domains of life [3, 4]. The classical functions of the cytoskeleton have been summarized as morphology determination, cell polarity formation, structural support, membrane constitution, cell motility, and receptor or channel localization in the plasma membrane [31–33].

The activity of actin, the main type of microfilament, is regulated by GTPases, which control the formation of actin filaments [34–36]. In patients with Alzheimer's disease (AD), actin filaments play a central role in maintaining and modifying synaptic connections [37]. As the key mediator between receptor activation during learning and a protein involved in regulating spine morphology [38, 39], actin not only plays a role in the nervous system but also has functions in the immune system [40]. For example, F-actin can mediate signaling in B cells and T cells [41, 42]. The dynamics of the actin cytoskeleton regulate adhesion and signal transduction in T cells/APCs [40]. SWAP-70 and HS1 are important downstream components of the TCR signaling pathway and are regulated by actin [43, 44].

The key function of intermediate filaments is to support the cell membrane, serving as a structural scaffold to maintain cell shape. Cell motility is significantly enhanced as a result of changes in intermediate filaments. Intermediate filaments are fixed to the membrane through transmembrane proteins such as cadherins, which are involved in the formation of cell-cell tight junctions and the distribution of traction forces that arise in the interspace between cells. Under stress stimulation, intermediate filaments are significantly upregulated to induce the rearrangement of the cytoskeleton [45, 46]. Keratins are proteins that form intermediate filaments of epithelial cell cytoskeleton and have an antiapoptotic function, regulate protein synthesis, and play a role in wound healing [25]. Epithelial cells obtain a specific pattern of keratin expression during differentiation and maturation; this pattern reflects the specificity of the tissue and the degree of maturation [25]. The different components of the cytoskeleton do not work alone, and microtubules, microfilaments, and intermediate filaments often interact with each other to complete cellular processes. They always participate in protein localization and cell signaling. A characteristic of differentiation is a change in cell shape that is dependent on the cytoskeleton. During mesenchymal stem cell differentiation, the actin cytoskeleton of mesenchymal stem cells changes during osteogenic and chondrogenic differentiation [47].

Previous studies have shown that adipocyte differentiation is associated with actin structure [48, 49]. Disruption of the actin cytoskeleton can regulate MKL1 and result in adipocyte differentiation [50]. Rearrangements in and the formation of processes by the cytoskeleton are associated with the synthesis of synaptopodin, which is a marker of differentiated podocytes [51]. Moreover, cell differentiation is regulated by activating or repressing some transcription factors and is linked to the cytoskeleton [52–57]. For example, Zoubiane demonstrated that microtubules were required for β-casein expression, which resulted in epithelial cell differentiation [55]; Ahmad discovered that the pattern of microtubules in HL-60 cells changed following differentiation, with α-tubulin appearing more regularly organized in the differentiated HL-60 cells [56]; Takiqawa also confirmed that the cytoskeleton, including microtubules and microfilaments, regulates the expression of a differentiated phenotype in chondrocytes [57].

3. The cytoskeleton and its role in cancer progression

The cytoskeleton is known to contribute to cancer. The cytoskeleton may induce cell proliferation and activate oncogenes, resulting in tumorigenesis [58]. In mammary carcinoma cells, the upregulation of WNT4 increased mesenchymal and cytoskeleton remodeling markers [59]. CKAP4 (cytoskeleton-associated protein 4) is a DKK1 binding protein expressed on the surface of cells, with DKK1/CKAP4 promoting pancreatic cancer and lung cancer [60]. DKK1 is considered a factor that can modulate the β-catenin pathway and stimulate cancer cells or noncancerous proliferation [61, 62]. Zyxin localizes to focal adhesion sites and stress fibers in response to mechanical cues and has been shown to control the assembly of the cytoskeleton, the generation of traction force, cell movement, and signal transduction. If zyxin is nonfunctional, the cytoskeleton may be disturbed, leading to cancer [59].

Many actin-bundling proteins are also linked to cancer progression and tumor chemoresistance [63]. Fascin proteins organize F-actin into parallel bundles and are required for the formation of actin-based cellular protrusions. The inhibition of fascin can interfere with the formation of filopodia and suppress the migration and invasion of tumors [64], making it possible to use fascin as a small molecular target to inhibit cancer metastasis.

Intermediate filaments interact with arcs and can inhibit the activity of arcs, which can transport intermediate filaments to cell nucleus. However, fewer intermediate filaments may alter the cell shape and lead to diseases such as tumors [65]. For example, the changes in nuclear architecture that are the pathological hallmarks of cancer cells are related to alterations in the lamins, with alterations in lamins A/C being verified in the colon [66], gut [67], lung [68], and prostate cancer [69].

4. The role of the cellular cytoskeleton in epithelial-mesenchymal transition (EMT)

Epithelial-mesenchymal transition (EMT) is a biological process resulting in the loss of polarity and cell junctions, and disturbances in the cytoskeleton [70]. The reorganization of the actin cytoskeleton is important for metastasis and the differentiation of epithelial cells to

mesenchymal cells [71]. When cells undergo EMT, the number of β-actin fibers is reduced and the distribution of β-actin becomes diffused. RhoA induces action fiber formation and regulates the cytoskeleton. The Rho family also plays a role in tumor migration and EMT [72]. Cellular transformation was closely associated with changes in the distribution and amount of cytoplasmic actin isoforms [73]. Actin filaments are formed by the polymerization of G-actin, which induces the formation of a leading edge in cancer cells undergoing EMT through interactions with binding proteins and contractile proteins such as myosin II, which accelerates the movement of actin fibers on the substrate to the leading edge [74].

Tubulin plays an important role in EMT induction and contributes to TGF-β-induced membrane extensions or protrusions of human carcinoma cells undergoing EMT in three-dimensional collagen gels [75]. Acetylated α-tubulin can serve as a new marker of EMT and is expressed at a high level on normal epithelial cells, while the expression of acetylated α-tubulin decreases during TGF-β-induced EMT [76]. β-III tubulin can modulate snail expression during EMT in HT-29 and LS180 colon cancer cells [77]. When human mammary epithelial cells undergo EMT, the expression of Twist or Snail downregulates the tubulin tyrosine ligase enzyme, leading to the detyrosination of α-tubulin. The accumulation of detyrosinated Glu-tubulin is vital for the formation of microtentacles. These results provide new insight into tumor progression, as increasing α-tubulin detyrosination could promote EMT [78]. Because of their effect on tumor migration during EMT, the inhibition of microtubules can be a useful target for antitumor drugs [79, 80].

During the EMT process, intermediate filaments are significantly rearranged, typically switching from cytokeratin-rich to vimentin-rich networks [81]. Intermediate filaments can be expressed in different types of cells. For example, keratins are specifically expressed in epithelial cells; type III (mostly mesodermal) proteins are expressed in mesenchymal cells [82–84]. Epithelial cells express different keratins that are considered almost specific markers, whereas mesenchymal cells, endothelial cells, and hematopoietic cells express vimentin [82, 85, 86]. Vimentin is a type III intermediate filament that is significantly upregulated during EMT in epithelial cells; thus, vimentin can be used as a marker of EMT [87]. E-cadherin is one type of cell adhesion molecule that regulates EMT [88]. Reduced CK8 expression is regarded as an indicator of EMT, leading to more malignant forms of cancer [89]. Breast milk exosomes containing high levels of TGF-β2 can induce changes in both benign and malignant breast epithelial cells, consistent with the development and progression of breast cancer, which occurs due to alterations in cellular shape and the actin cytoskeleton and the loss of cell-cell junctions [90]. TGF-β-induced EMT was found to restrain cell invasion, which may be alleviated by the overexpression of hyperactivated Ras [91]. Endocytosis has emerged as a highly interconnected infrastructure of various cellular circuitries that is essential for the execution of different cellular programs, including those promoting a canonical EMT program and relying on the activation of Wnt, Notch, or TGF-β signaling [92]. On the other hand, miR-200 can inhibit EMT and the migration of cervical cancer cells through RhoE, which is an actin-binding protein [93]. Therefore, the cellular cytoskeleton plays a role in EMT by activating Wnt, Notch, or TGF-β signaling pathways, triggering the reprogramming of gene expression patterns via transcriptional changes and the altered expression of mRNA, including epithelial (E-cadherin, claudins, occludins, desmoplakin, mucin-1, and cytokeratin-8, -9, -18) and mesenchymal markers (fibronectin, FSP1, vitronectin, vimentin, smooth-muscle actin, and FGFR2

IIIb and IIIc species variants) (**Figure 1**). Further in-depth study is required to determine the features of the dynamic expression and arrangement of intracellular filaments during cancer invasion and migration.

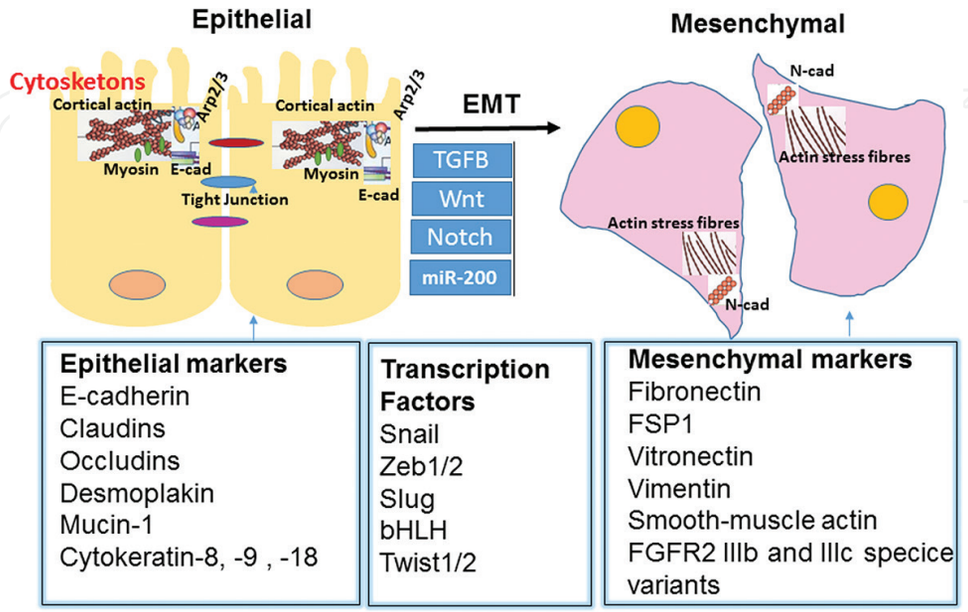


Figure 1. Cellular cytoskeletons in epithelial-mesenchymal transition process (EMT).

5. Mechanism of multidrug resistance (MDR) in relation to the cytoskeleton

Many patients develop drug resistance to anticancer agents, with the mechanisms including alterations in the ATP-binding cassette [94], microtubule dynamics, drug transport, and cell death [89], all of which involve tubulin and microtubules [95–97]. Microtubules have been considered a highly significant molecular target for anticancer agents, including microtubule-stabilizing agents. For example, paclitaxel binds to the β-tubulin subunit, accelerates the polymerization of tubulin, and stabilizes the resultant microtubules [98, 99]. Moreover, the paclitaxel-induced resistance of vimentin intermediate filaments to okadaic acid may occur through a microtubule-independent mechanism [100]. Townson also demonstrated that K8/18 filaments provided resistance to apoptosis in granulosa cell tumors by impairing FAS expression [101]. The organization of actin filaments associated with cellular differentiation may also influence the expression of P-glycoprotein (P-gp) through ezrin, radixin, and moesin in MDR osteosarcoma cells [92–104], which exhibit a significant increase in well-organized actin stress fibers [103], while inhibiting actin remodeling can suppress drug resistance in cancer [105].

The balance between polymerized and nonpolymerized tubulin will be a key determinant of the response to antimitotic-based chemotherapy. Cancer cells obtain mitotic drug resistance

properties through β I-tubulin mutations [106], which is important for maintaining microtubule structure and sensitivity to microtubule-targeting agents. β-tubulin mutations confer resistance to epothilone and taxanes in ovarian cancer cells. Moreover, mutations in both a- and β-tubulin have been found to confer resistance to colchicine and vinblastine in Chinese hamster ovary (CHO) cells [107, 108]. The upregulation of β III-tubulin was further associated with resistance to paclitaxel and docetaxel [109–113]. On the other hand, as a negative regulator of β III-tubulin, HDAC3 can also mediate drug resistance [113].

As a major intermediate filament in the cells of epithelial-derived tumors, cytokeratin K8/18 expression is involved in cytokeratin-dependent drug resistance [114]. Hepatocyte cytokeratin plays a role in bile formation and resistance to bile acid challenge; however, the loss of K8 significantly increased liver injury in response to toxic stress in mice [115]. Caulin also demonstrated that normal and malignant epithelial cells deficient in K8/18 were approximately 100 times more sensitive to TNF-induced death [116], indicating that interaction between the damaging agent and cytokeratin might trigger signaling responses for cell survival.

In our previous study, we found that tissue remodeling proteins such as KRTHB3, KRT7, KRT8, KRT17, TPM4, CRYAB, SEPW1, LGALS3BP, and VATI were overexpressed in resistant KB-v1 cells, implying that the intracellular vesicular transport of many drugs is partly controlled by cytoskeletal filaments [117]. Research into the cytoskeleton is experiencing increased interest and rapid advancement, which will provide a greater mechanistic understanding of the molecular pathways and mechanisms contributing to drug resistance and will enable the development of more patient-tailored therapies.

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