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Structures of Cytoskeleton and Disease Interactions

Hücre İskeleti Yapıları ve Hastalıklarla Etkileşimleri

Abdullah Melekoğlu[1], Oğuz Karahan[2*]

1.Kastamonu University, Faculty of Engineering and Architecture. Department of Genetics and Bioengineering,Kastamonu, Turkey
2.Alanya Alaaddin Keykubat University, School of Medicine, Department of Cardiac Surgery, Antalya, Turkey

ABSTRACT

Researchers reported different basics for different kind of diseases with advanced technology. Meanwhile, investigators are focused on to clarify the interactions of basic cellular mechanisms recently. Therefore, cytoskeletal researches are gain importance due to this tendency. The cytoskeletal structures are responsible for interconnects between cell nucleus, cytoplasm and also extracellular matrix, whereby it create a communication link between cellular molecules and signalization transport. The cytoskeleton is constructed from three kinds of protein filaments as: actin filaments, intermediate filaments, and microtubules. The nature of these structures is briefly outlined and the literature review that is reporting relationship between cytoskeleton components and common disorders is presented in this paper.

Key words: Cytoskeleton; actin filaments; intermediate filaments; microtubules; dis ease interactions

ÖZ

Araştırmacılar, ileri teknolojiye sahip farklı hastalıklar için farklı temeller bildirmişlerdir. Bu arada, son zamanlarda temel hücresel mekanizmaların etkileşimlerini netleştirmek için birçok araştırma yapılmıştır. Bu nedenle, hücre iskeleti araştırmaları bu eğilim nedeniyle önem kazanmaktadır. Hücre iskeleti yapıları, hücre çekirdeği, sitoplazma ve ayrıca hücre dışı matriks arasındaki bağlantılardan sorumludur, böylece hücresel moleküller ve sinyalizasyon iletimi arasında bir iletişim bağlantısı oluşturur. Hücre iskeleti, üç çeşit protein filamanından oluşur: aktin filamentleri, ara filamentler ve mikrotübüller. Bu makalede, bu yapıların niteliği kısaca özetlenmiştir ve hücre iskeleti bileşenleri ile yaygın hastalıklar arasındaki ilişkiyi bildiren literatür taraması sunulmuştur.

Anahtar Kelimler: Hücre iskeleti; Aktin filamentleri; ara filamentler; mikrotübül; hastalık etkileşimleri

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*Coresponding Authors: Oğuz Karahan. Alanya Alaaddin Keykubat University, School of Medicine, Department of Cardiac Surgery, Antalya, Turkey. +905063929320, oguzk2002@gmail.com

ORCİD: 0000-0003-0044-9476

INTRODUCTION

The structural integrity of organisms is provided by cytoskeleton that integrated system of biomolecules and organized spatial cellular interactions, basically [1,2]. Despite, the main structure of cytoskeleton is clarified, interactions between microstructural basis and its macroscopic reflections are still unclear [1]. Recent investigations revealed the important biomedical basis, with clarifying the complex interactions between cytoskeleton components that regulate the basic cellular events for predisposing response of organism [3]. The differences of the structural or architectural features of filaments provide the variations of bending rigidity. The cytoskeleton is consisting three major filamentous systems as; actin filaments, intermediate filaments, and microtubules, that are collaboratively responsible for the main functional tasks [1,3]. This introduction attempts to review together the main cytoskeletal components and disease interactions. Three main components were evaluated at three subtitle as actin filaments, intermediate filaments, and microtubules, separately.

Actin Filaments (Microfilaments)

Microfilaments are the thinnest filaments that composed to linear G-actin polymers. In eukaryotic cells, actin is the most abundant intracellular protein that is polymerize to form long, thin fibers. Actin monomers is a critical and conserved organizing structure and they have three main isoforms as α-actin, β-actin and ɣ-actin with different functions. α-Actin is usually related with contractile components of muscle tissues and also, β-actin is frequently associated with polymerization or other cellular interactions in most cell types [4,5]. The molecular weight of actin monomers (G-actin) is highly conserved 42 kDA proteins that is divided into two equal segment by a centered slit with each part containing two subdomains. Centered slit contains domains with a divalent ion (Mg^{2+} or Ca^{2+}) complexed triphosphate (ATP) or diphosphate (ADP) adhesion. G-actin, free globular monomers, can polymerized into long, helical filaments and they forms linear polymers called as F-actin. This polymerization can be induced with solutions which enriched with Mg^{2+}, K^{+}, or Na^{+} ions [6,7]. The main functions of actin cytoskeleton can be listed as follows [8];

- Its forms linear bands for preserve the shape of cell and strength of cell membrane,
- These intracellular bands also can provides specific functional units to the cell such as microvilli, filopodia, lamellipodia etc.
- The filamentous interactions of intracellular bands also helps cellular transportation system such as cytoplasmic streaming with signal transduction
- All these mechanistic interaction also gets a role in cellular growth, division, development, genetic information transfer and expression.

Actin polymerization is triggering by actin binding proteins with ordinary ways and also, disordered reactions are inhibited or suppressed by accessory proteins that regulate the balance for provide always high concentration of available construction materials. Profilin (enhanced polymerization with activating to ADP- ATP turnover and binds on monomeric (G) actin), cofilin (provides rotation with binding between two monomer and result with decomposition of filament with breaking the stability of filament) and thymosins (connecting with depolymerizing actin) are the main actin biding proteins that have different roles for actin polymerization or depolymerization. Arp 2/3 and formins are effective structuring initiators that forms the bottleneck of actin. Formins are responsible for the elongation and restructuring of unchained filaments. It consisting two main domain as formin homology 1 (FH1) and formin homology 2 FH2. FH2 allows to attaching the new subunit to attached to the barbed end of actin filaments with movement of release. Proline rich FH1 domain which contains various number of profilin binding site, binds on profilin and create profilin-ATP-actin complexes for accelerating filament elongation [9,12]. Arp 2/3 , core creator of branched filament structure, can be present in two situations as inactive or activated forms. A precursor protein is required for activating passive form which can be triggered by various signaling pathways [6].

Actin Filaments and Diseases

Responsibility of actin dysfunctions or deficiencies were investigated different kind of systemic

disorders. Disorders can be classified according to organ systems as follows;

Neurodegenerative diseases and actin cytoskeleton; The role of actin cytoskeleton in cell motility and signalization with creating specific functional units already described in the above. Therefore, researchers suggested that cellular structural alterations of cytoskeleton of neurons the formation of fibril-containing dystrophic neurites associated with senile demans can be related with this functional ability and they added that actin might be taking an important role in Alzheimer's disease (AD). Furthermore, actin cytoskeleton have cellular pathways that regulates synapse delivery and excitatory neurotransmission. Even these pathways are deteriorated in AD and the re-stabilization strategies on these pathways might be given therapeutically advance for AD. Briefly, investigators claimed that the defects in AD led to disorganized neuronal shape and size and/or movement of vesicle/organelle traffic along the neuritis with affecting the microtubule or actin filaments [12,13]. Moreover, the cofilin-actin rods stress response which is an indicator for dynamical function loss of actin cytoskeleton due to the stress is investigated for many types of neurodegenerative disease. Previous studies reported that these rods improperly formed in progressive AD, insensitive rod response with imbalanced dynamics of rods in Huntington disease (HD) [14]. On the other hand, insufficient functional cofilin levels were reported in Parkinson disease (PD) and mutant dysfunctional or unsatisfactory functional profilin levels were declared in Amyotrophic Lateral Sclerosis (ALS) [14].

Musculoskeletal diseases and actin cytoskeleton; Muscle fibrin protein dystrophin is an essential membrane-attached cytoskeleton protein that links supportive proteins to the actin filament. The pathologies between interactions of this protein or actin components might be lead to muscular dystrophies. The mutant gene that on dystrophin regulation is reported for Duchenne muscular dystrophy [15]. In addition, some other genetic mutations that caused to actin-mediated congenital myopathies were described in previous literature, for instance alpha-actin gene (ACTA1) mutation [16]. The disease related structural properties of F-actin was reported in intervertebral disc health and disease by Li et al. [17]. F-actin takes an important part in mechanotransduction and provide resistance between the extracellular matrix and cells of intervertebral disks. Therefore, the organization disorder in F-actin can caused to corrupt resistance of osmotic stress in vertebral disks [17].

Other diseases and actin cytoskeleton; Actin cytoskeleton has also task of podocyte foot process formation in renal glomerular capillary loop. This processes interdigitate with the foot processes of the neighboring cell, and forming a barrier which permits the entrance of fluids and small molecules but not to larger proteins, such as albumin. Therefore, researchers suggest that functional problems in actin components might be associated with proteinuria in renal disorders [18]. Current findings demonstrated that actin-cytoskeleton pathway is associated with the normal tissue transformation to the cancer development and metastatic progress such as colorectal cancer through cytoskeletal proteins [19]. It was found that actin cytoskeleton highly effective in the development of cardiovascular disorders by influencing myocardial function (heart failure) or affecting haemostatic balance (thrombosis) [20,21].

Microtubules

Microtubules are rigid hollow rods of about 25 nm in diameter. They are responsible to various cellular functions such as determination of cell shape, cell polarity and locomotion, transportation intracellular organelles, chromosome separation during mitosis. The microtubule associated cellular transport can be accomplished both directly with self locomotion of microtubules and indirectly by presenting motor proteins named as kinesin and dynein. Microtubule walls are created by polymerization of globular tubulin dimers and this formation is consisting with ring of 13 linear protofilaments around a hollow core. Tubulin is 55 kDA polypeptide that consists of two closely related heterodimers, called α and β-tubulin. Microtubule-associated proteins (MAPs) can provide the rapid cycles of assembly and disassembly of tubulin protein [6, 22,23]. Tau proteins accelerate the tubulin polymerisation and provide the stability. Phosphorylated MAPs cannot connect with microtubules and this condition means that

phosphorylation microtubules impairs the structures of microtubule [24]. Treatment strategies have developed according to microtubule dynamic and polymerization. For example, Colchicine, binds on tubulin and prevents its polymerization for constructing microtubule; another antimitotic agent Taxol binds to the microtubules directly and provides its stability which results with the inhibition of mitosis but does not affect other cellular abilities carried out by microtubules [6, 24].

Microtubules and Diseases

Neurodegenerative diseases and microtubules; Microtubules essential for vesicular trafficking, endocytosis and exocytosis and axonal polarity in neuronal system [12]. A genetic defect on regulation of superoxide dismutase (SOD) effectivity is determined as a pathogen factor for amyotrophic lateral sclerosis (ALS). Recent reports claimed that superoxide dismutase (SOD) mutations might be related with cytoskeleton components and vesicular transport motors. Also, it has been speculated that SOD may cause nitration of tubulin can be resulted motor neuron loss in ALS. Tau protein or/and microtubule deficiencies or functional disorders are also related with frontotemporal dementia and tauopathies (eg. Pick's disease, cortico-basal degeneration, progressive supranuclear palsy). Also gene mutation that occurs defective kinesin structures causes autosomal dominant spastic paraplegia type 10 [12,25].

Musculoskeletal diseases and microtubules; Microtubule assembly and bone formation is closely related and osteoblastic activity can be controlled through with this association. The formation of new bone formation was studied in previous reports with microtubule assembly inhibitors and these reports suggested that microtubule suppression results with stimulation of osteoblast differentiation [26]. In contrast, responsibility of microtubule associated proteins studied in osteogenesis. These studies demonstrated the anabolic effects of microtubule associated proteins with repression of osteoblastic activity [27]. These results present the regulator effects of microtubules on bone metabolism [26,27]. Microtubule network was also studied in regulating muscle cell morphology. Moreover, microtubule network integrity is indispensable for smoothly compliance of tubular myoblast cells during fusion and for appropriate fibrillar formation [28]. Hence, microtubule network was studied many kinds of musculoskeletal disorders.

Other diseases and microtubules; Microtubules are essential for cardiac adaptation and motor function as striated muscle. Maladaptive conditions and cardiac failure was reported in the defects of microtubule arrays. Colchicine, a microtubule depolymerizing agent is studied experimental heart failure models. Even, it is claimed that myocyte apoptosis can be inhibited with microtubule depolymerization [29,30]. In another study, the essential role of microtubules were described for podocytes of renal glomerulus and authors of this study indicated that regulation of microtubule dynamics might be new therapeutic target for glomerular adaptation in renal diseases with podocyte loss [31].

Intermediate Filaments

Intermediate filaments (IF) are 8-12 nm diameter networks that are consisted from extended α-helical rod IF proteins. Unlike other cytoskeletal filament types (actin filaments, microtubules), they are nonpolar filamentous structures that are more consistent and their forming infrastructure do not connect nucleotides as ATP [32]. IF protein family is divided in a six major classes according to tissue specificity. Classification and tissue distribution of IF summarized in Table 1 [3,33].

Keratins are the most diverse IF protein classes that are classically expressed from epithelial cells. It is expressed during the cell cycle in variable manner. Keratin have essential role for providing the integrity of epithelial cells. In contrast, Type III proteins are composed either homopolymer or heteropolymer IF filaments. In contrast, Type III proteins are composed either homopolymer or heteropolymer IF filaments. Vimentin is the most common type of this class which can expressed by leukocytes, blood vessel endothelial cells, some epithelial cells, and mesenchymal cells. Type IV IF proteins are typically neuropeptides which are responsible for the radial growth of an axon. Type V proteins are called nuclear lamins that are settles in cell nucleus and forms a nuclear network for transporting the knowledge of nuclear material [3,32,33].

Table 1. Classification, composition, and tissue distribution of basic intermediate filament proteins in mammals [3,33]

IF Protein	Protein Composition	Tissue Distrubution	Molecular Weight (10^{-3})
Type I	Acidic keratins	Epithelia	40 – 57
Type II	Basic keratins	Epithelia	53 – 67
Type III	Vimentin	Mesenchymal cells	57
	Desmin	Muscle cells	53
	Glial fibrillary acidic protein (GFAP)	Glial cells, astrocytes, stellate liver cells	50
	Peripherin	Diverse neuronal cells	57
Type IV	NF(neruofilament)-L	Neurons	62
	NF(neruofilament)-M		102
	NF(neruofilament)-H	Developing central nervous system	110
	Internexin		66
Type V	Nuclear lamins	All cell types (nucleus)	67-70
	Phakinin	Lens	45
	Filensin	Lens	83

Intermediate Filaments and Diseases

Neurodegenerative diseases and intermediate filaments; Peripherin defects was suspected for familial ALS. Because various genetic mutations encoding neurofilaments (NF) and peripherin found as influential factor in the pathogenesis of the disease. These studies claimed that filamentous aggregates renders motor neurons more sensitive against NMDA (N-methyl-D-aspartate)-mediated excitotoxicity. Also, it was reported that similar effects of genetic variances might of NF could be effective in axonal degeneration and Charcot-Marie-Tooth disease pathogenesis. Moreover, comprehensive data from previous studies support that cytoskeletal proteins highly released in axonal injury or severity of axonal injury might be related with serum concentration of NFs and also it can be related with severity of Parkinson disease [34].

Musculoskeletal diseases and intermediate filaments; Rheumatoid arthritis is an autoimmune disease and citrullinated vimentin is suspected as synovial autoantigen that is responsible for antibody reaction in development of this pathology [35]. The relationship between type 2 IF cytokeratin (epithelial keratin) and skeletal muscle maturity is shown in the literature. Vimentin and cytokeratin 8 might have important implications for activity and survival of the nucleus pulposus and these filaments were studied as cell marker of intervertebral cells (nucleus pulposus) [36].

Other diseases and intermediate filaments; The systemic results of genetic defects in intermediate filaments such as desminopathy was reported many kinds of organismal disorder and familial diseases. Two different kind of symptoms were observed in long-term follow-up study of a familial desminopathy as follows; cardiovascular disorders were more prominent for some of members while respiratory pathologies detected for others. Even, this infrastructural failure was manifested with musculoskeletal deformities or malignancy in some of the family members [37].

Conclusion: This paper is briefly summarizes the main features of cytoskeleton and its efficacy of almost all disease development or progression. All components of cytoskeleton together or individually have a role for different metabolic activity in different cell types and especially they are main actors for reactions at the cellular level. Therefore, better understanding of these structures will open new horizons for both the determining of the disease pathophysiology and developing new treatment strategies.

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