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Review

Management of cytoskeleton architecture by molecular chaperones and immunophilins

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ABSTRACT

Cytoskeletal structure is continually remodeled to accommodate normal cell growth and to respond to pathophysiological cues. As a consequence, several cytoskeleton-interacting proteins become involved in a variety of cellular processes such as cell growth and division, cell movement, vesicle transportation, cellular organelle location and function, localization and distribution of membrane receptors, and cell-cell communication. Molecular chaperones and immunophilins are counted among the most important proteins that interact closely with the cytoskeleton network, in particular with microtubules and microtubule-associated factors. In several situations, heat-shock proteins and immunophilins work together as a functionally active heterocomplex, although both types of proteins also show independent actions. In circumstances where homeostasis is affected by environmental stresses or due to genetic alterations, chaperone proteins help to stabilize the system. Molecular chaperones facilitate the assembly, disassembly and/or folding/refolding of cytoskeletal proteins, so they prevent aberrant protein aggregation. Nonetheless, the roles of heat-shock proteins and immunophilins are not only limited to solve abnormal situations, but they also have an active participation during the normal differentiation process of the cell and are key factors for many structural and functional rearrangements during this course of action. Cytoskeleton modifications leading to altered localization of nuclear factors may result in loss- or gain-of-function of such factors, which affects the cell cycle and cell development. Therefore, cytoskeletal components are attractive therapeutic targets, particularly microtubules, to prevent pathological situations such as rapidly dividing tumor cells or to favor the process of cell differentiation in other cases. In this review we will address some classical and novel aspects of key regulatory functions of heat-shock proteins and immunophilins as housekeeping factors of the cytoskeletal network.

Contents

Abbreviations: IMM, immunophilin; FKBP, FK506-binding protein; TPR, tetratricopeptide repeat; PPIase, peptidylprolyl-(*cis*/*trans*)-isomerase activity; Hsp, heat-shock protein; sHsp, small Hsp, Hsc, constitutively expressed heat-shock cognate 70-kDa; CHIP, carboxy-terminus of Hsc70-interacting protein; IF, intermediate filament; GFAP, glial fibrillary acidic protein; CCT, chaperonin-containing the T-complex polypeptide-1; TRiC, tailless complex polypeptide 1-ring complex;histone deacetylase; HDAC, histone deacetylase.

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1. Introduction

Cytoskeleton is the basic scaffold of the cell in which other subcellular components are spatially arranged, such that they are able to communicate efficiently between the internal and external environments of the cell. Although the folding system of this assortment of filamentous and tubular polymers composed of microtubules, microfilaments and intermediate filaments was discovered more than two decades ago, our understanding of the complex quality control pathway of these structures is still poorly understood and there are many unanswered questions that remain to be elucidated. The cytoskeleton is incomplete without its associated proteins. The proteins known to closely communicate with the cytoskeletal network include molecular chaperones that appear to protect the cytoskeleton in circumstances where cytoskeletal homeostasis is affected.

Molecular chaperones were first described as preferentially synthesized factors in organisms exposed to heat or other physiological stresses. In an attempt to restore cellular function under these conditions, some molecular chaperones prevent denaturation of proteins while others may dissociate protein aggregates, refold monomers, oligomers or simply direct them to their proteolytic cleavage. Nevertheless, chaperones are also synthesized constitutively and, under normal conditions, they also exert cardinal functions in the organization of the structures of the cell as well as in the functional efficiency of several signaling cascades. In this review it is analyzed the relationship between molecular chaperones and the organization of the structure and function of the cytoskeleton.

2. The cytoskeleton

The cytoskeleton constitutes the structural support of the living matter. It also plays key functional roles in the life time of the cells and during their replication. The cytoskeleton is present in all eukaryotic cells and was once thought to be an exclusive structure of eukaryotes, but homologues of the major scaffold proteins of the eukaryotic cytoskeleton have also been found in prokaryotes [1,2]. The cytoskeleton is a dynamic three dimensional filamentous structure that fills the cytoplasm maintaining the cell shape, enables the cell to move, and plays cardinal roles in the intracellular transport of vesicles, organelles and soluble proteins, during the cell division, the segregation of chromosomes, maintenance of proper cell shape, cell polarity and assembly of intracellular organelle-like structures. The three types of cytoskeletal elements that have been characterized in eukaryotic cells are tubulins, actins, and intermediate filaments (IFs).

2.1. Tubulin

Tubulin forms microtubules of about 25 nm in diameter consisting of straight 13 protofilaments that assemble into hollow tubules through lateral contacts to both sides of the protofilaments [3]. The cylinder yields a helical arrangement in which each turn of the helix spans three tubulin monomers (e.g., α, β, α). This generates a seam in the microtubule wall where, instead of the predominant αα and ββ lateral contacts, subunits are laterally adjacent to β subunits. Microtubules are organized from the minus end (in close vicinity with the centrosome) and extend through association of GTP-bound α-tubulin and β-tubulin heterodimers onto the plus end, which faces the cell periphery. The dimers are released from the minus end after hydrolysis, which destabilizes the intrafilament contacts. However, microtubules can rapidly release dimers from both ends and thus shrink, a stochastic event called *catastrophic collapse*, giving rise to dynamic instability of the filaments. Thus, tubulin filaments are highly dynamic elements within the cells. γ-Tubulin, which is homologous to α and β tubulins, nucleates microtubule assembly within the centrosome in a structure called microtubule organizing center (or MTOC). Around 12 to14 copies of γ-tubulin associate in the complex with other proteins called GRIPS (for gamma-ring proteins), this complex being capped at one end and thought to be the minus end terminal. Microtubule polymerization at this end is inhibited, and the GRIP proteins of the cap may be involved in mediating binding to the centrosome. Phosphorylation of a conserved tyrosine residue of γ-tubulin has been shown to regulate microtubule nucleation [4]. In vertebrate cells, but not in plants, a specific microtubule-based organelle is embedded within the organizing center, the centriole.

Microtubules set up the tracks of the mitotic spindle apparatus that are used to segregate chromosomes during mitosis and meiosis through dedicated motor proteins. Microtubules are key actors in organizing the spatial distribution of organelles in interphase cells, are stable components of cilia and flagella, and also serve to provide tracks for the transport of intracellular vesicles and other cargoes that are moved through cells by motor proteins such as dynein and kinesin, which show predominant retrograde and anterograde direction of movement on microtubules.

2.2. Actin

Actin forms a two-stranded, right-handed helical filament of about 7 nm in diameter with an axial rise of 5.4 nm per monomer that has a plus-/minus-end polarity and is also dynamic [5]. Owing to filament asymmetry, ATP-bound actin adds to the plus end (often called the *barbed end*) much faster than it does to the minus end (also called the