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Introductory Article

The cytoskeleton and disease

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Abstract
Cytoskeletal research in recent years has revolutionized cell biology and biomedicine. The cytoskeleton spans the cytoplasm and interconnects the cell nucleus with the extracellular matrix, thereby forming a structural link between molecules involved in cell communication on the one hand, and gene expression on the other. Since the cytoskeleton is involved in virtually all cellular processes, abnormalities in this essential cellular component frequently result in disease. In this introduction, the basic structure of the cytoskeleton is briefly outlined. Furthermore, the disease processes in which the cytoskeleton plays a decisive role, and which are reviewed in detail in the papers in this issue, are briefly introduced. The advances in our understanding of the cytoskeleton and its function in disease will lead to new diagnostic and therapeutic applications in the foreseeable future.

Keywords: cytoskeleton; nuclear matrix; disease mechanisms

Introduction

Cytoskeletal research in recent years has revolutionized the field of cell biology and biomedicine, with the accelerating emerging awareness of the complex interplay between cytoskeleton systems that provide the framework for nearly all cellular processes. Cytoskeletal filaments occur throughout the entire animal and plant kingdoms, and although micro-organisms may not produce these structures themselves, they often take advantage of them when infiltrating their eukaryotic host.

Structure and function of the cytoskeleton

Cytoskeletal systems consist of several filamentous networks that extend from the plasma membrane to the nuclear envelope and even the interior of the nucleus. The cytoskeleton also plays a role in anchoring the cell to its neighbours and to the extracellular matrix via specialized cell junctions that span the plasma membrane. A major fraction of total cellular protein, over 80% in some cells, is of cytoskeletal origin. The cytoskeleton is now known to consist of hundreds of different (associated) proteins cooperating in the organization of the complex machinery that is involved in essentially all structural and dynamic aspects of living cells, including maintenance of cell shape, cell movement, cell replication, apoptosis, cell differentiation, and cell signalling [1]. In view of the central importance and the incredible complexity of the cytoskeletal apparatus, advancing cytoskeleton research has become one of the central challenges of modern biology. Research in this field is now moving very fast and will certainly contribute to the development of more cytoskeleton targeted therapies in the next 10 years. In particular, a greater understanding of the cytoskeleton will provide benefits for diagnosis and therapy of human diseases, in the development of novel approaches for environmental monitoring, and in novel biotechnology applications.

The cytoskeleton of eukaryotic cells is composed of three major protein families that form filamentous structures running throughout the cell, ie microfilaments consisting of different actin isoforms, microtubules made of α- and β-tubulin, and the intermediate filaments, together with their associated molecular motors and regulatory protein complexes. The microfilaments and microtubules are assembled from highly conserved globular proteins, while the intermediate filaments are built from extended proteins with a central α-helical domain. Although these different proteins have a conserved substructure, they are characterized by considerable divergence with respect to their amino acid sequences in the non-α-helical head and tail domains. Various members of the intermediate filament protein family are expressed in a tissue-specific manner, as shown in Table 1. Next to these cytoplasmic filaments, the cell nucleus also contains supporting structures, such as the nuclear lamina, containing the lamins, one of the subfamilies of intermediate filament proteins. Finally, specific scaffolding structures may exist directly underneath the plasma membrane.
of specific cell types, such as the erythroid membrane cytoskeleton.

The functions attributed to these scaffolding fibres are manifold, but can be summarized as (a) functions that govern cell motility, (b) functions that govern cell proliferation, (c) functions that control and maintain cell morphology and tissue stability, and (d) functions in cell communication and intracellular signal transduction [2]. The extensive cross-talk between cytoskeleton systems is becoming recognized as critical for cell–matrix interactions and for maintenance of nuclear structure and function. In the past few years, the role of the cytoskeleton in multiple signal transduction pathways has been elucidated at the molecular level.

**The cytoskeleton and disease**

Cytoskeletal protein aberrations are the underlying reason for many pathological phenotypes. It is no surprise that modifications in such a crucial cellular structure lead to pathological conditions. Indeed, many diseases have now been associated with abnormalities in cytoskeletal and nucleoskeletal proteins, including several cardiovascular disease syndromes, neurodegeneration, cancer (invasion), liver cirrhosis, pulmonary fibrosis, and blistering skin diseases. The mechanisms by which many micro-organisms infect specific cells have been shown to depend on host cytoskeletal elements. Attempts to modulate the cytoskeleton by peptides or other specific drugs have already yielded interesting results and this will lead to new therapeutic agents in the foreseeable future. The impact on cancer treatment is a convincing example: anti-cytoskeletal (microtubule targeted) drugs are already used to inhibit cell division. The basic knowledge of microtubule-assembly processes will in future lead to more specific drugs that have fewer effects on healthy cells. Antibodies to the cytoskeleton are widely used for diagnostic purposes; for example, in cancer typing [3]. Research into the function, control, and maintenance of the cytoskeleton is therefore of major interest, not only to molecular biologists, cell biologists, and biochemists, but also to the medical, veterinary, and agricultural community.

The purpose of this review issue is to provide an update of cytoskeletal research, as it impacts on pathology. A wide range of topics has been chosen, to exemplify the significance of cytoskeleton knowledge for understanding disease mechanisms. We chose not to highlight the use of anti-cytoskeletal protein antibodies in pathology, as this is a field in itself, well developed and broadly accepted, and less important in terms of disease mechanisms [3]. A variety of cytoskeletal proteins were selected for discussion, as well as a range of organ systems, in which abnormalities of these proteins are responsible for often intriguing pathological processes. Any attempt to be comprehensive would have been futile, given the scope of the field and the explosion of knowledge.

The first three papers deal with the role that keratins play in congenital and acquired diseases in different organs. Lane and McLean [4] discuss keratins and skin diseases. The association of keratin mutations with genetic skin fragility disorders constitutes one of the most striking examples of cytoskeleton disorders. This has served as a paradigm for many other diseases and has been highly informative for the study of intermediate filaments and their associated components, elucidating the importance of this group of proteins for cell structure. These diseases have convincingly shown that, at least in the case of epidermal keratins, providing physical resilience to epithelial cells is their key function. Zatloukal and Denk [5] review how the keratin cytoskeleton is affected in liver diseases. Keratin intermediate filaments have been identified as a major intracellular target in a variety of liver diseases such as alcoholic and non-alcoholic steatohepatitis, copper toxicosis, and cholestasis. Keratin gene knockout mice have provided insight into the role of keratins in the hepatocyte: they are not merely providing mechanical stability as a key element in cellular structure, but constitute a target of toxic stress, the effects of which on the hepatocyte they modulate. The triad is completed by Owens and Lane [6], with a paper on keratin mutations and intestinal pathology. Limited evidence exists for simple keratin involvement in disease. Mutations in simple keratins have been found in patients with liver cirrhosis and chronic pancreatitis, and recently mutations in the simple keratin K8 were found in patients with inflammatory bowel disease. The effects of mutations in simple keratins would be expected to have mild effects on cells and indeed, distinct but less severe cellular abnormalities have been found. The authors discuss the evidence

**Table 1. Intermediate filament protein classification, composition, and tissue distribution**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Protein composition</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Acidic keratins</td>
<td>Epithelia</td>
</tr>
<tr>
<td>Type II</td>
<td>Basic keratins</td>
<td>Epithelia</td>
</tr>
<tr>
<td>Type III</td>
<td>Vimentin</td>
<td>Mesenchymal cells</td>
</tr>
<tr>
<td></td>
<td>Desmin</td>
<td>Muscle cells</td>
</tr>
<tr>
<td></td>
<td>Glial fibrillary acidic protein (GFAP)</td>
<td>Glial cells, astrocytes, stellate liver cells</td>
</tr>
<tr>
<td></td>
<td>Peripherin</td>
<td>Diverse neuronal cells</td>
</tr>
<tr>
<td></td>
<td>Synemin</td>
<td>Muscle cells</td>
</tr>
<tr>
<td>Type IV</td>
<td>NF-L</td>
<td>Neurons</td>
</tr>
<tr>
<td></td>
<td>NF-M</td>
<td>Neurons</td>
</tr>
<tr>
<td></td>
<td>NF-H</td>
<td>Neurons</td>
</tr>
<tr>
<td></td>
<td>Nestin</td>
<td>Neuroepithelial stem cells, muscle cells</td>
</tr>
<tr>
<td></td>
<td>α-Internexin</td>
<td>Neurons</td>
</tr>
<tr>
<td></td>
<td>Syncoilin</td>
<td>Muscle cells</td>
</tr>
<tr>
<td>Type V</td>
<td>Nuclear lamins</td>
<td>All cell types</td>
</tr>
<tr>
<td>Undeclassified</td>
<td>Phakinin</td>
<td>Lens</td>
</tr>
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<td></td>
<td>Filensin</td>
<td>Lens</td>
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that these mutations constitute a predisposing factor for inflammatory bowel disease.

The next section deals with acts in inflammation and repair. Chaponnier and Gabbiani [7] discuss actin isoforms in human disease. α-Smooth muscle actin has allowed us to identify the role of vascular smooth muscle cells in vascular development and vascular diseases and the role of myofibroblasts in wound healing, fibrocontractive diseases, and stromal reaction in cancer. The hallmark of a differentiated myofibroblast is an organized contractile apparatus consisting of α-smooth muscle actin-containing stress fibres. Recent data suggest that α-smooth muscle actin plays a direct role in myofibroblast contractile activity through its N-terminal domain AcEEED. Newly developed antibodies against α-skeletal and α-cardiac actins have shown that subpopulations of α-skeletal positive cardiomyocytes exist in the failing heart. Actin isoforms might be important in human disease but this needs to be further investigated. In the paper by Rottner et al [8], evidence is reviewed showing that in invading the host, infectious micro-organisms exploit the actin cytoskeleton. They have to overcome host defence mechanisms, which include mechanical and chemical barriers at the surface of the skin and mucous membranes, innate immunity, and the specific immune response. Only by clearing these barriers might micro-organisms reach the niche from which they can develop their pathogenic effects. Some micro-organisms have been found to induce actin rearrangements at the surface of infected host cells, resulting in the formation of pseudopod-like structures beneath intimately attached bacteria.

In the following section, a series of papers highlight the role that cytoskeletal abnormalities play in muscle- and neurodegenerative diseases. Clarkson et al [9] review the crucial role of actin cytoskeletal abnormalities in the development of congenital myopathy. Congenital myopathies constitute a heterogeneous group of disorders characterized by skeletal muscle weakness. Three major forms have been identified: actin myopathy, intra-nuclear rod myopathy, and nemaline myopathy. So far, five genes have been linked to congenital myopathy including α-actin, α- and β-tropomyosin, troponin-T, and nebulin; all are components of the thin filament of the sarcomere. The mutations identified within these genes have varying impacts on protein structure and give rise to different forms of congenital myopathies. Greater understanding of muscle formation and cause of disease has been and will continue to be gained from the study of the effect of mutations on protein function. Paulin et al [10] then discuss desminopathies in muscle disease. Desmin abnormalities lead to disorganization and loss of the desmin filament network and the accumulation of insoluble aggregates in striated muscles which destroy cell structure and interfere with function. Genes encoding desmin-associated proteins such as alpha-B-crystallin may also be involved. Knock-out mice have helped to reveal the fundamental role of desmin filaments in cell architecture, sarcomere alignment, myofibril organization, and the distribution of mitochondria. How intermediate filaments function in astroglial cells especially under severe mechanical or osmotic stress, in hypoxia, and in brain and spinal cord injury is reviewed by Pekny and Pekna [11]. Astocytes are the most abundant cells in the mammalian central nervous system (CNS), yet knowledge about their function in health and disease is limited. Recent experimental data in mice show that when astrocyte intermediate filaments are ablated, reactive glialosis in various CNS diseases is altered and the signs of CNS degeneration become more prominent. Dominant mutations in the GFAP gene have been shown to lead to Alexander disease, a fatal neurodegenerative condition in humans. This is further elaborated in the paper by Cairns et al [12], which focuses on the cytoskeleton in neurodegenerative diseases. The discovery of mutations in neuronal intermediate filament and tau genes had firmly established the importance of neuronal intermediate filament proteins and tau in the pathogenesis of neurodegenerative disease. Intermediate filament gene mutations cause Charcot–Marie–Tooth disease and amyotrophic lateral sclerosis. Tau gene mutations are responsible for fronto-temporal dementia with parkinsonism and tau polymorphisms are risk factors for progressive supranuclear palsy and corticobasilar degeneration. In vitro studies and transgenic animal models are presently being exploited to elucidate genotype–phenotype correlations and the details of cytoskeletal protein functions in cells of the nervous system.

The next group of papers deals with the role of cytoskeletal proteins in diseases of the lympho-haematological system. Birkenmeier and Barker [13] review how mutations in the genes encoding erythroid membrane skeletal proteins lead to hereditary haemolytic anaemias. Although the anaemia is usually the primary concern for the patient suffering from spherocytosis or elliptocytosis, primary or secondary effects are also encountered in other organ systems, as the seven erythroid membrane proteins are also expressed in a variety of other tissues. An example is the protein 4.1R, of which a deficiency leads to neurological symptoms. Research in this area is essential because the more known about the genetic mechanisms and the functional corollary of a gene mutation, the better will the developers of gene therapy (or other therapeutic modalities) be able to target the therapeutic approach. Calle et al [14] review the adhesive and motile behaviour of dendritic cells and the role of their cytoskeleton in cell adhesion and migration. As migration and cell–cell adhesion constitute essential elements in the development of an acquired immune response, disturbances of dendritic cell motility and adhesion have serious effects on the function of the immune system. This is the case in patients with the Wiskott–Aldrich syndrome (WAS), a syndrome characterized by immune dysreg-
The last paper of this review issue is dedicated to septins. Hall and Russell [17] argue convincingly why these proteins, which were discovered in yeast and have diverse cellular roles including polarity determination, cytoskeletal organization, membrane dynamics, vesicle trafficking, and exocytosis, belong in a cytoskeleton context. They do interact significantly with the cytoskeleton, notably actin and tubulin. There is substantial evidence to support the notion that septins play a role in neoplasia, neurodegenerative diseases, and infections.

References