Introduction

Cytoskeletal and nucleoskeletal interacting protein networks play critical roles in cellular function and dysfunction

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Within the cell, there are two major protein networks whose functions and interactions are critical for a large number of processes. These protein networks are the cytoskeleton localized in the cytoplasm and the nucleoskeleton present in the nucleus. They are separated by the nuclear envelope and, importantly, they are connected to each other through the linker of nucleoskeleton and cytoskeleton (LINC) complex embedded in the nuclear envelope. Together they play important roles not only in organization of cell structure and function but also in mechanotransduction and signaling pathways between the cytoplasm and nucleus and in regulation of transcription and gene expression.

The cytoskeleton is a complex fibrous reticular structure which is functionally very diverse.[1,2] It is composed of several types of cytoskeletal structures: actin filaments, microtubules (MTs), intermediate filaments (IFs), and spectrin.[1,2] There is both a cortical cytoskeleton, localized just beneath the cell membrane, and a cytoplasmic cytoskeleton.[1,2] The cortical cytoskeleton is comprised of a meshwork of actin filaments. Spectrin is associated with this actin network and links it to the cell membrane.[3] The cortical cytoskeleton provides the cell membrane with structural stability, flexibility, and elasticity and plays an important role in membrane shape changes in response to external forces.[1,2] The cytoplasmic cytoskeleton is composed not only of actin filaments, but also of MTs and IFs.[1,2] Spectrin is also associated with these structures and with the surface of organelle membranes where it supplies them with stability and aids in their interactions as well.[3–5] Cross-linking proteins, spectraplakins, are also involved in these interactions.[6,7] The cytoplasmic cytoskeleton is important in intracellular transport, stabilization of the cell, and force transmission.[1,2] Coordinated interactions between the cortical and cytoplasmic cytoskeletal proteins are essential for a number of cellular processes, including regulation of cell motility and migration, changes in cellular morphology, pinocytosis, endocytosis, cell adhesion, and signal transduction.[1–3,8,9] Exciting new research on these proteins has demonstrated that they have additional and combined roles in mechanotransduction, movement of the nucleus during cell locomotion, cell adhesion and migration, and formation and functioning of the immune synapse.[1,9–11] These cytoskeletal proteins form a dynamic and structured network that can respond to both internal and external signals and have the ability to reorganize as needed.[1,2,8,12,13] Their interactions with each other are involved in many of the crucial regulatory aspects of cell function and in maintenance of cellular homeostasis.[1,2,8] The importance of these proteins is evidenced in diseases in which loss, deficiency, or functional defects of a specific protein leads to physiological and pathophysiological consequences.

The LINC complex, which spans the nuclear envelope, acts as a bridge to link the cytoskeleton to the nucleoskeleton.[12–15] It has a critical function in transmitting forces generated in the cytoplasm to the structural elements of the nucleoskeleton, enabling communication of signals between the nucleus and cytoplasm.[10–15] It also plays an important role in maintaining the architecture of the nuclear envelope.[12–15] Protein components of the LINC complex associated with the inner nuclear membrane (INM) (SUN proteins) and the outer nuclear membrane (ONM) (KASH proteins) interact with nucleoskeletal proteins and cytoskeletal proteins, respectively, and are involved in a number of critical cellular functions which will be discussed in this thematic issue.[12–15]

Examinations of proteins associated with the nucleoskeleton have been more recent than those associated with the cytoskeleton, mainly due to technological advances in ability to identify these proteins in the nucleus. There is both a peripheral and an internal nucleoskeleton.[16,17] The peripheral nucleoskeleton lies in the periphery of the nucleus along the inner membrane of the nuclear envelope.[16,17] It is composed of the nuclear lamina, which is a complex network of nuclear lamins and associated proteins which include actin, nuclear myosin, emerin, titian, and spectrin.[16–22] It provides a structural framework for support of the nuclear membrane and nuclear architecture.[16–22] The peripheral nucleoskeleton also provides a platform for interactions with other functionally important nuclear

proteins and makes important contributions to chromatin organization, gene regulation, genomic stability, DNA replication, transcription, and DNA repair.[16–22] The internal nucleoskeleton also contains lamins, actin, and spectrin and is involved, among other roles, in organizing the genome and regulating gene expression.[16–22] Exciting new advances have been made in the complex interplay between structural proteins in the nucleus and transcriptional regulation, on the role these proteins play in interpretation of signals transmitted from the cytoplasm, and on their role in DNA repair.[18,21–26] Importantly, the roles these proteins play in various disorders and their mechanism of action are actively being investigated.

Recent studies have emphasized the importance of interaction of the cytoskeleton with the nucleoskeleton for the transmission of signals from the cytoplasm to the nucleus, where they are processed. Events are initiated when mechanical stimuli to the plasma membrane are conveyed to the cortical cytoskeleton. This leads to a mechanoresponse in which signals from the cytoplasm are transmitted to the nucleus where they undergo mechanotransduction and are converted into a biochemical response.[24,27] The LINC complex is critical in this process during which time the nucleoskeleton undergoes changes in structure, organization, or post-translational modifications (PTMs) that result in alterations in transcription and gene expression.[14,16,24,27] A well characterized example of this is the response of myofibroblasts to mechanical stress, in which the transforming growth factor beta (TGF-β) and Smad (a transcription factor) signaling pathway is activated after contraction in myofibroblasts.[27] Binding of TGF-β to its receptor on the plasma membrane leads to translocation of Smads from the cytoplasm into the nucleus.[27] Spectrin may play a role in this translocation. Within the nucleus, lamin A/C regulates this process by modulating the phosphorylation of Smads, which leads to TGF-β signaling.[27] Actin, and changes in its dynamics, play a role in regulating the MRTF-A/SRF (myocardin-related transcription factor-A/serum response factor [SRF]) signaling pathway in muscle and neuronal cells.[22,27] In the cytoplasm, G-actin binds to and sequesters MRTF-A. Mechanical stimulation can induce actin polymerization leading to release of MRTF-A from G-actin, allowing it to translocate to the nucleus. Polymerized actin in the nucleus does not bind to MRTF-A, enabling it, together with SRF, to activate MRTF-A/SRF target genes.[22,27] Thus, interactions between proteins in the cytoskeleton and nucleoskeleton play an important role in transmission of signals between the cytoplasm and nucleus that are important for a number of different cellular processes.

Advancements in our knowledge of the proteins associated with the cytoskeleton and nucleoskeleton and their interactions with each other will have significant impact on discerning just how, mechanistically, a deficiency or defect in these proteins can lead to disorders resulting from such deficiencies. In this thematic issue, a number of these structural proteins, their functions, and the new advances that have been made in their interactions with each other, and their roles in cell function are discussed. In addition, the pathological consequences of a deficiency in these proteins are highlighted as are potential mechanisms by which this may occur.

Contributions to this issue have been grouped into three broad areas: cytoskeletal proteins, cytoskeletal/nucleoskeletal proteins and the nuclear envelope, and nucleoskeletal proteins.

Cytoskeletal proteins

In the first article, Logan and Menko[28] review the dynamic and evolving roles of MTs in cellular function, the importance of their interaction with other cytoskeletal structures such as actin, myosin, and IFs, and their function as key integrators with these proteins in cytoskeletal coordination and in regulation of processes involving maintenance of cellular homeostasis. The lens, which grows and develops throughout an organism's life, is used as a model system for gaining greater insight into the expanding role of MTs in cellular functions. Recent investigations have demonstrated the importance of subpopulations of stable MTs (i.e. MTs that do not undergo cycles of polymerization and depolymerization) for a number of critical cellular processes. PTMs of subpopulations of these stable MTs play an important role in influencing MT interactions with other cytoskeletal elements and provide a structural framework for the mitotic spindle, centrioles, and cilia. They are important in regulation of crucial cellular functions such as intracellular transport of vesicles and organelles, cytokinesis, cell migration, and lens development and morphogenesis. Dynamic MTs, in contrast, are linked to reorganization and remodeling in cells. They act as a cornerstone for interactions with actin, myosin, and IFs and play a critical role in coordination of their activities. Interaction of these MTs with actin is important for growth dynamics, cell division, and cell migration. Their interactions with myosin are important in lens fiber migration and elongation, and their interactions with IFs, such as vimentin, are needed for organelle positioning, distribution of cell junctions, cell adhesion, wound repair, and cellular migration. There is increasing evidence that there are distinctive roles for stable MTs and dynamic MTs in the cell and that cellular homeostasis depends upon both groups of MTs and their interactions with other cytoskeletal proteins.

The article by Caporizzo *et al.*[29] focuses on the known physiological role of the cardiomyocyte MT network, the consequences of the pathological remodeling that can occur, and highlights some of the intriguing unanswered questions regarding the role of MTs in cardiomyocyte biology. Cardiomyocytes, rod shaped cells important in cardiac function, contain two groups of cytoskeletal networks: the contractile (i.e. sarcomeric) cytoskeleton, comprised of arrays of actin-myosin filaments organized into myofibrils, and the non-sarcomeric cytoskeleton, composed of actin, MTs, and IFs. The MTs and IFs form a cross-linked network responsible for intracellular transport, transmission of mechanical signals important in cardiac function, and organization of myofibrils and organelles. This review concentrates on the non-sarcomeric network and the extensive alterations that occur in MTs during both adaptive and pathological cardiac remodeling and which can

significantly alter the functioning of the cardiomyocyte. Post-translational regulation of MTs is a key determinant in their subcellular functionality. In heart failure, proliferation and PTMs of MTS are linked to mechanical impediment of cardiomyocyte contraction and relaxation. Specific PTMs can enhance MT stability by facilitating interaction with microtubule-associated proteins and IFs. This can lead to the increased myocyte stiffness and decreased cardiomyocyte contractile function which are observed in various forms of human heart disease. Interactions between perinuclear MTs and proteins associated with the LINC complex are important in cardiomyocytes in mechanotransduction of signals from the cytoplasm to the nucleus in response to cellular stress. This review highlights the interdependence of the cytoskeletal networks in the cardiomyocyte. It emphasizes the importance of taking this into account when designing protocols to perturb specific components of the MT network in the design of potential therapies which target the MT-dependent dysfunction that occurs in the progression of cardiovascular disease. It raises the possibility that reversing MT alterations could improve cardiac performance.

Goodman *et al.*[30] provide a comprehensive analysis of the function and importance of the multifunctional scaffolding protein, spectrin, and its critical roles in the cytoplasm and nucleus and in signaling pathways between these two cellular compartments. Goodman and his colleagues have created the Spectrinome using existing Human Proteome, Human Reactome, and Human Atlas data and have demonstrated how it can be used as a tool in visualizing and understanding the myriad of protein interactions and cellular functions in which spectrin is involved. Both erythroid and non-erythroid spectrins and various spectrin isoforms have been examined. First order (direct) and second order (indirect) interactions between spectrins and proteins in the nucleus and in the cytoplasm have been complied. In the cytoplasm, α- and β-spectrins are components of plasma and organelle membranes where they are important for cell–cell contact and for membrane shape, stability, flexibility, and elasticity. They play a role in transport of cargo along MTs and in signal transduction. In the nucleus, spectrin interacts with proteins involved in DNA repair acting as a scaffold in recruitment of repair proteins. It associates with lamins and other nucleoskeletal proteins and is critical for maintenance of nuclear architecture, mechanical stability, and elasticity of the nuclear envelope. Importantly, spectrins interact with proteins involved in a number of signaling pathways in which signals are transmitted from the cytoplasm to the nucleus. Among these is the TGF-β/SMAD signaling pathway. Spectrin also has its own E2/E3 chimeric ubiquitin conjugating ligating activity in red blood cells, and potentially in non-erythroid cells, which is involved in numerous cellular functions. This multitude of interactions of spectrin with other proteins in the cell suggests that defects or deficiencies in spectrin could lead to a multiplicity of disorders in addition to those already recognized, such as hereditary elliptocytosis and spherocytosis, Fanconi anemia (FA), B-cell malignant lymphoma, hepatocellular carcinoma, and spinocerebellar ataxia 5. The enormous progress that has been made in understanding the role of spectrin in cellular physiology and pathophysiology is portrayed by the Spectrinome, which will be extremely useful in charting future studies on a multiplicity of unanswered questions regarding spectrin's mechanistic role in a number of pathological processes.

The article by Machnicka *et al.*[31] reviews the important role of spectrin in cell surface activities such as cell adhesion and spreading, lamellipodia extension, cell–cell contact, and cell–extracellular matrix interactions. The interaction of αII-spectrin with proteins involved in actin polymerization and dynamics and its role in organization of the actin skeleton is important for these cell surface activities. Spectrins (αII-spectrin, βII-spectrin), either directly or indirectly, interact with different adhesion proteins. In epithelial and endothelial cells, αII-spectrin's interaction with specific adhesion molecules is required for stress fiber formation during cell spreading. αII-spectrin is also important in adhesive properties of neuronal cell bodies and neurites and in expression and organization of cell surface adhesion molecules involved in this process. In T lymphocytes, spectrins also play a role in immunological synapse formation. Spectrin is present at sites of immunological synapses in T lymphocytes and aids in initiation of cell adhesion. It regulates the localization and activity of actin, lymphocyte function-associated antigen 1, and specific adhesion protein CD54 in development of contact and signaling between T cells and antigen-presenting cells at the synapse. Spectrins are also important in specific areas of contact between cells at adherens junctions, tight junctions, and gap junctions where spectrin directly interacts with proteins involved in these junctional complexes. βII-spectrin and its interactions with actin are particularly important in some of the junctional complexes formed between epithelial cells. Pleiotropic effects of spectrin dysfunction likely reflect different roles of spectrin, depending on cell type and on the particular spectrin isoform involved.

King *et al.*[32] discuss the role and importance of cytoskeletal cross-linking proteins in coordinating and regulating the major cytoskeletal networks. One very important group of cross-linking proteins is the spectraplakins , which have the unique ability to bind to each of the major cytoskeletal elements (i.e. MTs, IFs, and actin) linking them together and coordinating their activities in the cell. This review concentrates on one subgroup of mammalian spectraplakins encoded by the *MACF1/ACF7* gene and known as actin cross-linking factor 7 (ACF7) or microtubule actin cross-linking factor 1 (MACF1). It focuses on the architecture, functions, and clinical potential of MACF1 and the *MACF1/ACF7* gene. Spectraplakins have a number of key functional domains, each of which interacts with specific components of the cytoskeleton. They function in the coordination and stabilization of the cytoskeleton showing predominance in specific tissues or in different stages of development. The authors discuss the role of MACF1 in disease pathogenesis. A specific mutation in the *MACF1* gene results in decreased expression of MACF1 and a disorder in which structure and motility of cells in skeletal muscles are affected. A link has been demonstrated

between MACF1 expression and cancer metastasis. Since MACF1 expression is more predominantly expressed in high-grade tumors such as breast cancer, it has been suggested that it could serve as a potential biomarker for a variety of metastatic cancers. Loss of MACF1 has a profound negative effect on the cytoskeletal dynamics, cellular motility, and cell adhesion involved in intestinal wound healing and may be an important factor in ulcerative colitis and Crohn's disease. Due to the pervasiveness of MACF1's regulation of the cytoskeleton, it is recognized as contributing to a growing number of disorders.

Cytoskeletal/nucleoskeletal proteins and the nuclear envelope

The article by Starr[33] focuses on the importance of the LINC complex in development and, particularly, on the importance of its interactions with proteins associated with the nuclear envelope that serve as effectors and force generators and which mediate nuclear positioning, a process critical during development. Two important components of the LINC complex are the SUN proteins, which are associated with the INM and interact with the nuclear lamina, and the KASH proteins, which are associated with the ONM and interact with cytoplasmic effectors (MTs, IFs, and actin). The SUN and the KASH proteins interact with each other within the perinuclear space. This review focuses on recent findings on the network of LINC proteins at the nuclear envelope, their importance in transmission of forces generated in the cytoplasm to the nucleus, and their function throughout development using *Caenorhabditis elegans* as a model. *C. elegans* contains one of the best-understood networks of LINC complexes and the data obtained from it are highly relevant to humans since almost all of the findings obtained are functionally conserved in humans. The interactions between the SUN and KASH proteins are summarized. How they maintain the architecture of the nuclear envelope, and the importance of their interactions with nucleoskeletal and cytoskeletal proteins for regulation of a number of cellular processes, particularly critical during development, is discussed. These processes include: nuclear positioning, in which KASH proteins interact with MT motors to move nuclei in somatic tissues; anchoring nuclei in syncytial cells; movements of meiotic chromosomes during prophase to enable homologous chromosome pairing; migration of nuclei through constricted spaces, as occurs in development and disease processes; and repair of DNA damage, through both the inhibition of non-homologous end joining (NHEJ) and the promotion of homologous recombination (HR). The involvement of the LINC complex in transmission of signals from the cytoplasm to the nucleus, how the LINC complexes are regulated and function in these processes, and how this is related to disease progression are of great importance and are a subject of extensive ongoing investigations.

Ostlund *et al.*[34] review mutations in genes encoding the nuclear lamins and associated nuclear envelope proteins which are linked to pathogenic mechanisms underlying a broad range of diseases, known as the laminopathies. Two of the major components of the LINC complex, the KASH and SUN proteins, interact and serve as a bridge to connect the nucleoskeleton to the cytoskeleton. Emphasis is placed on the molecular genetics of the nuclear lamins and the LINC complex. Genes encoding the lamins are divided into two types, A-type (the *LAMNA* gene) and B-type (the *LAMNB1* and *LAMNB2* genes). Mutations in these genes and those encoding KASH, SUN, and other nuclear envelope proteins cause the inherited diseases, the laminopathies. This review focuses on those laminopathies affecting A-type nuclear lamins, the SUN and nesprin (which contains a KASH domain) core proteins, and the LINC complex-associated protein, emerin. Diseases associated with mutations in A-type lamins include Emery–Dreifuss muscular dystrophy, Charcot–Marie–Tooth Disease type 2B1, and progeroid syndromes, notably the Hutchinson–Gilford Syndrome. Diseases linked to mutations in genes encoding SUN proteins, KASH proteins, and emerin include cerebellar ataxia, cardiomyopathy, and muscular dystrophy. Worman, Gundersen, and co-workers have recently shown that pathogenic mutations in genes encoding these nuclear envelope proteins lead to defective nucleocytoplasmic connections. Defects in coupling of actin filaments in the cytoplasm to nesprins can affect nuclear movement and lead to defects in nuclear positioning and cell polarity. Recent data are discussed which demonstrate that proper nuclear positioning, centrosome orientation, and establishing and maintaining nuclear polarity are essential for cell migration and proper function and development of organs. Mutations in genes encoding nuclear envelope proteins, which lead to defects in these processes, are thought to be important components of the pathogenic mechanisms underlying a number of diverse disorders such as the laminopathies.

Sankaran *et al.*[35] describe the critical role the nucleoskeleton plays in control of gene expression and how this is subject to regulation by external forces. Particular emphasis is placed on nuclear actin structure, which is a key architectural parameter that supports and regulates gene expression. This review describes the important role actin plays in regulating gene expression in mesenchymal stem cells (MSCs) during differentiation. In the bone marrow, physical force generated in the marrow space during dynamic exercise can be transmitted to MSCs. In the cell, this force is transferred from the cytoskeleton to the nucleoskeleton through tethering of actin in the cytoplasm to LINC complexes. Forces exerted on the LINC complex are transmitted into the nucleus causing structural rearrangements of the nuclear scaffolding, where the chromosomes are localized. Mechanistic models on how this occurs are described. External stimulation by both biomechanical and biochemical pathways transferred from the cytoskeleton to the nucleus can alter nuclear actin structure which can undergo modifications by enzymes that regulate its polymerization. Structural changes in actin can directly alter the arrangement of nuclear lamins and chromatin structure, which can profoundly affect gene expression by enhancing access of transcription factors to specific gene targets. Gene availability can, therefore, be modulated not only through transcription factors and enzymes that remodel heterochromatin

but by enzymes that mediate actin polymerization in the nucleus and by changes in nucleoskeleton structure. This, in turn, is mediated by the ability of actin to transmit external forces to the nucleus via its connections to nesprins associated with the LINC complex. These factors may be critical determinants in MSC differentiation and indicate that modulation of nuclear actin structure by force-activated pathways may represent a key architectural parameter that is important for stem cell differentiation.

Nucleoskeletal proteins

Arun *et al.*[36] present new findings in which they have examined, in human populations, novel missense alleles of the Sigma1R receptor (Sigma 1R; *SIGMAR1*), a protein localized in endoplasmic reticulum and nuclear envelope membranes, which associates with the nuclear membrane proteins emerin, lamins A/C, and BANF1 (barrier to auto-integration factor 1, an essential chromatin protein). Sigma1R binds with high affinity to addictive drugs (cocaine, methamphetamine) and drugs used to treat a range of neurological disorders. Cocaine enhances association of Sigma1R with emerin, lamin A/C, and BANF1, which leads to transcriptional repression of MAOB1, a gene that plays a role in removal of dopamine from neural synapses. Arun *et al.* have hypothesized that Sigma1R functions as a regulator of emerin and its protein binding partners in the brain, and possibly other tissues, and that mutations in Sigma1R may alter nuclear lamina function. Since human genetic variation in Sigma1R has not been studied in large populations, they examined the frequency of missense alleles of Sigma1R among 60,706 unrelated individuals in the ExAC database. They report on the identification of novel Sigma1R missense variants, two of which are of particular interest due to: (1) the widespread frequency of these variants in specific ethnic groups, and (2) analysis of the atomic structure of Sigma1R indicates that the molecular location of the affected residues in Sigma1R has the potential to perturb binding of Sigma1R to emerin or to other nuclear lamina proteins and disrupt its function. These findings pave the way for studies on: the mechanism of interaction of Sigma1R with emerin; whether Sigma1R's variants interact with emerin; whether cocaine and other drugs affect Sigma1R's association with emerin and the nuclear lamina and whether variants of Sigma1R can manipulate this response; and whether any of these variants have the potential to alter an individual patient's response to therapeutic or addictive drugs.

In the article by Dialynas *et al.*,[37] results of new studies are presented on mechanisms involved in maintenance of heterochromatin stability in polytene chromosomes in *Drosophila*. Repair of DNA double-strand breaks (DSBs) in pericentomeric heterochromatin ('heterochromatin') is particularly challenging since the abundance of highly repeated DNA sequences increases the risk of ectopic recombination. Chiolo and her collaborators have previously shown that in *Drosophila* and mouse cells, after production of DNA DSBs, repair sites in heterochromatin relocalize to the nuclear periphery. This process depends upon assembly of actin filaments at the repair sites by actin-related protein-2/3 (ARP2/3) and its activators Scar and Wash; it requires nuclear myosins, which 'walk' along these filaments acting as transporters, and the myosin activator, Unc45. In *Drosophila* larval salivary glands, polytene chromosomes are present which contain multiple copies of chromosomes that form from successive replications of each chromatid without segregation. Genomic instability and mutagenesis is associated with under-replicated regions of polytene chromosomes in *Drosophila*. Knowledge on the extent of DNA repair in heterochromatin in polytene chromosomes has been lacking. The authors have now carried out studies on this important area which lay the foundation for understanding the mechanism of genome stability in other polytene chromosomes, including those present in mammalian tissue and those that form in response to certain chemotherapeutic treatments and contribute to cancer formation by inducing polyploidy and are also found in many tumor types. The present study shows that heterochromatic chromocenters of the polytene chromosomes reorganize in response to ionizing radiation and that ARP2/3, Scar, or Unc45 is needed for this process and is required for heterochromatin stability, suggesting that this reorganization enables heterochromatin repair. These studies on polytene chromosomes, combined with the previous studies on heterochromatin repair in *Drosophila* and mouse cells, indicate that actin polymerization and myosin motors are critical in heterochromatin repair and genomic stability in different organisms and tissue types.

Sidorenk and Vartiainen[38] review the important roles of actin, the nuclear lamina, and lamina binding proteins in regulation of transcription. The transcription complex MRTF-A/SRF is used as an example. SRF is a transcription factor which is a key regulator of cell growth, migration, cytoskeletal organization, differentiation, and muscle-specific or neuronal gene expression. Expression of SRF target genes is promoted by three important co-activators, which are myocardin-related transcription factors (MRTFs): myocardin, MRTF-A, and MRTF-B. Nuclear actin plays a key role in regulating MRTF-A/SRF activity in the cell by influencing the subcellular localization and nuclear activity of MRTF-A. Nuclear actin polymerization is required for this process and can occur in response to specific signals such as cell spreading, which requires mechanical coupling between the cytoplasm and nucleus via the LINC complex; biochemical signals can also be involved. Nuclear actin polymerization is thought to deter binding of MRTF-A to actin monomers, which has an inhibitory effect on MRFT-A activity. MRTF-A thus acts as a mechanical sensor that links actin to gene expression mediated by SRF. Emerin as well as A- and B-type lamins are also required for cell-spreading-induced polymerization of nuclear actin and activation of MRTF-A. The LINC complex is reported to be important in this process. Activation of this transcriptional response to mechanical stimulation can also be mediated by another transcription complex, YAP/TAZ, which may functionally interact with MRTF-A to coordinate transcriptional responses. The linkage of actin to a number of other processes that regulate gene expression, such as chromatin

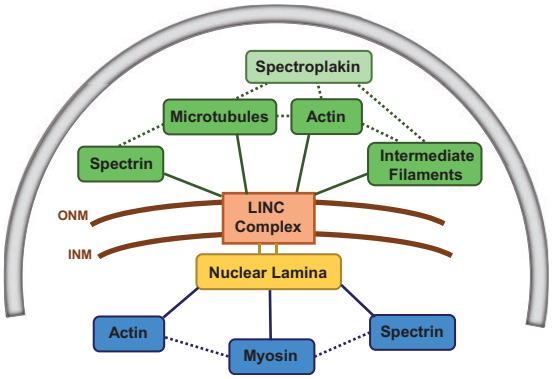

Figure 1. Representation of the areas of the cytoskeleton and nucleoskeleton which are covered in this thematic issue. The components of the cytoskeleton which are discussed are the MTs, actin, IFs, and spectrin. They have been shown to interact with each other. The cross-linking protein, spectraplakin, binds to MTs, actin, and IFs and cross-links them together. These proteins associate with the LINK complex, which spans the nuclear envelope and associates with both the ONM and the INM. The LINK complex connects the cytoskeleton with structural elements in the nucleoskeleton. It interacts with the nuclear lamina and the associated nucleoskeletal proteins, including actin, myosin, and spectrin. The interactions of these proteins with each other, the nuclear lamina, and the LINC complex are discussed in this thematic issue.
INM: inner nuclear membrane; LINC: linker of nucleoskeleton and cytoskeleton; ONM: outer nuclear membrane.

remodeling, is also discussed in this review. Nuclear actin and other components of the nucleoskeleton have thus emerged as important regulators of transcription and in maintaining the mechanical balance in cells by controlling cytoskeleton gene expression.

Lambert[39] reviews the important role that the major nucleoskeletal proteins, nuclear lamins, actin, myosin, spectrin, and the LINC complex, play in repair of DNA damage. These proteins are well known for their essential roles in a number of nuclear processes; however, less well known are the critical roles they play in DNA repair. A-type and B-type lamins are important for repair of DNA DSBs. Lamins A/C play a role in both NHEJ and HR repair pathways. Their importance in DSB repair is emphasized by disorders, the laminopathies, in which there are mutations in the *LAMNA* gene. Nuclear actin plays a dynamic role in repair of DNA DSBs by both NHEJ and HR. Polymerization of actin into filaments is required for this process. In contrast, actin in monomeric form is a key component in several chromatin-modifying complexes which pay pivotal roles in DNA DSB repair. Myosin partners with actin in repair of DSBs by HR in heterochromatin and is important in movement of DSBs to the nuclear periphery to facilitate the repair process. Nuclear actin/myosin are also involved in HR repair of DSBs in transcriptionally active euchromatin. The LINC complex plays also an important role in repair of DNA DSBs, where the SUN1 protein inhibits NHEJ and promotes HR at these sites. It is additionally involved in repair of DNA interstrand cross-links (ICLs) and the recruitment of FAN-1 nuclease to sites of damage. Non-erythroid α-spectrin (αSpII) plays a critical role in DNA ICL repair, acting as a scaffold in recruitment of repair proteins to sites of damage in telomeric and non-telomeric DNA. In the bone marrow disorder, FA, there is a defect in DNA ICL repair which correlates with a deficiency in αSpII due to loss of FA proteins which are proposed to stabilize αSpII. The importance of αSpII in DNA repair is seen in studies on FA cells in which restoration of levels of αSpII to normal corrects the DNA repair defect and chromosome instability that occurs after DNA ICL damage. The role of nucleoskeletal proteins in DNA repair is a rapidly expanding field and one in which continued investigations should shed light on the pathogenesis of an ever-expanding number of disorders.

Taken together, the articles in this thematic issue should make a significant contribution to enhancing our knowledge and understanding of the intracellular protein networks present in the cell, the proteins associated with these networks and their critical interactions with each other, and the key role they play in many essential cellular processes in health and disease (Figure 1). It is hoped that expanding our knowledge in these areas will lead to development of more mechanistic studies on how these processes function and to exploration of new avenues of research on steps involved in disease progression.

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