Biochimica et Biophysica Acta 1838 (2014) 511–513

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Preface

Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters

The cytoskeleton consists of filamentous systems composed of polymers of actin, tubulin or intermediate filament proteins, which supply the cell with networks of structures both highly dynamic and very stable. The cytoskeleton is involved in numerous functions including maintenance of cell's internal scaffold, provision of mechanical stability, locomotion, intracellular transport of organelles, as well as chromosome separation in mitosis and meiosis. Through the recent application of molecular and proteomic approaches, we now know that the interactions between membrane channels, receptors and transporters, and cytoskeleton can either be direct or indirect, the latter being mediated through scaffolding or actin-binding proteins that serve as links between these integral proteins and the actin-based cytoskeleton. Bidirectional relationships are established where cytoskeleton and associated proteins affect the activities of membrane channels, receptors and transporters, and are also key downstream effectors of different signaling pathways. The present issue of Biochimica et Biophysica Acta—Biomembranes summarizes the main aspects of the state of the art on the reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters.

Actin is a major cytoskeleton protein found ubiquitously within the cells that is involved in almost all biological events, particularly events related to motility. Membrane channels and transporters are continuously renewed, and actin and actin-based cytoskeleton complexes are dynamically involved not only in the intracellular trafficking, but also in the regulation of channel activity. Sei Sasaki, Naofumi Yui and Yumi Noda [1] review the interplay between actin and ten membrane channel proteins, with a particular focus on their direct binding properties.

Various extracellular stimuli activate cellular responses via membrane receptors among which a group of seven-transmembrane domain-containing proteins, referred to as G protein-coupled receptors, directly couple with the intracellular GTP-binding proteins (G proteins) across cell membranes, triggering various cellular responses by regulating the activity of several enzymes as well as membrane channels. Atsushi Inanobe and Yoshihisa Kurachi [2] examine how **membrane channels act as integrators** of G-protein-mediated signaling.

Many types of membrane channels and receptors localize to cholesterol and sphingolipid-enriched regions of the plasma membrane known as **lipid microdomains or "rafts"**. Growing evidence shows that many of their structural and functional properties depend upon interactions with and dynamic rearrangement of the cytoskeleton. Brian P. Head, Hemal H. Patel and Paul A. Insel [3] summarize general features of lipid rafts and their role in several aspects of cellular function, including polarity of endothelial and epithelial cells, cell migration, mechanotransduction, lymphocyte activation, neuronal growth and signaling, and a variety of disease settings.

T cells constitute a crucial arm of the adaptive immune system and their optimal function is required for a healthy immune response. After the initial step of **T cell-receptor** (TCR) triggering by antigenic peptide complexes on antigen presenting cell, the T cell exhibits an extensive cytoskeletal remodeling which leads to the formation of an "immunological synapse" characterized by regulated clustering, segregation and movement of receptors at the interface. Such response requires determinative cytoskeletal alterations, achieved via major actin and microtubule remodeling. Sudha Kumari, Silvia Curado, Viveka Mayya and Michael L. Dustin [4] discuss the diversity of TCR-responsive molecular regulators and potential role in specific steps of T cell activation. T cell activation also involves a dramatic increase of intracellular **Ca^{2+} concentration** via a rapid release of Ca^{2+} from intracellular stores (as endoplasmic reticulum), eliciting the opening of Ca^{2+} release-activated Ca^{2+} channels of the plasma membrane and a sustained influx of extracellular Ca^{2+}. Noah Joseph, Barak Reicher and Mira Barda-Saad [5] examine the role of the signaling pathways upstream and downstream of Ca^{2+} influx required for an appropriate T cell response.

B cell activation is initiated by the ligation of the B cell receptor with antigen and ultimately results in the production of protective antibodies against potentially pathogenic invaders and in the generation of antibody-secreting plasma cells and long-lived memory cells. B cells undergo dramatic molecular and morphological reorganizations following recognition of antigen. Wenxia Song, Chaohong Liu and Arpita Upadhyaya [6] summarize the recent progress in our understanding of the molecular mechanisms that govern how the actin cytoskeleton regulates B cell receptor-triggered B cell activation.

Interaction of cells with the extracellular matrix is fundamental to a wide variety of biological processes (e.g. cell proliferation, cell migration, embryogenesis, etc.). Cell–matrix interactions are frequently mediated by the integrin family of cell adhesion molecules, linked to the actin cytoskeleton by adaptor proteins, particularly **talin**, which transduces signals across integrins in both the inside-out and outside-in directions. Mitali Das, Sujay Subbayya Ithychanda, Jun Qin and Edward F. Plow [7] present an overview on the structure of talin and its regulation of integrin activation, and discuss its potential role in integrin crosstalk.

The localization and organization of membrane channels and receptors in specific regions of the plasma membrane is essential for their correct function. Membrane-associated guanylate kinase (MAGUK) proteins play key roles for this organization, as the **synapse-associated protein 97 (SAP97)** (for example in synapses or cardiac intercalated disks). Chantelle Fourie, Dong Li and Johanna M. Montgomery [8] highlight the role of SAP97 as a regulator of neuronal excitability, synaptic function and plasticity in the brain, but also in the pathophysiology of a number of neurological disorders. **Zonula Occludens (ZO)**

0005-2736/$ – see front matter
http://dx.doi.org/10.1016/j.bbamem.2013.10.014

proteins are ubiquitous scaffolding proteins also belonging to the large family of MAGUK-like proteins, which provide the structural basis for the assembly of multiprotein complexes at the cytoplasmic surface of intercellular junctions and link them to the filamentous cytoskeleton. Jean-Claude Hervé, Mickaël Derangeon, Denis Sarrouilhe and Nicolas Bourmeyster [9] present an overview of these intimate spatial relationships between ZO proteins (particularly ZO-1) and connexin-made intercellular channels and a few other membrane channels.

Members of the **protein 4.1 family**, expressed in most tissues, play important roles in tethering plasma membrane voltage-gated and ligand-gated channels, G-protein coupled receptors as well as a number of erythrocyte membrane proteins to the cortical actin–spectrin cytoskeleton via spectrin, behaving as hubs for membrane protein organization. Anthony J. Baines, Hui-Chun Lu and Pauline M. Bennett [10] hypothesize that differential regulation of 4.1 proteins, and also ankyrins, allows highly selective control of cell surface protein accumulation and, hence, function.

Spectrins are cytoskeletal proteins essential for the determination of cell shape, the resilience of membranes to mechanical stress, the positioning of particular transmembrane proteins within the plane of a membrane, and the organization of organelles and molecular traffic. B. Machnicka, A. Czogalla, A. Hryniewicz-Jankowska, D.M. Bogusławska, R. Grochowalska, E. Heger and A.F. Sikorski [11] explain how this dynamic mechanical scaffold supporting the membrane bilayer controls the mobility and perhaps the activity of membrane integral proteins, which are membrane channels, transporters and receptors.

Dystrophin and its associated proteins were originally identified in skeletal muscle, where the complex they form plays a structural role in linking the actin cytoskeleton to the extracellular matrix, stabilizing the sarcolemma during repeated cycles of contraction and relaxation, and transmitting force generated in the muscle sarcomeres to the extracellular matrix. However, the dystrophin complex, also present at membrane specializations in many non-muscle cells (e.g. synaptic sites in neurons) is involved in a number of signaling pathways. Bruno Constantin [12] describes how such complex contributes to build a complete signalplex with ion channels, trimeric G-proteins, G-protein-coupled receptors, plasma membrane calcium pump and/or NOS to enable efficient and regulated signal transduction.

The Chloride Intracellular Channel proteins (**CLICs**) are distinct from most ion channels in that they have both soluble and integral membrane forms. CLIC proteins are associated with the ERM (ezrin, radixin and moesin) proteins, and both CLIC and ERM proteins are controlled by the Rho family of small GTPases. L. Jiang, J.M. Phang, J. Yu, S.J. Harrop, A.V. Sokolova, A.P. Duff, K.E. Wilk, H. Alkhamici, S.N. Breit, S.M. Valenzuela, L.J. Brown and P.M. Curmi [13] review the relationships between Rho GTPases, CLIC proteins, ERM proteins and the membrane/actin cytoskeleton interface.

The transient receptor potential (**TRP**) protein superfamily consists of a diverse group of relatively non-selective channels permeable to cations (including Na^+, Ca^{2+}, Mg^{2+}) that bear structural similarities to *Drosophila* TRP. Tarik Smani, Natalia Dionisio, José J. López, Alejandro Berna-Erro and Juan A. Rosado [14] explain how the interactions of TRP channels with the cytoskeleton and scaffolding proteins are essential for their cellular location and, therefore, the regulation of channel function, whereas, conversely, cation currents through TRP channels modulate cytoskeleton rearrangements.

Eukaryotic cells harbor complex scaffolds of filamentous polymers that collectively constitute the cytoskeleton. The actin and microtubule cytoskeletons are comprised of the same fundamental components across cell types, i.e. the α and γ-actins and α and β-tubulins, respectively. Motor proteins (as kinesin and dynein families) use ATP hydrolysis to move cellular cargoes along cytoskeletal tracks. This mechanism is predominantly responsible for the **trafficking and membrane localization of channels**. David F. Steele and David Fedida [15] provide an overview of the current state of knowledge on the involvement of the actin and microtubule cytoskeletons in the trafficking, targeting and expression of different membrane channels.

Heterotrimeric G-proteins participate in signal transduction by transferring signals from hormonal or neurotransmitter cell surface receptors to intracellular effector molecules, particularly adenylyl cyclases, phosphodiesterases, phospholipases and ion channels, but also via cytoskeletal dynamics. Jeffrey M. Schappi, Aleksandar Krbanjevic and Mark M. Rasenick [16] discuss the reciprocal interactions between heterotrimeric G protein signaling and elements of the cytoskeleton, influencing cell morphology, motility, division, and transport functions.

Mechanosensitivity is a universal property of cells but the transducers for mechanical inputs are not yet clearly characterized. They include the cytoskeleton and its mechanochemical components (as the actin and tubulin-based transporters), cell surface proteins such as the integrins, and ion channels. By focusing on mechanosensitive channels found in animal cells, Boris Martinac [17] overviews the present knowledge and ideas about the ways in which the connections between cytoskeleton and ion channels may contribute to mechanosensory transduction in these cells.

Membrane channels form supramolecular regulatory complexes (with regulatory proteins and scaffolding proteins) which provide a very fine regulation of their activities. Such fine regulation can even be more accurately tuned because of the existence of different channel populations, differentially modulated depending on their specific localization. Mónica Gallego, Aintzane Alday, Hiart Alonso and Oscar Casis [18] describe how, in the adrenergic regulation of cardiac ionic channels, the location of the components of the transduction signaling pathway in **membrane microdomains** determines the correct and safe behavior of the heart.

The cytoskeleton plays key roles in modulating both the electrical activity (through ion channels and exchangers) and mechanical (or contractile) activity of the heart. Cytoskeletal alterations contribute significantly to structural ventricular remodeling and dilatation finally resulting in reduced cardiac function. Vasco Sequeira, Louise L. Nijenkamp, Jessica A. Regan and Jolanda van der Velden [19] describe how cytoskeletal changes are both a cause and a consequence of contractile dysfunction and cardiac remodeling in **heart failure** patients.

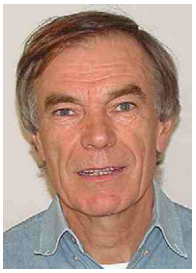
Diseases linked with membrane ion channels, termed "**channelopathies**", are increasingly found in a large spectrum of human pathologies including ageing. Some of them now appear to be caused by defects in non-ion channel polypeptides, as cytoplasmic sub-membrane adapters. Crystal F. Kline and Peter J. Mohler [20] focus on disease-causing mutations that alter interactions between ion channels and auxiliary ion channel components in a diverse set of human excitable cell disease.

I wish to thank all authors and co-authors for their commitment and the anonymous reviewers who contributed by their critical constructive remarks to the excellence of this issue.

References

[1] S. Sasaki, N. Yui, Y. Noda, Actin directly interacts with different membrane channel proteins and influences channel activities: AQP2 as a model, Biochim. Biophys. Acta 1838 (2014) 514–520.
[2] A. Inanobe, Y. Kurachi, Membrane channels as integrators of G-protein-mediated signaling, Biochim. Biophys. Acta 1838 (2014) 521–531.
[3] B.P. Head, H.H. Patel, P.A. Insel, Interaction of membrane/lipid rafts with the cytoskeleton: impact on signaling and function: Membrane/lipid rafts, mediators of cytoskeletal arrangement and cell signaling, Biochim. Biophys. Acta 1838 (2014) 532–545.
[4] S. Kumari, S. Curado, V. Mayya, M.L. Dustin, T cell antigen receptor activation and actin cytoskeleton remodeling, Biochim. Biophys. Acta 1838 (2014) 546–556.
[5] N. Joseph, B. Reicher, M. Barda-Saad, The calcium feedback loop and T cell activation: How cytoskeleton networks control intracellular calcium flux, Biochim. Biophys. Acta 1838 (2014) 557–568.
[6] W. Song, C. Liu, A. Upadhyaya, The pivotal position of the actin cytoskeleton in the initiation and regulation of B cell receptor activation, Biochim. Biophys. Acta 1838 (2014) 569–578.
[7] M. Das, S. Subbayya Ithychanda, J. Qin, E.F. Plow, Mechanisms of talin-dependent integrin signaling and crosstalk, Biochim. Biophys. Acta 1838 (2014) 579–588.

[8] C. Fourie, D. Li, J.M. Montgomery, The anchoring protein SAP97 influences the trafficking and localisation of multiple membrane channels, Biochim. Biophys. Acta 1838 (2014) 589–594.
[9] J.-C. Hervé, M. Derangeon, D. Sarrouilhe, N. Bourmeyster, Influence of the scaffolding protein Zonula Occludens (ZOs) on membrane channels, Biochim. Biophys. Acta 1838 (2014) 595–604.
[10] A.J. Baines, H.-C. Lu, P.M. Bennett, The Protein 4.1 family: Hub proteins in animals for organizing membrane proteins, Biochim. Biophys. Acta 1838 (2014) 605–619.
[11] B. Machnicka, A. Czogalla, A. Hryniewicz-Jankowska, D.M. Bogusławska, R. Grochowalska, E. Heger, A.F. Sikorski, Spectrins: A structural platform for stabilization and activation of membrane channels, receptors and transporters, Biochim. Biophys. Acta 1838 (2014) 620–634.
[12] B. Constantin, Dystrophin complex functions as a scaffold for signaling proteins, Biochim. Biophys. Acta 1838 (2014) 635–642.
[13] L. Jiang, J.M. Phang, J. Yu, S.J. Harrop, A.V. Sokolova, A.P. Duff, K.E. Wilk, H. Alkhamici, S.N. Breit, S.M. Valenzuela, L.J. Brown, P.M.G. Curmi, CLIC proteins, ezrin, radixin, moesin and the coupling of membranes to the actin cytoskeleton: A smoking gun? Biochim. Biophys. Acta 1838 (2014) 643–657.
[14] T. Smani, N. Dionisio, J.J. López, A. Berna-Erro, J.A. Rosado, Cytoskeletal and scaffolding proteins as structural and functional determinants of TRP channels, Biochim. Biophys. Acta 1838 (2014) 658–664.
[15] D.F. Steele, D. Fedida, Cytoskeletal roles in cardiac ion channel expression, Biochim. Biophys. Acta 1838 (2014) 665–673.
[16] J.M. Schappi, A. Krbanjevic, M.M. Rasenick, Tubulin, actin and heterotrimeric G proteins: Coordination of signaling and structure, Biochim. Biophys. Acta 1838 (2014) 674–681.
[17] B. Martinac, The ion channels to cytoskeleton connection as potential mechanism of mechanosensitivity, Biochim. Biophys. Acta 1838 (2014) 682–691.
[18] M. Gallego, A. Alday, H. Alonso, O. Casis, Adrenergic regulation of cardiac ionic channels: Role of membrane microdomains in the regulation of kv4 channels, Biochim. Biophys. Acta 1838 (2014) 692–699.
[19] V. Sequeira, L.L.A.M. Nijenkamp, J.A. Regan, J. van der Velden, The physiological role of cardiac cytoskeleton and its alterations in heart failure, Biochim. Biophys. Acta 1838 (2014) 700–722.
[20] C.F. Kline, P.J. Mohler, Defective interactions of protein partner with ion channels and transporters as alternative mechanisms of membrane channelopathies, Biochim. Biophys. Acta 1838 (2014) 723–730.



Jean-Claude Hervé performed his doctorate (1984) on the morphology of cardiac gap junctions under the supervision of Prof. J. Délèze at the Department of Physiology, University of Poitiers (France), where he worked as a National Centre for Scientific Research (CNRS) researcher. He then spent two years (1988–90) as a Research Visitor at the Laboratory of Physiology of University of Oxford (UK), where he examined the effects of temperature on calcium currents of cardiac myocytes, before joining the Institute of Physiology and Cell Biology of the University of Poitiers. His recent research focuses mainly on the modulation of the direct cell-to-cell communication via gap junctional intercellular channels, finely tuned by the metabolic state of communicating cells and by humoral factors. Jean Claude also serves as an executive guest editor for different international journals, among them *Biochimica Biophysica Acta*, *Progress in Biophysics and Molecular Biology*, *Current Pharmaceutical Design*, *Biology of the Cell*, *Small GTPases*, and *Mini-Review in Medicinal Chemistry*.

Jean-Claude Hervé
Institut de Physiologie et Biologie Cellulaires, FRE 3511, CNRS, Université de Poitiers, PBS, Bât: B36 - 1 rue Georges Bonnet, 86022 POITIERS Cédex, France