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BioArchitecture

The organization and regulation of biological space

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BioArchitecture is a term used to describe the organization and regulation of biological space. It applies to the principles which govern the structure of molecules, polymers and mutiprotein complexes, organelles, membranes and their organization in the cytoplasm and the nucleus. It also covers the integration of cells into their three dimensional environment at the level of cell-matrix, cell-cell interactions, integration into tissue/organ structure and function and finally into the structure of the organism. This review will highlight studies at all these levels which are providing a new way to think about the relationship between the organization of biological space and the function of biological systems.

Introduction

The triumph of biology is the control of physics and chemistry in time and space. With the imaging revolution we can now visualize the molecular basis of this control. The ability to change the structures of polymers, molecular complexes and single molecules provides extraordinary flexibility in the organization and function of biological processes. The term bioarchitecture has been coined to capture the pivotal role which spatial organization plays in the evolution and function of biological systems. This review will look at the underlying principles which yield the rich tapestry of biological organization and the functional consequences based on the contributions to BioArchitecture in the first year of publication.

Polymers of the Cytoskeleton

The actin microfilament. The ability to both visualize and measure the physical properties of the actin cytoskeleton at the molecular level has been revolutionized by the development of multiple super-resolution microscopic techniques and the application of atomic force microscopy to living cells.[1] This is complemented by the development of microfluidic approaches to measure changes in the chemistry of individual actin filaments under conditions in which the microenvironment can be changed moment to moment.[2] Combination of these techniques will allow modeling of individual molecular interactions between an actin filament and actin binding proteins and visualization of these same interactions in a cellular context. The ability to live image the dynamics of actin filaments has also provided new levels of understanding of the microfilament. Fluorescence decay after photoactivation has been successfully used to measure time-dependent changes in the levels of G-actin and the spatial distribution of G-actin in live cells.[3] This allows for an evaluation of the changes in G-actin which accompany changes in microfilament organization and dynamics. Dynamic changes in the organization of microfilaments accompanying exocytosis have now been visualized using confocal microscopy in living tissue.[4] Intravital imaging of this process has not only provided the opportunity to follow reorganization of the microfilaments as exocytosis proceeds but has also highlighted the difference between biology visualized in cell culture compared with the same process in living tissue.[4]

The regulation of assembly of specific populations of actin filaments at specific intracellular sites has been an issue of increasing interest. Surprisingly, the mechanism of regulation of the assembly of the microfilament in the striated muscle sarcomere has been unclear. Recent experiments now indicate that the formin protein family member FHOD3 is involved in myofibril assembly and maintenance.[5] It is the phosphorylated form of the muscle-specific isoform of FHOD3 that is localized to myofibrils. Similarly, studies in yeast have shown that the two yeast formins are subject to strict spatio-temporal regulation which contributes to the regulated organization of actin cables in this system.[6]

The actin filament itself continues to be a subject of intense investigation. Computer simulations have been used to identify the minimal requirements to generate an actin-like motor system.[7] This involves ATPase activity in the filament, filament polarity in polymerization/depolymerization rates and bound nucleotide-dependence of the subunit-subunit interactions. There is also evidence that the initial assembly form of the actin filament undergoes a 'maturation step' to a more obviously double helical form with time.[8] The role of nuclear actin is also of increasing interest and in particular the roles of both polymeric and monomeric actin. The discovery that the Arp4 and Arp8 components of the chromatin remodeler INO80 stabilize monomeric actin provides insight into how actin is stoichiometrically incorporated into the INO80 complex.[9]

Tropomyosins are becoming recognized as core components of the microfilament which confer functional specificity to

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spatially segregated populations of microfilaments.[10] The spatial segregation of tropomyosin isoforms is dramatically illustrated in the central nervous system where a brain specific tropomyosin is localized to the presynaptic terminal whereas two other isoforms are localized to the postsynaptic terminal.[11] The unique roles of specific tropomyosin isoforms has been revealed in a number of approaches. Manipulation of a single tropomyosin isoform has been found to be sufficient to inhibit mesenchymal-like cell invasion without leading to 'amoeboid'-like motility.[12] Gene knockout studies have confirmed a lack of functional redundancy between tropomyosin genes and identified specific isoforms which are required for embryonic stem cell proliferation.[13]

Actin binding proteins are involved in regulating microfilament function in a range of processes. Cortactin was found to regulate cell motility via an unexpected mechanism, its ability to control trafficking of fibronectin-containing vesicles through actin filament branch formation.[14] Refilins have been identified as actin bundling proteins which can regulate perinuclear microfilament organization which is linked to cell mechanosensing signaling.[15]

The most highly specialized microfilament based structure is the repeating sarcomeric organization of the striated muscle contractile apparatus. The observation that myosin binding protein-C can directly interact with the actin filament has led to the identification of a potential mechanism for modulating the sliding of the actin and myosin filaments.[16] Further insight into the interaction between actin and tropomyosin in the sarcomere has come from manipulation of conserved aspartate residues which indicate that Asp-137 causes a local flexible region in the middle of tropomyosin.[17] Whereas the contractile apparatus can be considered a structural 'spinoff' from the actin cytoskeleton, there has been no evidence for an evolutionary intermediate. The recent report of a troponin-I like protein in the water bear suggests the possibility that the role of troponins in striated muscle contraction might, in fact, precede the evolution of the striated organization of the contractile apparatus itself.[18]

Cellular membranes can both contribute to specialization of the actin cytoskeleton and be the target of specialized actin filament function. In the Drosophila oocyte polarized endocytosis appears to result in specialized vesicles which act as vehicle for local action of actin regulators.[19] Evidence is also emerging that the spectrin-adducin membrane skeleton directly organizes the cortical actin filaments at adherens and tight junctions.[20] In cochlear hair bundles the interconnection of actin-filled stereocilia mechanically gate mechanoelectrical transduction channels.[21] Conversely, the actin cytoskeleton is involved in the rapid repair of the plasma membrane following formation of a discontinuity in the membrane.[22] A specific population of actin filaments are required for mechanical stabilization of the sarcoplasmic reticulum membrane in striated muscle.[23] In the Golgi, myosin 1b is involved in both spatially organizing microfilaments and in mediating the function of these filaments in membrane remodelling.[24]

Actin microfilaments are subject to extensive regulation by a range of signaling systems. Studies of cancer cell metastasis are revealing how signals from Ras and Rho GTPases can either oppose or cooperate via their effects on the actin cytoskeleton to regulate cell migration and invasion.[25] In the nervous system, signaling through Rac 1 GTPase directs changes in actin polymerization which are required for both myelination and demyelination of peripheral nerves.[26] During epiboly in zebrafish, the formation of the actin-myosin ring is regulated by an anti-apoptotic Bcl-2 homolog Nrz which appears to act via control of the opening of a calcium channel.[27]

Microtubules. The role of microtubules in chromosome segregation is not only one of the most important functions of the cytoskeleton but also remains a frontline target for chemotherapy. The attachment of microtubules to the kinetochores of the chromosomes is a highly choreographed process involving numerous proteins. A newly identified component of the kinetochore, the formin mDia3, has been shown to be a substrate for the kinase Aurora B.[28] On the other side, the transforming acidic coiled-coil 3 protein has been shown to recruit ch-TOG and clathrin heavy chain to the microtubules of the mitotic spindle.[29] At the other end, recent experiments indicate that astral microtubules deliver dynein to the cell cortex where it participates in aligning and tethering the mitotic spindle.[30]

Depolymerization of microtubules has to occur in a spatially and temporally regulated manner to ensure efficient remodelling of the microtubule system. Two members of the kinesin superfamily, Kinesin-8 and Kinesin-13 play a key role in controlling mitotic spindle morphology and remodelling. Recent data has provided clues to the mechanisms which govern the localization of these microtubule destabilizing enzymes. The Kinesin-8s have been found to have an additional microtubule binding domain in their tails which are required for chromosomal positioning and function.[31] One of the Kinesin-13s, MCAK, is localized to the growing tips of microtubules by interaction with microtubule end binding (EB) proteins.[32]

The positioning of microtubule organizing centers is essential for the establishment of cell polarity and the organization of intercellular space. In the formation of the immunological synapse the reorientation of the microtubule organizing center is mediated by recruitment of multiple members of the protein kinase C family by diacylglycerol.[33] In Chlamydomonas positioning of a photosensory organelle depends on a specific four-membered microtubule rootlet.[34] The mechanism by which the microtubule organizing center is localized in cells is of considerable interest and a recent model proposes that it is based on microtubule length-dependent generation of force in *C. elegans*.[35] In some differentiated cells microtubules are organized into non-centrosomal arrays and in epithelial cells there is some evidence that centrosomal proteins are recruited to the microtubules located at the cell cortex.[36]

Microtubules play a pivotal role in the polarity of neurons. In the dendritic spine of neurons the localization of PAR-1 regulates local microtubule dynamics which in turn regulates spine morphology.[37] In the axons of peripheral neurons, mutations in the small heat shock protein HSPB1 impact microtubule stability with resulting impact on axoplasmic transport.[38]

Intermediate filaments. The role of intermediate filaments in a wide range of cellular processes is becoming increasingly realized and considerable effort is being directed to understanding

the mechanisms which determine their organization. There is increasing evidence that intermediate filament organization is controlled in an isoform specific manner by the different plectins.[39] There is also increasing evidence that the intermediate filaments appear to be highly dynamic and engage in rapid cycles of assembly and disassembly.[40]

Beyond the Cytoskeleton

Signaling mechanisms rely on the organization of cellular space and the ability to change molecular architecture to transmit or affect biological outcomes. The ESCRT proteins have been found to play dual signaling roles by delivering ubiquitinated surface receptors to lysosomes and on the other hand to deliver Src to focal adhesions and invadopodia.[41] The conformational shift in cortactin architecture which releases autoinhibition of its activity requires additional factors in addition to phosphorylation by ERK1/2.[42]

It should not be surprising that the architecture of both RNA and DNA is becoming increasingly relevant to a range of biological processes. New mRNA containing foci have been identified in the cytoplasm of transformed cells expressing ALK tyrosine kinase which may be involved in the regulation of mRNA translation or turnover.[43] In the nucleus, the discovery of 'chromosome kissing' is now implicated in the modulation of termination of chromosome replication.[44]

The regulation of the placement and organization of the major organelles of the cell is a major architectural challenge and new insights have been gained into the underlying mechanisms. Golgi fragmentation in the G_2/M phase of the cell cycle is linked to Aurora-A recruitment to the centrosomes which provides a way for the cell to inhibit G_2/M progression until the organization of the Golgi is suitable for cell division.[45] The ability of the cell to correctly position the nucleus is a major mechanical challenge and genetic studies have revealed a role for both kinesin-1 and dynein in this process.[46]

Finally, the organization of cell architecture is pivotal to the function of cells in a tissue/organ environment. The postsynaptic density protein PSD-95 has been found to directly contribute to the shaping of the neuronal dendritic field by influencing the distance between microtubules which in turn impacts on the decision of a dendrite to branch rather than form a spine.[47] At the level of formation of neuronal circuits, studies in transparent embryos have supported a model in which neuronal architecture is driven by use-dependent testing of synapses; a switch in which 'form follows function.'[48] In the case of tumor biology, the respective roles of different cells which form the tumor have implicated LIMK as a potential drug target for cancer therapy based on LIMK function in the invading cells.[49]

Conclusion

Thinking in terms of the organization of biological space from the level of the individual molecule to the formation of tissues/organs and the formation of the organism is increasingly valuable as we move to a holistic understanding of biological systems. We can look forward to BioArchitecture contributing to the process both as a journal and as an experimental approach.

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