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Seminars in Cell and Developmental Biology
Editorial - The Future of Cellular Organisation

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It is an intuitive notion that a highly organised multicomponent system, such as the cell, requires mechanisms and machinery to establish, maintain, and adapt its organisation to meet functional requirements. Yet, we still have only a fragmented understanding of how this works. This special issue doesn't attempt to provide a comprehensive overview of this vast topic covering several fields but aims to provide snapshots of the interests and visions of several scientists, who are, or are poised to emerge as, leaders in this area of research.

We are now used to the idea that a cell is like a city - there is a transport network, much like roads or railways (the cytoskeleton), upon which cargo carrying vehicles (molecular motors) can move to transport cellular components to the right place at the right time. Indeed, something in that vein is typically found in the lay summaries of this editor's grant applications. Building on that analogy, the transport network requires renewal, maintenance and repair to limit broken rails, potholes and defective vehicles. Twelvetrees considers this problem in the neuron where it is perhaps most prescient. How is a microtubule transport system with nanoscale components maintained on the macroscopic scale of the axon that can be up to 1 meter long, with only limited capacity for local protein synthesis? Focusing on the tubulin proteins, cytoplasmic dynein and kinesin-1, the author asks where the components are synthesised and complex molecular machines assembled, how they are moved to the right place in the axon and prevented from running amok before they get there and how are they degraded when not required? It is also becoming clear that motors can damage their tracks; how are those potholes repaired? The implications for our understanding of neuronal health and neurodegeneration are clear.

Webb, Mukhopadhyay, and Roberts consider another microtubule-based system and its motors – intraflagellar transport (IFT) in the primary cilium, where questions related to those posed above are being answered at a remarkable atomic level of detail, informing our understanding of their function at the cellular level. The authors review significant recent progress driven by advances in single particle cryo-electron microscopy and cryo-electron tomography on the molecular architecture of the IFT machinery. They consider the coordination of teams of dynein-2 and kinesin-2 motors to direct transport from the cilium base to the tip and back again, discussing how switches in direction might be triggered. This work has important implications for understanding the ciliopathies that can result from dynein-2 mutations.

Nazockdast and Redemann describe the equally important mechanical role of the microtubule cytoskeleton in the mitotic spindle. They consider the origin and propagation of the forces important for spindle self-organisation, chromosome alignment and segregation, by considering roles of molecular motors of the dynein and kinesin families, assembly and disassembly of microtubules and their intrinsic elastic properties and interaction with the wider cellular milieu. The authors highlight how the integration of light microscopy and

electron tomography with computational modelling promises to provide a complete model of spindle formation and function. This might be important for a full understanding of how these mechanisms are and can be further targeted in cancer.

Moving away from microtubules, their associated proteins, and molecular machines, Carroll provides a perspective on the spatial organisation of cellular signalling pathways, focusing on the rapamycin complex 1 (mTORC1) kinase which controls cell growth and metabolism. I am tempted at this point to over-extend the city transport analogy with talk of fuel gauges, but I'll refrain. Nonetheless, it is now very well established that mTORC1 localises to lysosomes where it encounters its activator Rheb in a process regulated by amino acid and growth factor signalling. Perhaps less well appreciated outside of the field, is the proposition that mTORC1 can function at many other sites including the Golgi apparatus, plasma membrane, endosomes and the endoplasmic reticulum and indeed even at inter-organelle contact sites between some of these compartments and lysosomes. This begins to provide answers the question: where is mTOR? Spatial regulation of activity gives the potential for a refined response to signalling inputs and to generate outputs that specifically meet functional requirements. It is conceivable that through improved understanding of these 'off lysosome' mTORC1 pathways, it could be better targeted in cancer and diseases of age.

Finally, Stalder and Gershlick consider sorting at the Golgi and trafficking to the plasma membrane. They elegantly and comprehensively bring us up to date on current knowledge, and highlight where we still have a much to learn about the molecular machinery that enables the generation of an increasingly appreciated wide range of carriers and routes from the Golgi, and how dysregulation of secretion may contribute to pathology.

It seems worth adding my own (arguably still fairly new) lab's take on one potentially useful direction of travel. All the authors in this issue provide fundamental molecular level mechanistic insights into aspects of cellular organisation. Perhaps, what is less common, is to use this information to ask whether we can devise new means of acutely manipulating these systems. This is relevant, in part, because of many direct connections to human disease, and therefore a potential to develop therapeutics. However, this does not have to be at the level of drug discovery which typically requires resources beyond that of most academic labs. Our deep understanding of these proteins and systems can give us an edge in developing assays that enable the discovery or design of reagents that highlight the mechanisms that *have the potential* to be drug targets and produce useful tools that lead to the next advances in understanding. In doing so, we can help to bridge the gap between the fundamentals of cellular organisation, its role in disease, and begin to apply that knowledge towards health and wellbeing.