Editorial

The five 'W's of transport

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The EMBO Journal Focus Issue on transport presents a collection of reviews that synthesise recent insights into the mechanics and regulation of intra- and intercellular transport. This special issue brings together diverse aspects of this broad field, addressing the **what**, **where**, **when**, **how** and **why** of moving things around within and between cells.

Cells and tissues are highly organised and compartmentalised. At the most basic level, cells need to discriminate inside from out and to control what passes across their limiting membranes; this is achieved by a wide variety of channels, transporters, translocation machineries and vesicle-based mechanisms. Moreover, for many biological macromolecules, the site of synthesis and action are far apart. Therefore, even at the micrometer scale of the cell, active transport mechanisms are essential: for long-distance trafficking, to overcome cellular barriers (membranes) and to ensure selectivity and directionality of movement. Very different systems operate for different types of cargo, and the **'what'** of cellular transport includes everything from small ions and metabolites to nucleic acid and proteins, and even organelles and viruses. While translocation of small molecules across membranes is an important issue in its own right, these reviews focus primarily on the larger-scale transport of nucleic acids, proteins and lipids.

All cells rely on regulated transport, but highly compartmentalised eukaryotes clearly face a much more complex task as the size of objects being transported and the distances increase. Complexity is further exacerbated in multicellular organisms, where intercellular communication involves direct exchange between cells or transport through the extracellular milieu.

As mentioned above, overcoming compartment boundaries to move macromolecules from **where** they are made to where they are needed is a key aspect of transport. RNA is synthesised in the nucleus but moves into the cytoplasm for translation, producing proteins that may function in specific organelles or cytoplasmic locations, or that are secreted. Many proteins also shuttle between nucleus and cytoplasm. Bidirectional transport across the nuclear membrane barrier must therefore be both efficient and highly regulated. In their review, Thomas Güttler and Dirk Görlich discuss how the nuclear envelope is crossed, focussing particularly on recent major advances in our understanding of the structural basis of nuclear export.

Nucleocytoplasmic shuttling of proteins provides one prominent example of protein transport. A second major protein trafficking system involves vesicle-based transport of proteins to and from the plasma membrane and between organelles: the exo- and endocytic pathways. Various aspects of this complex system are discussed in three reviews here.

Vivek Malhotra and Patrick Erlmann address one of the early steps of protein secretion: exit from the endoplasmic reticulum. In particular, they explain how the system copes with proteins that are too large to be accommodated by normal COPII vesicles budding off from the ER.

Exocytosis is counterbalanced by the endocytic pathway, internalising extracellular factors and proteolipid membranes. Jatta Huotari and Ari Helenius consider the life cycle of an endosome and its contents, from formation at the plasma membrane to eventual degradation or recycling of the cargoes carried within it. Of course, these trafficking pathways require the generation of vesicles from lipid bilayers. Britta Qualmann, Dennis Koch and Michael Kessels review the current state of knowledge on the mechanics of this process, which is critically dependent on the BAR domain protein family, whose job it is to bend and sculpt membranes. Here, as in nucleocytoplasmic transport, structural insight has proved the key to understanding the process.

Many proteins will pass through the secretory and endocytic pathways, but for intercellular signalling molecules in particular, this passage must be tightly regulated. As intercellular communication regulates the birth, fate and death of a cell, it is essential to control both the **'where'** and the **'when'** of signal activation and termination. Spatial information is often achieved by exploiting the intrinsic polarity of many cell types to release or sense signals across a particular membrane compartment. For this, directional transport is key, and temporal regulation is also achieved by controlling when signalling factors are trafficked between compartments. These issues are discussed by Ben-Zion Shilo and Eyal Schejter.

Vesicles are the vehicles by which proteins transit the exo- and endocytic system, and the highways along which they and other cargoes move are provided by the cytoskeleton, primarily microtubules. Elucidating **how** microtubule-based transport is used (and abused) in the cell is therefore central to our understanding of transport. Huotari and Helenius touch on this issue when considering endosome motility. A more in-depth analysis of how cargoes are transported by microtubule motor proteins is given by Mark Dodding and Michael Way, who concentrate on how viruses exploit host trafficking systems to navigate their way into, through and out of their target cells. While viruses are pathogenic—unwanted—cargoes, the mechanisms by which they hook up to motors presumably reflect endogenous systems used by cellular factors. Another type of important cargo vehicle are the ribonuclear protein granules (RNPs), in which mRNAs can be transported from the nucleus to disparate sites in the cell for local translation. Michael Doyle and Michael Kiebler describe a striking example: targeting

and transport of RNPs specifically to the axons or dendrites of neurons. There, local protein synthesis can have profound effects on spatially organised neuronal activity, thereby regulating behaviour, learning and memory.

mRNAs are not the only nucleic acids subject to active transport. Recently, much attention has focussed on small RNAs and their roles in gene expression. The effects of these miRNAs, siRNAs and related molecules are not necessarily limited to the cell in which they are produced; small RNAs can move between cells and induce systemic gene silencing. As discussed by Charles Melnyk, Attila Molnar and David Baulcombe, the underlying mechanisms for this remain best understood in plants, where the phenomenon was first described. However, small RNAs can be transported extracellularly in animals as well—often via the release and uptake of exosomes.

In all these reviews, an overriding theme is how directionality is imparted on the system. The inherent polarity of a microtubule, along with the mechanisms that define their orientation in a cell, provides a clear route marker. In the classical view, kinesin motors move towards the plus ends of microtubules, whereas dyneins are responsible for travel in the reverse direction. This is, however, an oversimplification: Dodding and Way explain that cargoes have the potential to bind to both motors simultaneously, and either competition or coordination is required to define direction. Moreover, Doyle and Kiebler propose that directionality may actually be determined by defined sites of cargo capture rather than unidirectional motility. The situation is similarly complicated in the exo- and endocytic systems: vesicles need to be targeted to very distinct destinations in the cell, so identity and specificity must be tightly defined. Huotari and Helenius highlight the importance of both lipid- and protein-based mechanisms to achieve regulated directional transport: the lipid phosphoinositide ‘code’ and the Rab proteins.

Rabs are small GTPases, and provide just one example where nucleotide switches contribute to transport. In the case of the Rabs and Sar1, GTP binding and hydrolysis are coupled to vesicle association, hence helping define compartment

identity. GTPases also have a role in vesicle scission: Sar1 functions in ER exit, whereas the dynamin GTPase is directly involved in the fission step of endocytosis. For the Ran GTPase that is central to nuclear–cytoplasmic transport, compartmentalised localisation of GEFs and GAPs, and differential effects of Ran on importins and exportins, determines directionality in the system. Last, the ATPase cycle of molecular motors provides the energy required for this active transport process, as does ATP binding and hydrolysis for a number of membrane translocation systems. Common to all these different processes is that the nucleotide cycle makes the transport system directional and irreversible, and hence able to perform its critical function of moving molecules from source to destination.

Why all this complexity? Cellular functions must be compartmentalised and yet coordinated, and this inherently requires systems to transport the substrates and products of metabolic reactions, as well as the factors that enable communication between compartments—at all levels. It is no surprise that pathogens exploit these systems to their own advantage, whereas hosts in turn have evolved avoidance mechanisms in this evolutionary arms race.

While this review series highlights some of the most notable aspects of intra- and intercellular transport, it does not aim to provide a comprehensive overview; the examples discussed emphasise the complexity and diversity of transport systems, as well as some of the common principles in this broad and fascinating field. Take a look at our selection of articles on the topic recently published in the EMBO Journals, available online.

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Isabel Arnold and Katherine Brown

EMBO, Heidelberg, Germany

E-mail: k.brown@embojournal.org or i.arnold@embojournal.org