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Precision drug targeting: understanding the intracellular transport mechanism

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Editorial

Membrane trafficking, the intracellular transport machinery used by eukaryotic cells to transport molecules from one organelle to another plays a key role in regulating cellular homeostasis. Eukaryotic cells have evolved to be highly compartmentalized allowing diverse biochemical reactions to be carried out in distinct membrane bound organelles. This requires molecules to be constantly transported between organelles. A host of protein families including Rab GTPases aid the trafficking machinery in packaging, targeting and transporting the cargo molecules to appropriate locations. Pathogens hijack this machinery to infect cells. A better understanding of this system can help us in therapeutics and drug design. Current drug delivery strategies are designed to predominantly target specific tissues but understanding of the membrane trafficking machinery is not leveraged adequately to target specific organelles within cells to improve efficacy of the drugs. Recent advances in molecular and genomic technologies, robotics and image analyses have greatly increased our understanding of sub cellular localization mechanisms. Compared to a broad diffusion based drug delivery, targeting of drugs to specific sub cellular compartments greatly increases its effectiveness and also requires a much smaller dosage.

Availability of genomic tools like GFP conjugated constructs has enabled visualization of proteins of interest in real-time using fluorescence microscopes. This in conjunction with specific molecular cloning, regulation and over-expression studies has yielded greater insight into the mechanisms of intracellular trafficking and the machinery involved. High-throughput systems coupled with robotics have provided a means for screening of large collections of molecules in a genome-wide setting thereby enabling rapid discovery of potential inter actors. Similarly, advances in image analysis techniques and informatics have enabled processing of large volumes of data and studying cellular features in an automated manner. Recent years have seen significant progress in understanding of the sorting signals and targeting of vesicles to specific sub cellular organelles. Viruses are known to hijack the internalization/endocytic pathway to infect cells and studies have shown that a series of coordinated interactions with the host intracellular trafficking pathways is essential for replication, assembly and release of viruses. Better understanding of this mechanism has led to development of inhibitory drugs that specifically target the way viruses invade the host cells. For example, drugs have been designed using synthetic peptides that inhibit HIV virus entry by preventing conformational changes required for fusion of capsid and cell membranes. Increased potency has been observed in drugs designed for targeted inhibition.

Nanomedicine has brought about a paradigm shift in the way drugs are delivered. The trade-off between drug concentration, target specificity and toxicity has always been key to drug delivery systems and drug potency. Nanoparticles carrying drugs provide a controlled delivery system for targeting to specific cell types. Its size makes it easy for internalization by cells and specific coatings/charges they carry help in targeting these particles to distinct sub cellular structures. Chemotherapy agents are increasingly being delivered using nanocarriers and studies have shown that nanocarriers protect drugs from degradation; they also have higher specificity and lower cellular toxicity. However, use of nanoparticles as therapeutic agents are still in early stages and much work is needed to understand the trafficking mechanisms and efficiently designing drugs. The internal transport machinery within our cells allow for a multitude of biochemical processes to be performed in parallel. Disruption to this system has known to cause disease and understanding of this complex network can help prevent diseases and infection. Therapeutic advances made from study of this system can help improving efficiency of drug delivery and reducing toxicity. In conclusion, the membrane trafficking machinery offers a system that can be used to greatly improve drug targeting not only to specific tissues or cell types but also to very specific subcellular organelles within a cell.

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Conflict of interest

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