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Cover Story

Intracellular trafficking of cell-penetrating peptide–avidin complexes

For any drug or biomolecule to exert its bioactivity, in most cases it needs to enter into cells and migrate to the necessary cellular compartment, where it can interact with its target molecule(s). Unfortunately, a large number of biomolecules are poorly translocating through the lipid bilayer of the plasma membrane making them inefficient and their use problematic. Cell-penetrating peptides (CPPs) are effective transport vectors possessing the ability to facilitate the efficient uptake of various cargos ranging from small peptide sequences to larger biomolecules, such as proteins and nucleotides. Internalization of CPP–cargo complexes depends highly on the nature of the cargo molecule as well as the characteristic properties of the carrier peptide. Most of the cellular uptake occurs via endocytosis, and a large fraction of the internalized CPP–cargo complexes are found inside endocytic vesicles. The intracellular trafficking, final destination and ultimately the fate of these complexes inside the cells are still unclear and currently under intense investigation. In this issue, there are two articles that specifically deal with this issue to provide new insights into more effective targeting of cargo to the desired cellular compartment [1,2].

A Perspective by Professor You-Yeon Won and his group in this issue deals with the complexity of intracellular trafficking of polycation/DNA complexes and presents questions that are critically important for further advances in non-viral gene delivery [1]. Not all polycationic gene carriers have the same mechanism of endocytosis. Polyplexes are internalized by either clathrin-mediated or caveolae-mediated endocytosis. Endosome compartments resulting from clathrin-mediated endocytosis develop into lysosomes, while those from caveolae-mediated endocytosis do not. Lipid-based gene carriers are internalized predominantly via clathrin-mediated endocytosis, while polyplexes carriers can be endocytosed by different mechanisms. It is still not completely understood what properties of cationic polymers are mainly responsible. The same is true for the endocytic pathways when cell-penetrating peptides (CPPs) are used for endocytosis. This particular issue is discussed in depth in the article by Professor Pooga and his colleagues in this issue [2].

The intracellular trafficking of internalized material was examined using the Cos cell line where the recycling and endo-lysosomal endosomes are spatially segregated by the *trans*-Golgi ring [3]. The article by Räägel et al. in this issue [2] brings new insights into intracellular trafficking of 3 different CPPs (Arg_9, Tat, and Transportan) attached to an avidin cargo. The article demonstrates that CPP–avidin complexes are not targeted to the recycling endosomes after internalization, instead follow the endo-lysosomal pathway inside vesicles with different pH values. A closer analysis of the vesicles entrapping the CPP–cargo complexes reveals that all used CPPs induce 3 distinct subpopulations of vesicles with distinct pH values and concentrations of the CPP–cargo complexes. Although trafficking of the CPP–cargo complexes to low-pH structures was observed in a time- and concentration-dependent manner, a distinct population of vesicles with non-acidic pH and elevated concentration of CPP–avidin complexes was observed. Even after 12 h a fraction of CPP–cargo complexes were not yet targeted for degradation. Räägel et al. propose that the prolonged near-neutral pH and the elevated intravesicular concentration of the CPP–cargo constructs could provide the complexes with conditions favorable for leaking out of the entrapping vesicles, making the cargo molecule available for exerting its activity. The findings in this article offer new data about the intracellular trafficking of CPP–cargo complexes.

Better understanding of the intracellular trafficking process is critical for developing highly efficient transport vectors, as it allows design of the vectors with effective release of biomolecules into the cytoplasm of the target cells. For now, it appears that caveolae-mediated endocytosis is preferred for effective escape of the carriers from endosomal structures. The information described in the two articles in this issue is significant in designing the better delivery vehicles for all drugs.

References

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