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Editorial

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Introduction to the Special Issue: traveling the intracellular highway to gene therapy

This special issue on Vector Trafficking kicks off a short series that will review our current knowledge of cell entry, intracellular motility, and nuclear delivery of gene therapy vectors. Trafficking of viral vectors, such as adenovirus, adeno-associated virus, lentivirus, and herpes simplex virus, will be reviewed. Nonviral vector trafficking, including nuclear delivery of the DNA payload and quantitative modeling of intracellular barriers to vector trafficking, will also be covered. The cell entry pathways that toxins use will also be featured, as these pathways can be considered as possible alternate routes for gene delivery, and have already proven advantageous for the delivery of various therapeutic toxins.

Studying intracellular vector trafficking can be an essential component of improving vector design. While we might not be concerned with the mechanisms of vector trafficking when experiments are successful, understanding vector–cell interactions becomes an important focus when gene expression does not reflect the dosage of input vector, or if the host has an unexpected response.

'Vector trafficking' encompasses the events that mediate the movement of a gene delivery vector from the cell surface to the nucleus. For many vectors, these events have only recently been elucidated. Overviews on the various cell entry pathways of viruses,[1] toxins,[2] and macromolecules[3] have provided us with a map of possible vector routes. Extensive research on endogenous cytoskeletal trafficking mechanisms has further established that cellular factors might contribute to the uptake and motility of incoming molecules.[4] These studies illustrate that the cytoskeleton provides an intracellular highway for molecular traffic from one subcellular location to another, including from the cell surface to the nucleus.[5] Many host molecules that facilitate endocytosis, endocytic motility, or nuclear targeting to mediate vector trafficking are now being identified. In many studies that examine the effect of various trafficking inhibitors or cytoskeletal disruption agents, the contribution of cytoskeletal elements or associated trafficking molecules has been identified. Biochemical methodologies, such as subcellular fractionation, have helped investigators identify the intracellular destinations of different vectors. The use of immunohistochemical techniques with confocal or electron microscopy has enabled researchers to visualize the intracellular localization of different vectors during gene transfer. More recently, time lapse and video photomicrography have allowed us to visualize the trafficking of fluorescently tagged vectors in 'real time'.

From these studies, we have learned not only about the location of vectors after cell entry, but more importantly, the intracellular obstacles to gene transfer. The observation that certain nonviral vectors undergo efficient cell binding and internalization but poor gene expression has highlighted the intracellular barriers to efficient gene transfer.[6] These barriers include inefficient internalization, endosomal escape, cytosolic trafficking, and nuclear delivery. As viruses have evolved mechanisms to penetrate these barriers, studies on viral trafficking can benefit the development of both viral and nonviral gene transfer vectors.[7] Studies on the intracellular trafficking of other pathogens, such as plant and bacterial toxins, have revealed alternate routes of cell entry that could potentially facilitate gene therapy vector delivery.[8,9] Such pathways, including nonclathrin-mediated routes of endocytosis, might avoid delivery to degradative compartments of the cell, and thus could be paths exploited for vector use.[10]

Our aim here is not only to provide a comprehensive overview of vector trafficking, but in a larger sense, provide a foundation of knowledge in intracellular trafficking as it relates to gene and molecular therapy so as to inspire the continual and creative development of improved vector design.

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