Perspective: Viva la natural vesicle

Naturally occurring exosomes are ideal for therapies — and are better for the job are than artificial nanoparticles, says Philip W. Askenase

Exosomes are a sensational biological discovery. These minute lipid sacs — among the smallest of biological particles known as nanovesicles — are produced and then secreted by all cell types in all animal species. Bacteria produce very similar nanovesicles.

Exosomes are present in all body fluids and seem to be involved in nearly all biological processes. The main function of exosomes is to enter cells, either nearby in the tissues or systemically after transiting through the bloodstream, to deliver the genetic information that they carry. In particular, exosomes transfer microRNAs (miRNAs) — small ribonucleotide polymers of about 22 bases. The extracellular miRNAs carried by exosomes can lead to alterations of DNA in the nuclei of targeted acceptor cells. The modifications to cellular DNA, in turn, alter the production of proteins and, therefore, change cell function. Exosomes are unanticipated universal nanoparticles that can mediate previously undiscovered biological processes, and alter molecular and metabolic pathways of cells and whole organisms.

These universal nanoparticles of life are likely to be of great medical importance. They might give researchers a better understanding of disease mechanisms, lead to new diagnostic tests and, perhaps most importantly, provide a means to deliver new therapies. But this will happen only if researchers study these natural entities more intensively.

Unfortunately, biomedical engineers have instead fixated on a different and less promising avenue: the development of artificial nanoparticles that imitate the function of natural exosomes for drug and small RNA delivery. Compared with naturally occurring exosomes, which have evolved an optimal composition over billions of years, engineered nanoparticles have a number of downsides. Unlike exosomes — which can cross natural tissue barriers such as the blood–brain barrier, can have effects for four to five days after administration and can enter the bloodstream[1] — artificial nanoparticles cannot cross such barriers and are rapidly eliminated by mechanisms that detect foreign entities. Natural exosomes in the blood avoid physiological clearance mechanisms, but engineered nanoparticles are taken up and destroyed.

Exosome membranes are composed of unusual proportions of lipid components that give them a high surface viscosity and rigidity. This composition aids their survival in harsh conditions that kill cells. Such properties might be derived from the ancient origins of exosomes' antecedent vesicles in noxious primordial seas near the beginning of biological evolution — even before the development of bacteria.

Exosomes' remarkable resistance to harsh conditions, such as the acidic and digestive-enzyme-rich environment of the stomach, means that they could be given orally as therapeutics[1]. Not only would this be more acceptable to and comfortable for patients, especially children, than intravenous, intraperitoneal and subcutaneous routes. But oral administration has also been shown to be a superior delivery method in mice.

Their stability and resilience are only part of what makes exosomes a natural choice for delivering genetic and anti-inflammatory molecules as therapies, both locally and systemically. They also lend themselves to therapeutic use in numerous other ways. It is likely that exosomes can be isolated from healthy individuals, and that a biologically active subpopulation can easily be enriched by a purification method called antigen or antibody affinity chromatography to promote therapy. Exosomes can also, in some instances, be used across species, without concern for immunological or genetic incompatibility, because miRNAs are often universal. Exosomes from plants might even have some medical use. And because exosomes do not contain full-length DNA, they are unlikely to cause cancer.

Exosomes also have an advantage over artificial drug carriers when it comes to targeting. Some exosomes can bind to selected antigen-specific antibody chains on their surfaces[2]. This gives exosomes an unrivalled ability to specifically target acceptor cells expressing particular surface antigens. Their uniquely targeted gene-altering miRNA cargo is also simple for researchers to load because activated exosomes can associate with miRNAs of choice by mere incubation[3]. Exosomes could therefore be used both to battle pathogens and to facilitate gene therapies for a variety of disorders.

Research indicates that exosomes might be effective therapies for diseases such as cancer, multiple sclerosis, rheumatoid arthritis, stroke, spinal-cord injury, myocardial infarction and lung fibrosis. Furthermore, investigations have begun into the use of exosome therapy for neurological conditions such as Alzheimer's disease, Parkinson's disease and even autism spectrum disorder. However, much more work is needed before RNA-carrying exosomes can fulfil their therapeutic potential. One important task is to determine the nature of the surface molecules on exosomes that allow them to bind to targeting antibodies, as well as the molecular arrangements that allow them to also associate with selected therapeutic RNAs. Artificial nanoparticles do not have these capabilities. Now is the time for researchers to usher in a new era of therapeutic possibilities using RNA-delivering, natural exosome vesicles.

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