nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Review

Therapeutic application of extracellular vesicles in acute and chronic renal injury☆

Jordi Rovira[a,b], *Fritz Diekmann*[a,b,c,*], *Josep M. Campistol*[a,b,c], *María José Ramírez-Bajo*[a]

[a] *Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Centre de Recerca Biomèdica CELLEX, Fundació Clínic per la Recerca Biomèdica (FCRB), Barcelona, Spain*
[b] *Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[c] *Departamento de Nefrología y Trasplante Renal, Institut Clínic de Nefrologia i Urologia (ICNU), Hospital Clínic, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 24 February 2016
Accepted 28 April 2016
Available online 15 May 2017

Keywords:
Extracellular vesicles
Acute and chronic renal injury
Regenerative therapy

ABSTRACT

A new cell-to-cell communication system was discovered in the 1990s, which involves the release of vesicles into the extracellular space. These vesicles shuttle bioactive particles, including proteins, mRNA, miRNA, metabolites, *etc.* This particular communication has been conserved throughout evolution, which explains why most cell types are capable of producing vesicles. Extracellular vesicles (EVs) are involved in the regulation of different physiological processes, as well as in the development and progression of several diseases. EVs have been widely studied over recent years, especially those produced by embryonic and adult stem cells, blood cells, immune system and nervous system cells, as well as tumour cells. EV analysis from bodily fluids has been used as a diagnostic tool for cancer and recently for different renal diseases. However, this review analyses the importance of EVs generated by stem cells, their function and possible clinical application in renal diseases and kidney transplantation.

☆ Please cite this article as: Rovira J, Diekmann F, Campistol JM, Ramírez-Bajo MJ. Uso terapéutico de las vesículas extracelulares en insuficiencia renal aguda y crónica. Nefrologia. 2017;37:126–137.

* *Corresponding author.*
E-mail address: fdiekman@clinic.ub.es (F. Diekmann).

Uso terapéutico de las vesículas extracelulares en insuficiencia renal aguda y crónica

Palabras clave:
Vesículas extracelulares
Insuficiencia renal aguda y crónica
Terapia regenerativa

RESUMEN

En la década de los 90 se descubrió un nuevo sistema de comunicación célula-célula, que consiste en la liberación de vesículas cargadas con partículas bioactivas (proteínas, mRNA, miRNA, metabolitos, etc.) en el espacio extracelular. Este tipo de comunicación se ha conservado durante la evolución, hecho que justificaría que la mayoría de los tipos celulares puedan generarlas. Estas vesículas extracelulares (VE) pueden regular diversos procesos fisiológicos, así como el desarrollo y progresión de enfermedades. En los últimos años se ha extendido el estudio de las VE generadas principalmente por células madre adultas o embrionarias, células sanguíneas, células del sistema inmune y nervioso, así como células tumorales. El análisis de VE en fluidos corporales ha sido utilizado como herramienta de diagnóstico en cáncer y recientemente para distintas enfermedades renales. Sin embargo, en esta revisión pretendemos analizar la importancia, función y posible aplicación clínica de las VE generadas por células madre en enfermedades renales y en trasplantes.

Introduction

The use of cell therapies to slow the progression of kidney diseases is a very promising approach due to the immunomodulatory and regenerative capacities of these therapies.[1–5] The renal protection effect of mesenchymal stem cells (MSCs) is not only due to the capacity to transdifferentiate, but also to the impact of its activity on damaged tissue.[1] Before using these therapies in routine clinical practice, there are a number of safety aspects that need to be investigated further: the possibility that a recipient's immune system rejection; the genetic cells stability; poor long-term differentiation; and the likelihood of virus transference.[6–8] Therefore, it has been promoted the study of the mechanisms underling protective and regenerative capacity of stem cell therapy; the idea is to design alternative cell-free therapies. There are studies showing that MSC-secreted factors or MSC-conditioned media may have the same protective effect as MSCs on tissue damage and contribute to the immunomodulation of inflammatory states.[9–13] The analysis of the conditioned medium evidenced the presence of growth factors, cytokines and extracellular vesicles (EVs). EVs may carry and transfer proteins, lipids and genetic material to resident cells in damaged tissue. EVs actively contribute to the therapeutic capacity of MSCs, in particular to the reprogramming of resident cells through the transference of mRNA and miRNA.[9,14–25] Once demonstrated that EVs have the same therapeutic capacity as MSCs, EVs are being proposed as cell-free therapy being safer for patients.[26]

EV-mediated cell–cell communication is a mechanism that has been preserved throughout evolution in both eukaryotic cells and prokaryotic cells.[27] Since its discovery 30 years ago,[28] EVs have been shown to be produced by a large variety of cell types: blood, dendritic, endothelial and epithelial cells, as well as nervous system cells, adult and embryonic stem cells and even cancer cells.

EVs are formed by a lipid membrane and can transmit regulatory biological signals by transferring membrane and cytosolic proteins, lipids, mRNA, miRNA, mitochondrial DNA and genomic DNA that regulate various physiological processes, as well as in the development and progression of diseases.[29–34] All cells can produce EVs as a normal mechanism of paracrine–endocrine communication; however in case of cell damage, EV production is increased and vesicular content is modified, to alert the adjacent cells, progenitor cells and the immune system. The body uses these processes to restore homeostasis in the damaged tissue. Only progenitor cells and MSCs can generate EVs with intrinsic protective or regenerative capacity.

As for the progression of diseases, it has been shown that the microenvironment defines the content of EVs. In arteriosclerosis in particular, vascular endothelial cells subjected to stress induced by calcium generate EVs that promote tissue mineralisation.[35]

Regarding cancer, it has been postulated that progenitor cells undergoing mutations, may be the origin of cancer stem cells,[36] which produce EVs involved in the development and progression of cancer. These EVs promote angiogenesis,[37] allow tumours to escape immune vigilance,[38] induce the elimination of therapeutic molecules that activate apoptosis[39] and actively participate in the degradation of the extracellular matrix required for metastasis.[40] They act as paracrine–endocrine effectors by transporting bioactive molecules from cell to cell within the microenvironment, or by being remotely transported by body fluids.[41]

The origin and size of EVs allows us to differentiate between exosomes (EXs) and microvesicles (MVs) (Fig. 1). EXs are small vesicles (70–150 nm) that are endosomal in origin; therefore their membranes are enriched with cholesterol, ceramides and sphingolipids, and their content corresponds to that which is present in the endosomal compartment. By contrast, MVs are larger (150–1000 nm) and they are