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Exosomes and Exosome-like Nanoparticles: Applications for Biomedicine

Luana Magalhães[1], Mário Fernandes[1-3] and Andreia C Gomesa[1]*

[1]*Centre of Molecular and Environmental Biology (CBMA), University of Minho, Portugal*

[2]*Institute of Science and Innovation for Sustainability (IBS), University of Minho, Portugal*

[3]*Departamento de Química Inorgánica, Universidade de Vigo, Spain*

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***Corresponding author:** Andreia C Gomes,Centre of Molecular and Environmental Biology (CBMA), University of Minho, Campus of Gualtar, 4710-057 Braga, Portugal

Abstract

With the rise of the average life expectancy in the last century, the prevalence of life-threatening diseases has greatly increased. Thus, the need for effective, cost efficient and easy to produce therapeutic systems, combined with recent technological advances, boosted nanotechnology research. Since their discovery more than 30 years ago, naturally occurring exosomes are an increasingly interesting vehicle for drug delivery, with the disadvantage that they are difficult and expensive to extract, characterize and their encapsulation efficiency is poor. Liposomes, known since the mid-60's, can be used for various types of therapies for their capacity to encapsulate almost any molecule, with efficient production and encapsulation processes, but are less biocompatible. A new type of systems, exosome-like nanoparticles, that combine the advantages of these two systems, mitigating their limitations, show potential to be excellent therapeutic options with almost no side-effects.

Keywords: Nanotechnology; Liposomes; Exosome-like; Exosomes; Nanoparticles

Introduction

In recent decades, in the nanotechnology field, many new approaches have been developed, in basic and clinical research, to obtain a better diagnosis and an early effective therapy for the most debilitating diseases such as cancer or neurodegenerative disorders [1]. Extracellular vesicles are naturally occurring molecular vehicles, having an important role in the transport of molecules-being misfolded proteins to be degraded in the lysosome, or nucleic acids - and in intercellular communication [2,3]. Extracellular vesicles can be divided into three subpopulations according to their size and origin: exosomes, Microvesicles and apoptotic bodies [1]. These vesicles naturally do what some of the industrially manufactured nanoparticles aim to do: the encapsulation of molecules and their controlled release into a target cell [4]. Exosomes are becoming an increasingly interesting vehicle for the delivery of drugs due to their biocompatibility, capacity to cross biological barriers and to encapsulate hydrophilic and lipophilic molecules [3,5-7]. However, exosomes can also be difficult to extract and to characterize, and the costs of extraction and encapsulation of bioactive molecules can be high. Moreover, the encapsulation process can be difficult, very time-consuming, and can lead to poor encapsulation efficiencies [4.8].

Similarly, to exosomes, liposomes have a bilayer of lipid molecules, that can be synthetic or natural occurring ones, on the membrane of cells or vesicles [9,10]. This type of intensively studied synthetic vesicles have been used for various types of therapies, from imaging to the treatment of a wide range of diseases, since they can encapsulate almost every molecule [4,11]. These nanocarriers, while similar to exosomes to a certain degree, have a simple and efficient production process, and can encapsulate bioactive drugs more efficiently than exosomes, with the drawback that they can be far less biocompatible than these natural occurring nanovesicles [9]. Mitigating the drawbacks of these two systems, while retaining their excellent properties, exosome-like liposomes have been recently considered for therapy, with some very interesting systems-that can encapsulate biomolecules efficiently and deliver them safely in the targeted area - have been developed through various types of approaches. These can be considered as some of the most promising drug

delivery nanoparticles, and more research in the area may lead to a more efficient and safe delivery of biomolecules.

Advantages and drawbacks of exosomes in drug delivery

Exosomes are the smallest in the extracellular vesicle class [12], with a diameter of 30 to 150 nm, which is why they are considered nanovesicles, are highly heterogeneous and with different molecular and charge compositions, depending on the type of producing cell [2], its structure is formed by a lipid bilayer with associated proteins on its membrane [13]. Exosomes can be produced by almost all human cells [14], wherein the mechanism is maintained for several classes of organisms. Exosomes can also be considered a waste disposal mechanism [1]. For drug delivery, exosomes have some advantages, one of which is to encapsulate lipids, proteins, DNA, mRNA, non-coding RNA or other bioactive substances [1,12], they can also circulate in biofluids and thus transport messages from one cell to another; when the exosome reaches the recipient cell, it can modify its behavior depending on the message received. Exosomes are an efficient platform for drug delivery, due to their biodistribution, biocompatibility and low immunogenicity. Moreover, they can also cross most biological barriers, allowing the delivery of biomolecules in all organs of the human body [12].

Advantages and drawbacks of liposomes in drug delivery

Liposomes have a spherical structure with one or more phospholipid bilayer [9,10], which can be classified according to size (small, large, and giant); number of bilayer (unilamellar, oligolamellar and multilamellar) and charge (neutral; anionic and cationic) [10,11]. While liposomes' size can range from 50 to 200nm, they are more efficient when they have 100 to 140nm since they have a longer half-life in the blood stream. Moreover, these particles are not so easily detected by the immune system and are relatively more difficult to be recycled or eliminated from the body [10,15]. Liposomes can encapsulate antimicrobial drugs, nucleic acids, and antioxidants, within their bilayer or their aqueous area. This delivery is directed and controlled [16]. Since liposomes can be made by various types of naturally occurring or synthetic lipids, the toxicity of the system must be extensively studied, often limiting the use of these systems for various types of therapies [9,11].

Exosomes-like liposomes: fusing the advantages of liposomes with exosomes.

Exosome-like nanoparticles often have a similar size to liposomes (60nm–150nm) [17,18], joining the advantages such as the ease of production, tuning of the formulation, and encapsulation efficiencies of liposomes with the biocompatibility, longer circulation time, stability, and ability to cross biological barriers better than exosomes. Moreover, the cytotoxicity of this type of nanocarrier is often negligible since their composition is like naturally occurring exosomes. This type of nanoparticles can be obtained from various processes, such as the fusion of liposomes with exosomes [19], their extraction from plants [20,21], or serial extrusion of animal cells [17,22,23]. Exosome-like vesicles from plants are some of the most like exosomes, as they have a composition very similar to exosomes from human cells. More than that, their encapsulated molecules are like the ones found in animal exosomes, but differ in number, containing a lesser quantity of both nucleic acids and proteins than the animal ones [24], being non cytotoxic and being able to deliver biomolecules for the treatment of various diseases such as brain tumors [25].

Conclusion

Exosome-like nanoparticles, while newly discovered, have already been the target of multiple studies, with some interesting results [1,2]. In fact, their biocompatibility is excellent, and they can effectively encapsulate a fair number of biomolecules, being an interesting therapeutic option on their own, when they are extracted from plants. Studies in animals prove that they can effectively bioaccumulate in the desired therapeutic area and attenuate some of the most debilitating diseases as brain tumors or cancer [2,11,15]. While liposomes and exosomes remain more commonly studied and used systems for therapy, the advantages of exosome-like nanoparticles cannot be ignored as they continue to rise in interest among the scientific community.

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