Review Article

Exosomes as Immunotheranostic Nanoparticles

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ABSTRACT

Background: Exosomes are small biological membrane vesicles that measure 30 to 100 nm in diameter. They are involved in a wide array of biological activities, such as cell-cell communication, signal transduction, transport of genetic materials, and modulation of immune response. Evidence indicates that they can be used as not only therapeutic agents targeted against disease but also diagnostic biomarkers for pathologic conditions.

Objective: In this review, we endeavor to present exosomes as immunologic agents that can be used as pioneering cancer vaccines to prime the immune system and explicate their therapeutic and diagnostic capabilities.

Methods: An extensive literature search for studies that involved the use of exosomes as immunotheranostic nanoparticles was conducted using PubMed, ISI Web of Knowledge, and Google Scholar. Clinical trials that involved exosomes were also compiled by searching the clinicaltrials.gov database.

Results: In its therapeutic facet of application, exosomes can be used as vehicles for drug or gene delivery. These biological vesicles have been found to have excellent host biodistribution and biocompatibility, issues often presented with gene delivery vehicles. Diagnostically, exosomes may prove to be useful biomarkers that are able to surpass current setbacks of modern diagnostic testing, which include invasive methods. Finally, current evidence has implied that the use of exosomes could form the basis for the development of future cell-free cancer vaccines.

Conclusion: Exosomes have numerous functions, and their double-edged features make the scope of their clinical applications, as both a diagnostic and therapeutic tool, immense. (*Clin Ther*. 2014;36:820–829) Crown Copyright © 2014 Published by Elsevier HS Journals, Inc. All rights reserved.

Key words: Exosomes, immunotherapy, cancer vaccine, theranostics, nanoparticles, nanomedicine.

INTRODUCTION

Exosomes are small biological membrane vesicles that measure 30 to 100 nm in diameter.[1] They are involved in a wide array of biological activities, such as cell-cell communication, signal transduction, transport of genetic materials, and modulation of immune response. Evidence indicates that they can be used as not only therapeutic agents targeted against disease but also diagnostic biomarkers for pathologic conditions.[2,3] Technology that uses dual concomitant capability of therapy and diagnostics has been

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termed *theranostics* and is a promising field in nanomedicine.[4]

In its therapeutic facet of application, exosomes can be used as vehicles for drug or gene delivery. Because these biological vesicles have been found to have excellent host biodistribution and biocompatibility, they can be selectively loaded and the drug combination optimized compared with current gene delivery modalities that have had issues with immunity and delivery past the blood brain barrier (BBB). Moreover, exosomes have not only natural stability in the blood but also natural targeting properties, and unlike conventional drug delivery systems, they have ability to deliver functional RNA into cells.

As for their diagnostic scope, exosomes may prove to be useful biomarkers that are able to surpass current setbacks of modern diagnostic testing. Because RNA-loaded exosomes can be found in virtually all body fluids (including blood, saliva, cerebrospinal fluid, breast milk, and urine), diagnostic methods that use these fluids, which are inherently noninvasively collected, can be devised. This is potentially a cost-effective and more efficient system of diagnosis, as opposed to the more traditional methods that use needles or excision biopsies. As such, exosomes are a useful in vitro and in vivo diagnostic tool.

Finally, current evidence has implied that use of exosomes could form the basis for the development of future cell-free cancer vaccines. By acting as shuttles for antigen presentation, exosomes play a role in modulation of the immune system—a key attribute that has led to their consideration as potential tools for cancer vaccines. In this review, we endeavor to present exosomes as immunologic agents that can be used as pioneering cancer vaccines to prime the immune system and explicate their theranostic (ie, their therapeutic and diagnostic) potential.

STRUCTURE AND COMPOSITION OF EXOSOMES

The structure of exosomes has been said to resemble a saucer or a flattened sphere, consisting of a lipid bilayer membrane,[1] with their dimensions and morphologic features comparable to internal compartments of the endosomes.[5] Exosomes contain an abundance of proteins with numerous functions, with some common protein constituents presented in **Figure 1**.[6,7] These proteins include but are not limited to Rabs,[8,9] annexins,[10] adhesion molecules,[6,8,11] heat shock proteins,[12] and, perhaps most characteristically, tetraspanins.[13] Lipid compounds also form an important component of exosomes, including those such as cholesterols, phosphatidylcholines, phosphatidylserines, and diglycerides[14] (**Table I**).

PHYSIOLOGIC FUNCTIONS OF EXOSOMES

Exosomes possess a plethora of functions and can be considered an alternative method of intercellular communication. First described as a mechanism to extrude redundant proteins, exosomes were observed in vivo and in vitro to facilitate transferrin receptor release in reticulocyte maturation into erythrocytes.[15] This release of proteins using exosomes has also been established to occur in soluble cytokine receptor extrusion and specifically that of extracellular release of tumor necrosis factor (TNF) receptor 1 from synovial fibroblasts of individuals with rheumatoid arthritis.[16]

Exosomes have been observed to contain not only RNA, such as microRNA (miRNA) and messenger RNA (mRNA), but to transfer RNAs to nearby cells—a process coined as *RNA shuttling*.[17] This transferred RNA has been reported to be translated and therefore induces new functions to receptor cells, as seen in human and murine mast cells, for example.[17]

Aside from their transfer of RNA, exosomes have been implicated in many immunologic interactions, which ultimately potentiate stimulatory actions on the immune system (**Figure 2**).[18] For instance, exosomes secreted by B cells have been reported to stimulate $CD4^+$ T cells in both murine and human B-cell lines.[5] Moreover, evidence suggests that tumor antigens can be presented to T cells through exosomes derived from dendritic cells and can aid in the elimination of tumor masses in vivo and in vitro.[8,19,20] Studies such as this one indicate that antigen presentation through exosomes plays an important role in mounting and stimulating immune responses. In fact, stimulation of the immune system in this manner has recently been implicated in immune surveillance, whereby *Mycobacterium*-infected host macrophages cells have been found to secrete exosomes that induce a proinflammatory response in uninfected cells through exposure to pathogen-associated molecular patterns.[21] Moreover, this phenomenon has also been documented in host cells infected with other bacterial species, such as *Salmonella* Typhimurium or *Toxoplasma gondii*–infected macrophages.[22]

As opposed to their immunostimulatory actions, immunosuppressive modulation by exosomes has been found not only in immune cells but also in tumor cells

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