Review Article

Potential of Cancer Cell–Derived Exosomes in Clinical Application: A Review of Recent Research Advances

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ABSTRACT

Background: Exosomes are 30- to 100-nm, membrane-bound vesicles that are released by most types of cells, including tumor cells. Exosomes contain a great variety of bioactive molecules, including signal peptides, microRNA, lipids, and DNA. In cancer, tumor cells aberrantly secrete large quantities of exosomes to transport paracrine signals or to contribute to tumor–environment interaction at a distance.

Objective: The goal of this review was to discuss the recent advances on the mechanism of cancer-derived exosomes in tumor regulation.

Methods: Pertinent articles and abstracts were identified through searches of PubMed for literature published from 1983 to December 2013. Search terms included *exosome, tumor, cancer, diagnosis,* and *therapy*.

Results: All of the exposed evidence points to communication between cancer cells and their surroundings, either mediated by cancer cell–derived exosomes or by stromal cell–derived exosomes. This communication probably supports tumor proliferation, motility, invasion, angiogenesis, and premetastatic niche preparation. In addition, recent research implies that cancer cell–derived exosomes play a suppressive role in cancer-directed immune response.

Conclusions: The biomarkers detected in bodily fluid–derived exosomes imply a potential for exosomes in cancer diagnosis. Also, exosomes could be used as a vehicle to selectively deliver therapeutic nucleic-acid drugs or conventional drugs for tumor therapy. The tolerability and feasibility of cancer exosomes in diagnosis and therapy need to be further evaluated. (*Clin Ther*. 2014;36:863–872)

Key words: cancer, diagnosis, exosomes, therapy.

INTRODUCTION

Cells are known to deliver proteins and molecules between the intracellular organelles by membrane vesicles containing definite receptors to ensure traffic specificity. The research accumulated over the past 10 years has demonstrated that a heterogeneous group of vesicles is also released from the cell surface and is used as intercellular signalosomes in information exchange, even over a long distance.[1] These membranous vesicles, released by a variety of cells and generally termed *extracellular vesicles,* can be divided into 3 main classes: exosomes, microvesicles (100–1000 nm), and apoptotic bodies (1–5 μm).

Exosomes are 30 to 100 nm in diameter and shed from many different types of cells under both normal and pathologic conditions.[2] These exosomes can be formed through inward budding of endosomal membranes, giving rise to intracellular multivesicular bodies that later fuse with the plasma membrane, releasing the exosomes to the exterior.[3] They are released from many different cell types in the body, such as red blood cells, platelets, lymphocytes, dendritic cells (DCs), and tumor cells.[4] Depending on the cellular origin, exosomes contain various cellular proteins. These proteins may be different

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from proteins that are normally located in the plasma membrane, including major histocompatibility complex (MHC) molecules, tetraspanins, adhesion molecules, and metalloproteinases.[5,6] Exosomes also contain signal proteins and/or peptides, microRNAs (miRs), mRNAs, and lipids that can be transferred to a recipient cell by fusion of the exosome with the target cell membrane.[7,8] It has been proposed that this transfer of protein and RNAs from one cell to another might represent a novel mechanism of intercellular communication.[9,10]

Initially, exosomes were described as vesicles released by reticulocytes. They were thought to function as a way to remove unnecessary proteins, such as the transferrin receptor, during the process of maturation into erythrocytes.[3] Emerging evidence indicates exosomes as important mediators of cellular communication. Exosomes are involved not only in normal physiologic processes, such as lactation, immune response, and neuronal function, but also in the development and progression of diseases, such as liver disease, neurodegenerative diseases, and cancer.[11] However, the detailed mechanisms of exosomes in physiologic and pathologic regulation are still being researched.

Exosomes can also be isolated from various bodily fluids, such as breast milk, serum, plasma, malignant ascites, and urine.[4] Therefore, ex vivo analysis of exosomes may provide biomarker-discovery platforms and facilitate disease diagnosis and monitoring.

The goal of this review was to discuss the recent advances on the mechanism of cancer-derived exosomes in tumor regulation.

MATERIALS AND METHODS

Pertinent articles and abstracts were identified through searches of PubMed for literature published from

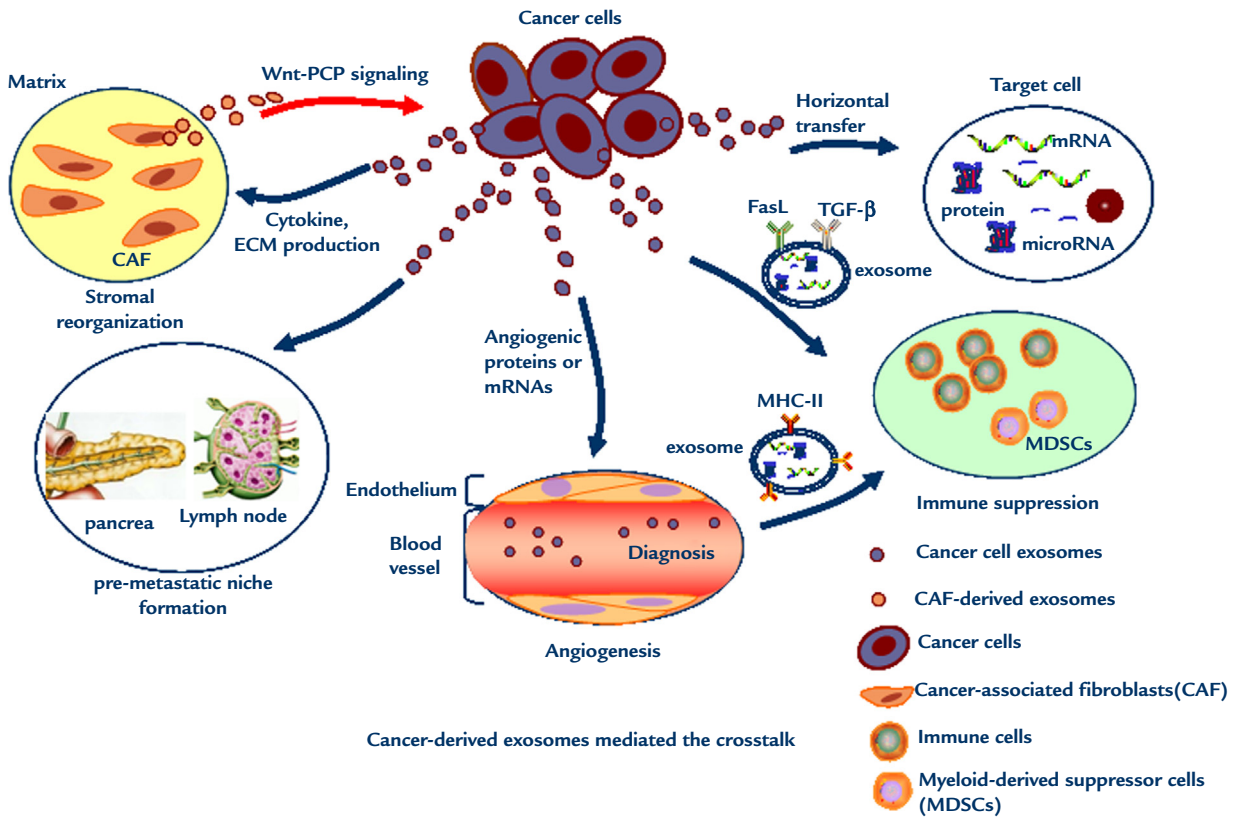

Figure. Cancer-derived exosomes are implicated in transferring miRNAs, mRNA and proteins to target cells. They are able to reorganize extracellularmatrix, alter the premetastatic niche and promote angiogenesis. They also create an immunosuppressive microenvironment by impairing the immune cells, by inducing the apoptosis of T cells through FAS-FASL ligation.