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Editorial

Exosomes and Their Role in Cancer Development, Diagnosis and Therapy

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Dear editor

Local or distant intercellular communication is essential for multicellular organisms. Distant communication is performed by signaling molecules like extracellular vesicle (EV)(1). EVs are divided into three types: microvesicles, apoptotic bodies, and exosomes which are different in term of size and origin(1). Exosomes with a size 40 to 100 nm have the smallest size among all and originated from endosomes. They are double layer membrane, containing different types of nucleic acids, proteins, lipids and approximately are produced by all cells. Exosomal membrane contain different surface proteins such as LAMP, CD9 and CD63 which can recognize specific cell types by their surface ligands(2).

Tumor cells generate and Release further lipids, proteins and nucleic acids compared to normal cells in membrane-encapsulated exosomes. Tumor exosomes are vehicles for intercellular communications and providing supportive niche for emergence, development, multiplication and metastasis of cancer cells and designation of metastasis location in the body(3). Studies have also demonstrated that cancer cells are interconnected to induce chemoresistance through exosome signaling. Exosome signaling also contribute to tumor metastasis and recurrence (4).

Exosomes have an excessive potential to use as new biological tumor markers for various diseases because of high stability of them in most body liquids and correspondence of their substance to cell of origin. Cancer derived exosomes can be used as non-invasive biomarker for early diagnosis as their content reflect the (epi)genetic changes of their origin tumor cells(5). The most common method for exosome isolation is differential centrifugation. Another common exosome isolation method is based on monoclonal antibodies(MAbs), ultrafiltration and high performance liquid chromatography(HPLC)(5). The purity of isolated exosomes is evaluated by measuring CD63 as a specific surface marker of exosomes using ELISA(6). Exosomal proteins as the representative of their origin cell proteins can be measured for diagnosis of different diseases(7). Rupp and

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their colleagues revealed EpCAM and CD24 as exosomal breast cancer markers by monoclonal antibody-based technique(8). Khan and their colleagues indicated that relative quantity of Survivin in serum isolated exosomes of patients with prostate cancer is significantly higher than of normal people(9). Recently rapid and high-throughput devices for exosomal diagnosis without a purification step is more interested, such as microfluidic chips(10).

Tumor-derived exosomes are involved in pathogenesis and microenvironmental establishment of cancer. So, prevention of the generation, secretion and circulation of tumor exosomes can effectively inhibit the cancer progression(3). Nao et al demonstrated the suppressing cancer metastasis by inhibition of cancer-derived exosomes via anti CD9 and CD63 antibodies(11). Exosomes from numerous cancers display integrin b1, while normal cells did not; So, integrin b1 is a potentially good therapeutic target(11).The integrin expression on exosomes surface, can facilitate the migration of exosomes into target cells. Exosomes can applied as excellent vectors for transfer of nucleic acids and proteins to cells(11). Also, exosome-mediated cancer therapy has good potential for cancer stem cell (CSC) targeting. CD44 is a surface marker of CSCs, so attaching anti-CD44 antibody to surface of a drug-loaded exosome could induce CSC death. Furthermore, other CSC markers such as CD200, CD24, EpCAM and CD133 can be targeted. Numerous drugs cannot go across the blood brain barrier (BBB) because confine the treatment efficacy for metastatic disease. However, isolated exosomes from endothelial cells of brain could transfer a drug across the BBB(12). Therapeutic agents can be incorporated into exosomes using active or passive methods. Passive methods involved the incubation of exosomes or exosome-donor cells with specific drug. Active methods include: exosome sonication, extrusion, freeze-thawing, electroporation and incubation with membrane permeabilizers. Also, therapeutics molecules can directly be attached to exosomes surfaces via covalent bonds(13).Unfortunately, the efficiency of all these methods for drug incorporation into exosome is low. Upregulation of selective proteins or RNAs in cell of origin is greatest way to produce specific protein or RNA-loaded exosomes(14). Katakowski et al showed that miR-146b-enriched exosomes, prevent glioma cells growth, and inhibit progression of rat xenograft of gliomas cells(15).

dendritic cells(DCs)-derived exosomes can activate T cells For long-term by presenting antigens to them(16). Due to the great potential of DC derived exosomes, they have been applied in human clinical studies as cell-free exosome-based tumor vaccines. DC derived exosomes can be modified to have a higher surface costimulatory molecules and lower level of immunoregulatory molecules(17). Other findings showed that stimulating of B cells along T cells with engineered DC derived exosomes can improve their immunogenicity(18). Donor cells can be engineered via surface display technology to

produce modified exosomes with specific receptors against particular cell type. Also, the specificity of exosomes against tumor cells can enhanced by attaching anti-tumor MAbs or aptamers on exosome surface(19, 20). Applying aptamers on the exosome surface in order to cancer cell drug delivery can be an interesting area in future researches(20).

In summary, we will need to expand our concept about exosomes in the cancer pathogenesis. When the safety, efficacy and specificity of exosomes have been completely understood can be used as new alternative in in the field of cancer therapy.

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