Medicine, Drug discovery

Exploring the potential of engineered exosomes as delivery systems for tumor-suppressor microRNA replacement therapy in ovarian cancer

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Abstract

MicroRNA (miRNA) plays a pivotal role in cancer biology. Exosomes are stable in circulation and selectively picked up by cancer cells, indicating that they can serve as a miRNA carrier. The aim of this study was to explore the possibility of exosomes as a carrier for miRNA replacement therapy for ovarian cancer (OC). First, exosomes were purified from primary-cultured omental fibroblasts of OC patients. miR-199a-3p was selected as a TS miRNA, and the synthesized miR-199a-3p was loaded into exosomes by electroporation. Treatment with miR199a-3p-loaded-exosomes (M199-exosomes) drastically increased miR-199a-3p expression level in OC cell lines. M199-exosomes suppressed c-Met expression, a direct target of miR-199a-3p, and thereby inhibited cell proliferation and invasion. In a xenograft study, M199-exosomes also drastically inhibited peritoneal dissemination in OC mice model. These results suggest that miRNA replacement therapy using exosomes shows promise for treatment of OC. Given that omental fibroblasts can be obtained from most OC patients, patient-derived exosomes can be utilized as a DDS for future molecular-targeted therapies.

Background & Results

[Background] Considering pivotal roles of microRNA (miRNA) in cancer biology, tumor suppressor (TS) miRNA remains to be an attractive molecular target; however, most of all clinical trials with TS miRNAs have failed due to difficulties of miRNAs delivery to cancer tissues efficiently, and therefore the development of a novel drug delivery system for miRNA is warranted. Exosomes are known to be stable in circulation and specifically picked up by cancer cells, indicating they can serve as a promising miRNA carrier. The aim of this study is to pursue the possibility of engineered exosomes as a carrier for miRNA replacement therapy for ovarian cancer (OC).

[Methods & Results] Secreted exosomes were purified from human fibroblasts primary cultured from omentum obtained during gynecological surgery. miR-199a-3p was selected as TS miRNA. Synthesized miR-199a-3p tagged with Alexa-488 was loaded to exosomes by electroporation. Subsequentially, the effect of 199a-3p-loaded exosomes (M199-exosomes) was analyzed in vitro and in vivo. Treatment with M199-exosomes drastically increased the expression of miR-199a-3p in 3 different OC cell lines. M199-exosomes suppressed c-Met expression, a direct target of miR-199a-3p, and thereby inhibited cell proliferation and invasiveness of OC cells significantly. In a xenograft study, intraperitoneal treatment with M199-exosomes drastically inhibited peritoneal dissemination in mice.

Significance of the research and Future perspective

miRNA replacement therapy using engineered exosomes showed promising treatment effects to ovarian cancer peritoneal dissemination. Given that most OC patients undergo omentectomy and thereby exosomes from omental fibroblasts can be obtained from those, engineered exosomes can be utilized as a drug delivery carrier for a future molecular-targeted therapies for OC.

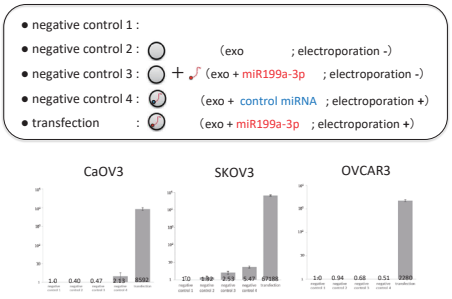

Figure 1. miRNA RT-PCR. miR-199a-3p loaded exosomes were efficiently picked up by ovarian cancer cells.

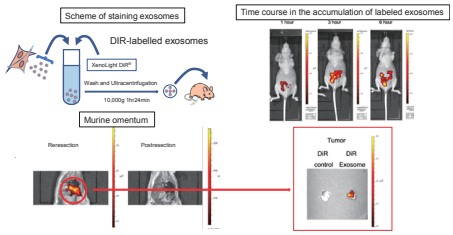

Figure 2. Representative pictures taken by IVIS imaging system of animals. DIR-labelled exosomes were selectively picked up by tumors.

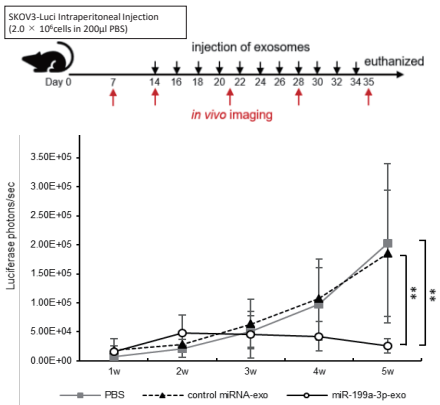

Figure 3. miR-199a-3p loaded exosomes inhibit ovarian cancer peritoneal dissemination in xenograft ovarian cancer model mice. Luciferase activities of peritoneal tumors of mice injected intravenously with PBS, control miRNA loaded exosomes, or miR-199a-3p loaded exosomes were measured weekly. **; P<0.01.

Patent

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URL

Keyword exosome, ovarian cancer, peritoneal dissemination, microRNA