

Exosomes from cerebral endothelial cells suppress chemotherapy-induced peripheral neuropathy and sensitize anti-tumor effects of platinum drugs

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Introduction: Platinum-based drugs are commonly used to treat cancers. However, peripheral neuropathy is a common adverse effect of platinum based chemotherapy. Neurotoxicity often requires platinum drug dose reduction thereby, compromising therapeutic efficacy of platinum drugs to suppress tumor progression.

Methods and Results: Using differential ultracentrifugation, we isolated exosomes from the supernatant of cultured human primary cerebral endothelial cells (CEC-exos). Ovarian tumor was induced in mice by implantation of human ovarian cancer cells. Platinum-induced symptoms of peripheral neuropathy start from distal axons. Thus, we examined the direct effect of platinum drugs on distal axons of dorsal root ganglia (DRG) neurons using a microfluidic device that permits distal axons to grow into the axonal compartment from their parent cell bodies localized to the soma compartment. We found that addition of oxaliplatin or carboplatin into distal axons significantly suppressed axonal elongation, whereas application of CEC-exos into the distal axons completely abolished oxaliplatin-inhibited axonal growth. In vivo, treatment of mice bearing ovarian cancer with platinum drugs (n=7/group) induced peripheral neuropathy measured by tactile and cold allodynia, and reduction of sensory nerve conduction velocity and epidermal nerve fibers compared to the control mice (n=7/group). However, tumor bearing mice treated with platinum drugs along with CEC-exos (n=7/group) exhibited significant reduction of platinum-drug induced peripheral neuropathy. Moreover, CEC-exos in combination with platinum drugs significantly decreased tumor size by 80-91% compared to platinum drugs alone which reduced tumor growth only by 50-72%. In sciatic nerve tissues, CEC-exos in combination with platinum drugs significantly increased miR-15b, -26a, and -214, and substantially reduced axonal damage protein levels of PTEN, SARM1, and TRPV1. In tumor tissues, the combination treatment significantly increased miR-15b and -26a, and reduced their target chemoresistant protein levels of P-gp and ABCC1.

Conclusion: Our data demonstrate that CEC-exos abolish platinum-drug induced peripheral neuropathy by reversing the platinum-inactivated neuroprotective network, and that CEC-exos suppress a chemoresistant network of miRNAs/protein-coding genes to enhance the anti-tumor effect of platinum drugs.