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Adipose-derived mesenchymal stem cells extracellular vesicles mitigate neurotoxicity induced by antineoplastic drugs in sensory neurons

Chiara D'Aprile[1], Adele Naghshbandieh[1,3], Valentina Fabbro[1], Ermanna Turano[2], Ilaria Scambi[2], Federica Virla[2], Mauro Caprioli[2], Raffaella Mariotti[2], Cristina Meregalli[1], Arianna Scuteri[1]

[1]*Experimental Neurology Unit and Milan Center for Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Italy*
[2]*Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy*
[3]*PhD Program in Neuroscience, University of Milano-Bicocca, Italy*

Chemotherapy-induced peripheral neuropathy (CIPN) constitutes a major clinical side effect, manifesting as paraesthesia, numbness, and dysesthesia, that often necessitates dose reduction and/or discontinuation of therapy with platinum-based compounds and proteasome inhibitors [1]. Despite decades of investigation, no neuroprotective modality has achieved definitive clinical efficacy. Nevertheless, in vitro studies have highlighted the therapeutic promise of extracellular vesicles derived from mesenchymal stem cells (ASC-EVs). EVs are emerging as important mediators of intercellular communication and have been shown to carry a variety of bioactive molecules, including proteins, RNAs, and lipids, and in particular ASC-EVs contribute to cellular repair processes.

This study aimed to assess the neuroprotective potential of ASC-EVs towards the neurotoxic effects of cisplatin (CDDP) or bortezomib (BTZ) on sensory neuron primary cultures derived from embryonic (E15) Dorsal Root Ganglion (DRG).

Sensory neurons were treated with CDDP (6 μM) or BTZ (20 nM), either alone or in combination with EVs (1 μg/mL), for 24-48 hours. Neuronal viability was evaluated using bright-field microscopy, based on the count of viable cells identified by the birefringent neuronal soma.

Consistent with established neurotoxicity profiles, CDDP induced a pronounced, time-dependent decrease in neuronal viability at both 24 h and 48 h time points. However, co-treatment with ASC-EVs significantly rescued neuronal survival, indicating a potential neuroprotective effect.

In parallel, BTZ induced a distinct neurotoxic profile, with milder effects observed at earlier time points, likely reflecting differences in its action mechanism with respect CDDP[3]. Nevertheless, co-treatment with ASC-EVs also mitigated BTZ-induced toxicity, suggesting a potentially neuroprotective capacity.

These results support the hypothesis that the neuroprotective efficacy of ASC-EVs is dependent upon both the pharmacological profile of the chemotherapeutic agent used and the treatment duration, suggesting a time-dependent interplay between ASC-EVs activity and drug-induced neurotoxicity.

ASC-EVs appear to counteract the detrimental effects of chemotherapeutic agents through mechanisms that may likely involve oxidative stress and apoptotic molecular pathways, which are now under investigation. Moreover, further studies are required to optimize this therapeutic approach by precisely defining the most effective time window for ASC-EVs administration, identifying the specific molecular components responsible for the observed neuroprotective effects.

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