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Amniotic Fluid Mesenchymal Stem Cells Selected for Neural Specificity Ameliorates Chemotherapy Induced Hearing Loss and Pain Perception

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Abstract : Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects caused by anti-neoplastic agents, with a prevalence from 19 % to 85 %. Clinically, CIPN is a mostly sensory neuropathy leading to pain and to motor and autonomic changes. Due to its high prevalence among cancer patients, CIPN constitutes a major problem for both cancer patients and survivors, especially because currently, there is no single effective method of preventing CIPN. Hearing loss is the most common form of sensory impairment in humans and can be caused by ototoxic chemical compounds such as chemotherapy (platinum-based antineoplastic agents).In rodents, single or repeated cisplatin injections induce peripheral neuropathy and hearing impairment mimicking human disorder, allowing studying the efficacy of new pharmacological candidates in chemotherapy-induced hearing loss and peripheral neuropathy. RNA sequencing data from full term amniotic fluid (TAF) mesenchymal stemcell (MSC) clones was used to identify neural-specific markers present on TAF-MSC. Several prospective neural markers were tested by flow cytometry on cultured TAF-MSC. One of these markers was used for cell-sorting using Tyto MACSQuant cell sorter, and the neural marker positive cell population was expanded for several passages to the final therapeutic product stage. Peripheral neuropathy and hearing loss was induced in mice by administration of cisplatin in three week-long cycles. The efficacy of neural-specific TAF-MSC in treating hearing loss and pain perception was evaluated by administration of three injections of 3 million cells/kg by intravenous route or three injections of 3 million cells/kg by intra-arterial route after each cisplatin cycle treatment. Auditory brainstem responses (ABR) are electric potentials recorded from scalp electrodes, and the first ABR wave represents the summed activity of the auditory nerve fibers contacting the inner hair cells. For ABR studies, mice were anesthetized, then earphones were placed in the left ear of each mouse, an active electrode was placed in the vertex of the skull, a reference electrode under the skin of the mastoid bone, and a ground electrode in the neck skin. The stimuli consisted of tone pips of five frequencies (2, 4, 6, 12, 16, and 24 kHz) at various sound levels (from 0 to 90 dB) ranging to cover the mouse auditory frequency range. The von Frey test was used to assess the onset and maintenance of mechanical allodynia over time. Mice were placed in clear plexiglass cages on an elevated mesh floor and tested after 30 min of habituation. Mechanical paw withdrawal threshold was examined using an electronic von Frey anesthesiometer. Cisplatin groups treated with three injections of 3 million cells/kg by intravenous route and three injections of 3 million cells/kg by intra-arterial route after each cisplatin cycle treatment presented, a significant increase of hearing acuity characterized by a decrease of ABR threshold and a decrease of neuropathic pain characterized by an increase of von Frey paw withdrawal threshold compared to controls only receiving cisplatin. This study shows that treatment with MSCselected for neural specificity presents significant positive efficacy on the chemotherapy-induced neuropathic pain and the chemotherapy-induced hearing loss.

Keywords : mesenchymal stem cell, peripheral neuropathy, amniotic fluid, regenerative medicine
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