Human adipose-derived stromal cells and their conditioned medium induce a long lasting relief of painful symptoms in STZ-induced diabetic neuropathy

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Painful diabetic neuropathy is a neurological disorder that is a common complication of diabetes mellitus and one of main factors that adversely affect the patients' quality of life (Sun et al., 2012). Up to now there are no valid treatments for this condition; it is therefore necessary to explore new approaches. A new possibility might be the use of stem cells. In this study we evaluated the effect of mesenchymal stromal cells isolated from human adipose tissue (hASC) and of their conditioned medium (CM-hASC) on the neuropathic symptomatology, in a preclinical experimental mouse model of diabetic neuropathy induced by Streptozotocin (STZ, 80 mg/Kg for 3 days, intraperitoneal injection) (Noh et al., 2013). The development of mechanical allodynia after STZ was monitored by using a Dynamic Plantar Aesthesiometer (ranging up to 10 grams in 10 seconds). When allodynia was well established (14 days after STZ), mice were therapeutically treated by intravenous injection with either $1*10^6$ hASC or CM-hASC obtained from $2x10^6$ serum-free cultured cells. As control we evaluated the effect on neuropathic pain of the CM obtained from an human fibroblasts cell line (CM-hF). The effect of hASC and CM on allodynia was monitored over time and 7 days after the therapeutic treatment (21 days from STZ), six animals of each group were sacrificed for the biochemical evaluations. The effect of hASC was compared to CM: both hASC and CM-hASC were able to significantly reduce allodynia, although the efficacy of hASC was always higher than that of CM-hASC; on the contrary CM-hF was unable to evoke any antiallodynic effect in diabetic neuropathic mice. The anti-allodynic effect of hASC and their CM was very rapid since a slight but significant pain relief was already present 3 hours after treatment. Moreover the effect on pain was long lasting, in fact it was still evident 60 days after hASC and 30 days after CM-hASC administration and was very efficacious, reporting mechanical thresholds of hASC treated mice almost to the control values. When the pain relief started to vanish, the effect could always be restored by subsequent treatment; hASC and CM-hASC were effective also when treatment was performed at an advanced stage of the disease (6 week after STZ). Moreover our data suggest that both hASC and their CM were able to contrast the loss of body weight registered in STZ treated mice. In order to understand the mechanisms at the basis of the observed effects on pain, we started to study the involvement of neuroinflammation evaluating, in particular, the levels of the cytokines IL-1 and IL-10 in the main stations involved in pain transmission, such as: sciatic nerve, dorsal root ganglia and spinal cord. In all the nervous tissues obtained from neuropathic mice we observed a proinflammatory profile, characterized by high IL-1 and low IL-10 levels. Both hASC and CM treatments were able to restore a correct pro/antinflammatory cytokine balance. The data obtained in this study suggest that hASC treatment may be a favorable approach for neuropathic pain treatment and indicate that cells may eventually be substituted with their CM moving toward a cell-free therapy.

Noh et al. (2013) *Int J Biochem Cell Biol.* 45(8): 1538-1545.
Sun et al. (2012) *PLoS ONE* 7(6): e39647.