THERAPEUTIC EFFECT OF SYSTEMIC INJECTION OF HUMAN ADIPOSE STEM CELLS OR THEIR SECRETOME IN AN MOUSE MODEL OF DIABETIC NEUROPATHY

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Painful diabetic neuropathy is a common neurological complication of diabetes mellitus and one of the main factors that adversely affect patients' quality of life. Up to now the pharmacological treatments are not fully satisfactory, therefore it is necessary to explore new approaches. A new possibility might be the use of mesenchymal stem cells considering that they possess immunomodulatory properties, low immunogenicity and regenerative potential. Interestingly, it has been suggested that the effect of stem cells depends on secretion of a broad range of biologically active factors. In this study, we evaluated the effects of Mesenchymal Stem Cells isolated from human adipose tissue (hASC) and of their conditioned medium/secretome (CM-hASC) on the neuropathic symptomatology, in a mouse model of diabetic neuropathy induced by Streptozotocin (STZ, 80 mg/Kg i.p. once a day for three consecutive days). The development of mechanical and thermal allodynia after STZ was monitored by using respectively Von Frey test and Acetone test (50µL of acetone, cold-allodynia). When neuropathic pain was established (2 weeks after STZ), mice were treated by i.v. injection with either 106 hASC or CM-hASC obtained from 2x106 serum-free cultured cells. As control, we evaluated the effect on neuropathic pain of the CM obtained from 2x106 human fibroblasts (CM-hF). Another group of diabetic mice was treated at a more advanced stage of the disease, 6 weeks after STZ. Tissue levels of pro-inflammatory IL-1 and anti-inflammatory IL-10 cytokines were measured in the main stations of pain transmission (sciatic nerve, dorsal root ganglia and spinal cord) and we also evaluated loss of nerve fibers and skin thickness. Splenocyte release of T-helper 1 (Th-1) and Th-2 cytokines in colture media, was also evaluated. Alu sequences detection was employed for hASC localization. Furthermore, we assessed whether therapeutic treatments were able to improve other complications such as nephropathy. Both hASC and their secretome were able to reverse painful symptoms, although cell efficacy was higher than that of CM. Both effects were very rapid, since a significant relief was present already 3 hours after treatments, and long lasting, in fact they were maintained 14 weeks after hASC or CM administration; on the contrary CM-hF was unable to evoke any mechanical-antiallodynic effect in diabetic neuropathic mice. Moreover, both treatments were also effective when performed at an advanced stage of the disease. In all tissues obtained from neuropathic mice, we observed a pro-inflammatory profile, characterized by high IL-1 and low IL-10 levels. hASC and CM treatments were able to restore a correct pro-/anti-inflammatory cytokine balance both 1 week and 12 weeks after treatments and to restore skin innervation. In this model of diabetes, a Th1 polarization is present in the periphery and both treatments re-established the correct Th1/Th2 balance. We also observed an improvement of kidney damage. The data obtained suggest that hASC treatment may be a favorable approach for diabetic complications such as neuropathic pain, indicate that cells effect is likely to be mediated by their secreted products and suggest that cells may eventually be substituted with their CM.