Studying the mechanism of rat adipose derived stem cells in counteracting oxaliplatin-induced neuropathy: similarities with bevacizumab

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Oxaliplatin therapy of colorectal cancer induces a dose-dependent neuropathic syndrome in 50% of patients. Pharmacological treatments may offer limited relief; scientific efforts are being solicited to define a new therapeutic approach. Interestingly, adult mesenchymal stem cells (MSCs) offer a totipotent cellular source for replacing injured neural cells and at the same time represent a source of neuroprotective and anti-inflammatory mediators, opposing the effect of nerve damage. In our hands, adipose-derived stem cells (ASCs) injection (2x106 ASCs/rat i.v.) were able to counteract mechanical hyperalgesia induced by repeated oxaliplatin administration in rats (2.4 mg kg-1 i.p. for a total of 10 administrations). This effect reached a maximum 6h after ASCs administration and lasted up to 72h. Subsequent ASCs administrations induced a similar reduction of hypersensitivity, with a similar efficacy trend over time. The purpose of this study was to investigate a possible mechanism of action by which ASCs exert their effect. When neuropathy was established, 2x106 ASCs labeled with 1 μM of the fluorescent probe 5-(and-6-9-(((4-chloromethyl)benzoyl)amino) tetramethylrhodamine were injected in order to evaluate the localization of ASCs in the rat body. Labelled ASCs were detectable in the bloodstream 1 and 3 h after injection, the percentage gradually decreased and 24 h after ASCs administration no cells were found. At this time, ASCs were detected in the liver digested homogenate. No ASCs were found in the central nervous system and in the lungs. VEGF, EGF and TGF-β were assayed in plasma. EGF and TGF-β were not altered by oxaliplatin or ASCs treatments. On the contrary, VEGF concentration significantly increased in oxaliplatin-treated rats in comparison to the control group whereas ASCs were able to counteract this alteration, suggesting both a possible implication of VEGF in the development of neuropathic pain and a key role in ASCs pain relieving mechanism. This hypothesis was strenghtened by the reduction of oxaliplatin-induced hyperalgesia after an acute i.p. administration of the VEGF-antibody bevacizumab (dose-dependently, 1-15 mg kg-1). Moreover, plantar injection of the pain-related isoform VEGF165b (10-100 ng) in naïve rats, significantly decreased the pain threshold up to 3 h after administration in a bevacizumab-reverted manner (15 mg kg-1). These data led us to further investigate the mechanism by which ASCs could decrease VEGF-A. Phisiologically, VEGF-A signaling can be braked by a soluble splice variant of the VEGF receptor type 1 (sFlt1) able to bind and block VEGF-A signaling. Its local administration reverts VEGF-A-induced hyperalgesia and decreases tumor-induced hyperalgesia. In our model of oxaliplatin-induced neuropathy the recombinant sFlt1 intrathecally injected (25 and 75 ng/rat) reduced hyperalgesia with similar efficacy to bevacizumab but with higher potency. The modulation of VEGF-A becomes a key mechanism in the ASC-mediated pain relief.