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Title: Human dental stem cells of the apical papilla associated to BDNF-loaded pharmacologically active microcarriers (PAMs) enhance locomotor function after spinal cord injury.

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Abstract: There is no treatment for spinal cord injury (SCI) that fully repairs the damages. One strategy is to inject mesenchymal stem cells around the lesion to benefit from their immunomodulatory properties and neuroprotective effect. Our hypothesis was that the combination of dental stem cells from the apical papilla (SCAP) with pharmacologically active microcarriers (PAMs) releasing brain-derived neurotrophic factor (BDNF) would improve rat locomotor function by immunomodulation and neuroprotection. BDNF-PAMs were prepared by solid/oil/water emulsion of poly(L-lactide-co-glycolide) and nanoprecipitated BDNF and subsequent coating with fibronectin. SCAP were then seeded on BDNF-PAMs. SCAP expression of neuronal and immunomodulatory factors was evaluated in vitro. SCAP BDNF-PAMs were injected in a rat spinal cord contusion model and their locomotor function was evaluated by Basso, Beattie, and Bresnahan (BBB) scoring. Impact on inflammation and neuroprotection/axonal growth was evaluated by immunofluorescence. Culture on PAMs induced the overexpression of immunomodulatory molecules and neural/neuronal markers. Injection of SCAP BDNF-PAMs at the lesion site improved rat BBB scoring, reduced the expression of inducible nitric oxide synthase and increased the expression of bIII Tubulin, GAP43, and 5-HT. These results confirm the suitability and versatility of PAMs as combined drug and cell delivery system for regenerative medicine applications but also that BDNF-PAMs potentialize the very promising therapeutic potential of SCAP in the scope of SCI.