Influence of IN-1 antibody and acidic FGF-fibrin glue on the response of injured corticospinal tract axons to human Schwann cell grafts.

Authors: Guest J.D., Hesse D., Schnell L., Schwab M.E., Bunge M.B., Bunge R.P.

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Abstract:

Two strategies have been shown by others to improve CST regeneration following thoracic spinal cord injury: 1) the administration of a monoclonal antibody, IN-1, raised against a myelin-associated, neurite growth inhibitory protein, and 2) the delivery of acidic fibroblast growth factor (aFGF) in fibrin glue in association with peripheral nerve grafts. Because autologous transplantation of human Schwann cells (SCs) is a potential strategy for CNS repair, we evaluated the ability of these two molecular agents to induce CST regeneration into human SC grafts placed to span a midthoracic spinal cord transection in the adult nude rat, a xenograft tolerant strain. IN-1 or control (HRP) antibodies were delivered to the injury/graft region by encapsulated hybridoma cells ('IN-1 ravioli') or daily infusion of hybridoma culture supernatant; aFGF-fibrin glue was placed in the same region in other animals. Anterograde tracing from the motor cortex using the dextran amine tracers, Fluororuby (FR) and biotinylated dextran amine (BDA), was performed. Thirty-five days after grafting, the CST response was evaluated qualitatively by looking for regenerated CST fibers in or beyond grafts and quantitatively by constructing camera lucida composites to determine the sprouting index (SI), the position of the maximum termination density (MTD) rostral to the GFAP-defined host/graft interface, and the longitudinal spread (LS) of bulbous end terminals. The latter two measures provided information about axonal die-back. In control animals (graft only), the CST did not enter the SC graft and underwent axonal die-back [SI = 1.4 +/- 0.1, MTD = 2.0 +/- 0.2, LS = 1.3 +/- 0.3, (n = 3)]. Results of IN-1 delivery from ravioli did not differ from controls, but injections of IN-1-containing supernatant resulted in a significant degree of sprouting but did not

prevent axonal die-back [SI = 1.9 +/- 0.1, MTD = 1.5 0.2, LS = 1.1 +/- 0.1, (n = 7)] and traced fibers did not enter grafts. Acidic FGF dramatically reduced axonal die-back and caused sprouting [SI = 2.0 +/- 0.1 (n = 5), MTD = 0.5 +/- 0.04 (n = 6), LS = 0.4 +/- 0.1 (n = 6)]. Some traced fibers entered SC grafts and in 2/6 cases entered the distal interface. We conclude that 1) human SC grafts alone do not support the regeneration of injured CST fibers and do not prevent die-back, 2) grafts plus IN-1 antibody-containing supernatant support some sprouting but die-back continues, and 3) grafts plus aFGF-fibrin glue support regeneration of some fibers into the grafts and reduce die-back.