

Adjunctive Immunomodulation Improves Efficacy of Autologous Minced Muscle Graft in a Porcine Model of Volumetric Muscle Loss

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Purpose: Volumetric muscle loss (VML) resulting from extremity trauma presents chronic and persistent functional deficits, restricted joint range of motion, and fibrosis, which cause disability. Current translational efforts attempt to promote regeneration of the muscle ablated by the original trauma, with 2 potential therapies currently feasible for human application, acellular biological scaffolds and autologous minced muscle grafts (~1 mm³ pieces of muscle tissue). We investigated the use of autologous minced muscle grafts, which is currently limited by the burden of autologous muscle tissue from a donor site. Our objective was to explore adjunct pharmacological immunomodulation to enhance graft performance and thereby reduce the donor tissue required. We hypothesized that repair of VML injuries by replacing ~50% of the defect mass with autologous minced muscle graft would improve neuromuscular function and that systemic immunomodulation using tacrolimus, a US Food and Drug Administration (FDA)-approved immunosuppressant, would enhance recovery of muscle strength.

Methods: Female Yorkshire Cross pigs (n = 7) were randomized to sham or a ~20% VML injury to the peroneus tertius muscle, and injuries were left nonrepaired, or surgically repaired with an autologous minced muscle graft derived from the adjacent injury; immediately following surgery animals were randomized to 1 month of immunomodulation using tacrolimus (Prograft, Astellas Pharam Inc; 0.075 mg/kg daily). Analysis of muscle function via peroneal nerve stimulation was conducted biweekly over 12 weeks.

Results: In vivo isometric torque was not different before surgery among surgical groups and the sham strength response through 12 weeks was stable (P = 0.121). From 2 to 12 weeks postinjury the nonrepaired VML group presented a ~28% strength deficit and delivery of tacrolimus in the nonrepaired did not ameliorate the strength deficit (~24%). However, graft repair with systemic tacrolimus tended to reduce the functional deficit approximately one-third to ~19% (P = 0.056).

Conclusion: Delivery of adjunctive tacrolimus with an autologous minced grafts at a ~50% replacement by mass of the original volumetric defect can promote modest recovery of isometric strength. Notably, delivery of ~50% minced grafts to the VML defect without adjunctive immunomodulation did not promote recovery of strength, which is contrary to prior reports in which a ~100% replacement promoted functional recovery. Further basic exploration of the interaction of immunomodulation and myogenesis is needed.