Insulin-like growth factor-I gene transfer by electroporation enhances skeletal muscle regeneration and function after injury

J.D. Schertzer and G.S. Lynch, Basic and Clinical Myology Laboratory, Department of Physiology, The University of Melbourne, Victoria 3010, Australia.

Although skeletal muscle has the ability to regenerate after injury, functional repair can be slow, inefficient, and is often incomplete. In addition to the tightly controlled induction of myogenic regulatory factors and other muscle specific genes, muscle damage and subsequent repair processes induce the release of various biologically active molecules which are critical for regeneration. Insulin-like growth factor-I (IGF-I) is particularly relevant given that levels are elevated after injury during the formation of new fibres or the growth of existing fibres. Given that several studies have demonstrated that IGF-I enhances various aspects of skeletal muscle regeneration, a basis exists for the administration of IGF-I to enhance muscle regeneration and to promote functional recovery after injury (Rabinovsky *et al.*, 2003; Takahashi *et al.*, 2003). However, a comparison of various delivery methods on the efficacy of IGF-I during skeletal muscle regeneration has not been performed.

The purpose of this study was to compare the time course of muscle regeneration following delivery of IGF-I to injured muscles *via* non-viral gene transfer or systemic protein administration. We assessed the time course of functional recovery during muscle regeneration following systemic administration of IGF-I protein *via* mini-osmotic pump (1 mg/kg/day) or electroporation-assisted plasmid-based gene transfer.

Twelve to fourteen-week-old male C57/BL10 mice were anaesthetised deeply (pentobarbitone sodium, 60 mg/kg) and tibialis anterior (TA) muscles were injured by an intramuscular injection of the myotoxic agent, notexin, which causes complete destruction of injected muscle fibres but does not damage muscle precursor cells that are activated for subsequent regeneration. Contractile properties of the TA muscle were measured *in situ* (with an intact nerve and blood supply) at 7, 14, 21 and 28 days post injury and the mice were killed by cardiac excision whilst anaesthetised. At 14 days post injury, tetanic force was 36% greater following electroporation-assisted IGF-I gene transfer compared to control ($P < 0.05$), whereas systemic IGF-I protein administration had no effect on tetanic force at this time. At 21 days post injury, tetanic force was 31% greater following electroporation-assisted IGF-I gene transfer and 35% greater following IGF-I protein delivery compared to controls ($P < 0.05$).

Our results show that IGF-I enhanced muscle regeneration and functional restoration after injury, regardless of the route of administration. However, electroporation-assisted plasmid delivery promoted functional recovery earlier than systemic IGF-I protein administration. The findings highlight the potential of IGF-I to minimise functional disability after injury and demonstrate that non-viral plasmid based gene transfer can be superior to continuous systemic protein administration.

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