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INTRODUCTION: Several experimental studies suggest that growth hormone-based therapies have the potential to accelerate and augment axonal regeneration while simultaneously act directly on muscle and Schwann cells (SCs) to minimize denervation atrophy prior to re-innervation. The purpose of this study was to assess the impact of growth hormone (GH) therapy on preventing the deleterious effects of chronic denervation (CD) injury on nerve regeneration and resulting muscle function. We hypothesized that systemic GH therapy can maintain chronically-denervated muscle and SCs, accelerate axonal regeneration, and improve murine extremity function in the setting of chronic denervation (CD) by preserving muscle mass and promoting motor reinnervation.

METHODS: We utilized a newly-developed, rat forelimb CD model to assess the effects of GH therapy on: a) improving nerve regeneration; and b) preventing muscle atrophy and augmenting muscle re-innervation and function. Four groups of rats were examined: (1) Group-1 (n = 8) underwent 8 weeks of median nerve CD injury followed by repair; (2) Group-2 (experimental, n = 8) underwent 8 weeks of median nerve CD followed by repair and treatment with highly purified lyophilized pituitary porcine GH (0.6 mg/day); (3) Group-3 animals (n = 8) underwent no median nerve CD injury; (4) Group-4 animals (n = 8) were naïve controls. All animals underwent weekly muscle functional testing followed by median nerve and flexor muscle harvest for nerve histomorphometry, muscle weight, atrophy, and re-innervation analysis. To enable the assessment of the effects of GH therapy on maintaining denervated muscle and SCs: Group-1 animals also underwent 8 weeks of contralateral sciatic nerve CD; Group-2 animals underwent 8 weeks of sciatic nerve CD (w/ GH treatment as stated above); Group-3 animals underwent 1 week of sciatic nerve CD; and Group-4 animals underwent no sciatic nerve CD. The sciatic nerve and lateral gastrocnemius muscle were harvested after completion of sciatic nerve CD injury time point to assess for SC proliferation/senescence markers (via qPCR) and muscle atrophy (via muscle weight and cross-sectional area muscle staining).

RESULTS: Median nerve regeneration was higher in GH-treated animals when compared to untreated controls as measured by axon density (p < 0.005), axon diameter (p < 0.0001), and myelin thickness (p < 0.0001). Furthermore, GH improved muscle re-innervation (27.9% vs 38.0% NMJs re-innervated; p < 0.02) and prevented muscle atrophy (865 ± 48.3 vs 1081 ± 101.4 μM 2; p < 0.02). GH-treated rats demonstrated greater functional muscle recovery as compared to untreated controls (hand grip: 1.8 ± 0.3 N vs. 1.0 ± 0.1 N, p=0.001). Lastly, Group 2 animals demonstrated higher expression of SC proliferation and migration markers, c-Jun & erbB-3, and less muscle atrophy (0.21 ± 0.02 g vs. 0.17 ± 0.01 g; P=0.55) when compared to Group 1 at 8 weeks after sciatic nerve CD.

CONCLUSION: Systemic GH therapy can improve nerve regeneration and maintain chronically-denervated muscle by promoting re-innervation and subsequent muscle function.

Inhibition of mTOR Signaling Reduces Mesenchymal Cell Migration To Sites Of Injury And Eliminates Heterotopic Ossification In A Mouse Model

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PURPOSE: Patients with fibrodysplasia ossificans progressiva (FOP) carry a genetic mutation in the type I bone morphogenetic protein (BMP) receptor ACVR1 leading to hyperactivity. This mutation leads to pathologic cartilage and bone formation at extra-skeletal sites of even mild soft tissue injury which cause severe pain, restrict function and motion, and ultimately lead to early death. Until now, strategies to treat patients with FOP have focused on candidate small molecule agents with...
unproven safety profiles or translational potential. Here we show that an FDA-approved drug with a previously proven record of safety is able to completely inhibit ectopic lesions in a mouse model of FOP carrying the same mutation.

METHODS: Mice carrying the floxed FOP mutation (ACVR1 R206H) received a simultaneous hindlimb injection of Ad.cre to induce gene transformation and cardiotoxin to induce local injury (Ad.cre/CTX). Mice were treated with either daily vehicle control or rapamycin (5 mg/kg) administered i.p. (n=10/group). The presence of mesenchymal cells at the injury site was determined using immunofluorescent staining for PDGFRα and Sca-1 five days after injury. Ectopic cartilage and bone were determined using histology and microCT imaging 21 days after injury. PLGA microparticles were synthesized to deliver rapamycin as a slow-release; flow cytometry was used to quantify release time profile. Finally, a separate set of mice underwent Ad.cre/CTX injection with resection of formed HO 3 weeks after injury and subsequent treatment with or without rapamycin to eliminate recurrence.

RESULTS: While mice which received Ad.cre/CTX without rapamycin produced ectopic bone consistently, treatment with rapamycin nearly eliminated HO based on both microCT imaging (34.0 mm³ v. 1.0 mm³, p<0.01). Furthermore, histologic imaging showed elimination of ectopic cartilage with rapamycin treatment based on H&E, pentachrome staining (red arrows) and SOX9 immunofluorescence. Finally, rapamycin reduced the presence of mesenchymal cells (PDGFβRα or aSMA+) at the injury site. PLGA microparticles released rapamycin during the first week after injury based on flow cytometry analysis. Mice that had resection of HO and were treated with rapamycin did not recur, while 100% of mice which had resection of HO without rapamycin developed new lesions at the resection site.

CONCLUSION: These findings demonstrate that rapamycin, an FDA-approved drug, eliminates ectopic cartilage and bone in a mouse model of FOP. This may occur through a reduction in the presence of activated mesenchymal cells at the injury site. These findings have prompted the initiation of clinical studies to assess efficacy of this potential therapeutic in humans. A slow-release microparticle may obviate repeated treatments in these patients. Rapamycin may also have a role in the management of FOP patients with ossified lesions, making surgical resection a reality for the first time.

17

Reduction Mammoplasty Improves Quality-of-Life in Adolescents with Macromastia: A Longitudinal Cohort Study

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PURPOSE: Macromastia, the benign overgrowth of one or both breasts, is a common condition with a well-documented negative impact on mental and physical health, self-esteem, and social functioning. Reduction mammoplasty during adolescence is relatively controversial; the psychological effects of treatment in this age group are largely unknown. This study seeks to measure changes in health-related quality-of-life (HRQOL) and breast-related symptoms following reduction mammoplasty in adolescents, and explore the effects of age and BMI category at time of surgery on postoperative quality-of-life outcomes.

METHODS: In this longitudinal cohort study, our group administered the Short-Form 36v2 (SF-36), Rosenberg Self-Esteem Scale (RSES), Breast-Related Symptoms Questionnaire (BRSQ), and Eating-Attitudes Test-26 (EAT-26) to 102 adolescents with macromastia and 84 unaffected female controls, aged 12 to 21 years. Patients with macromastia completed surveys preoperatively and postoperatively (at 6 months, 1 year, 3 years, and 5 years). Control subjects completed baseline and follow-up surveys at the same intervals. Higher scores in the SF-36, RSES, and BRSQ are associated with a better HRQOL, global self-esteem, and fewer/less severe breast-related symptoms, respectively. Higher scores in the EAT-26 are indicative of disordered eating thoughts and behaviors.