Topical Alpha-Gal Nanoparticles Enhances Wound Healing in Radiated Tissue

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BACKGROUND: Radiation is a common primary, adjuvant, and neoadjuvant therapy in oncologic patients. It is well known that surgery on radiated tissues is associated with significantly higher complication rates due to permanently compromised wound healing. It is thought that one cause of impaired wound healing is the aberrant inflammatory response that occurs in radiated tissues. Previous work has demonstrated that the topical application of naturally occurring antigen α-gal (Galα1-3Galβ1-[3]GlcNAc-R) nanoparticles (AGNs) onto wound surface accelerates macrophage recruitment. As we have already observed accelerated wound healing in both normal and diabetic wounds treated with topical AGN, we hypothesized that application of this natural antigen would similarly enhance healing of the wounds in irradiated tissue.

METHODS: To simulate human physiology, α-1,3galactosyltransferase knockout mice (KO), which do not produce the antigen and therefore can be stimulated to produce antibodies against it, were used. KO were exposed to the antigen to produce anti α-gal antibodies at titers comparable to those seen in humans. Ten days before wounding, dorsal skin was isolated using a low-pressure clamp as previously described and was irradiated with one session of 40 Gy. Bilateral 6-mm dorsal splinted full-thickness wounds were created and treated with AGN in a 2% carboxymethyl cellulose carrier, immediately after wounding and again on postoperative day 1. Control knocked out group underwent similar irradiation and wounding protocols but were treated with phosphate buffered saline (PBS) in 2% carboxymethyl cellulose. Wild-type mice, which are indolent to the antigen, went through the same radiation and wounding to eliminate confounding factors other than immunogenic response to AGN. Wounds were harvested from all animals up to 21 days after the wounding for histologic and immunohistochemistry measures. The extent of keratinocyte migration, neovascularization, and macrophage recruitment was assessed.

RESULTS: Full closure of all wounds by day 9 in the non-radiated control compared to no completely closed wounds in the radiated group confirmed the known inhibitory effects of irradiation on wound healing. In addition, histologic changes such as increased epidermal thickness in the skin surrounding the wound further confirmed the effects of irradiation on the skin. Histologic analysis demonstrated enhanced keratinocyte migration in the AGN-treated KO wounds, which was significantly improved in comparison to PBS-treated KO wounds noted by day 15 and until the end of the study (P < 0.01). On day 21, ≈63% of all α-gal–treated wounds were completely healed as opposed to only ≈17% in the PBS-treated group. In wild-type mice, treatment with AGN showed no improvement in keratinocyte migration or time to full closure.

CONCLUSIONS: Topical application of AGN onto radiated wounds significantly ameliorate the delayed wound healing in radiated tissue resulting in faster wound closure. We believe that this naturally occurring agent has great promise for clinical translation as it has demonstrated efficacy in not only normal wounds but pathologic (diabetic, radiated) ones as well.

Adipose-derived Stem Cell Sheets Prepared Using Temperature-responsive Dishes Promote Axonal Outgrowth in Cross-face Nerve Grafts

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BACKGROUND: Cross-face nerve grafting (CFNG) using an autologous nerve graft to connect the contralateral functioning facial nerve to the facial nerve on the paralyzed side is an established reconstruction procedure for facial palsy. However, it takes 6 months or longer to reinnervate the paralyzed side of the face after this procedure, and atrophy of the muscles of expression occurs if the denervation time is prolonged as a result of slow axonal outgrowth. Therefore, the outcome of CFNG remains uncertain. Adipose-derived stem cells (ASCs) are reported to have pluripotency and a paracrine effect that promotes axonal regeneration in peripheral nerves. We devised a novel CFNG procedure using an autologous nerve graft wrapped in an ASC sheet that was formed on a temperature-responsive dish and examined its therapeutic effect in a rat model of facial palsy.

METHODS: The rat model of facial paralysis was prepared by ligating and transecting the main trunk of the left facial nerve under inhalation anesthesia in 8-week-old Lewis rats. The ASC suspensions and sheets were prepared from rat subcutaneous adipose tissue using conventional culture dishes and temperature-responsive dishes, respectively. The sciatic nerve was collected and used as a CFNG connecting
the marginal mandibular branch of the left facial nerve and the marginal mandibular branch of the right facial nerve. A CFNG was transplanted in 8 rats (designated the control group), a CFNG coated with an ASC suspension (1.5 × 10^6 cells/1,000 ml) in 8 rats (a suspension group), and a CFNG wrapped in an ASC sheet (1.5 × 10^6 cells/3.5-cm diameter dish) in 8 rats (a sheet group). Nerve regeneration was then compared histologically and physiologically between the groups.

RESULTS: The time to reinnervation, assessed by observing the rate of contraction of the vibrissae muscles using a facial palsy scoring system, was significantly shorter in the sheet group than in the other 2 groups. Evoked compound electromyography showed significantly higher amplitude in the sheet group (4.2 ± 1.3 mV) than in the suspension group (1.7 ± 1.2 mV) and the control group (1.6 ± 0.8 mV; P < 0.01). Toluidine blue staining showed that the number of myelinated fibers was significantly higher in the sheet group (2,455 ± 603) than in the suspension group (1,379 ± 345) or control group (590 ± 586; P < 0.01).

CONCLUSIONS: CFNG in combination with ASC sheets prepared using temperature-responsive dishes promoted axonal outgrowth in autologous nerve grafts and reduced the time to reinnervation. ASC sheets may improve the therapeutic effect of CFNG in patients with facial palsy.

Functional Influence of Breast Implant Surface Texture With Micro Topographic Features on Capsular Contracture

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The shell texture of a breast implant is an important factor associated with a risk of capsular contracture often necessitating additional surgery. The objective of this study was to characterize differences of commercial available implants in terms of texture, topography, and wettability and the behavior of capsular contracture. The implants utilized in this study were BellaGel Smooth, BellaGel Textured, Bellagel Micro, or Motiva SilkSurface. The shell texture of these implants was characterized using a scanning electron microscopy, x-ray microtomography, 3- dimensional confocal laser scanning microscope, and contact angle goniometer. In addition, silicone breast implants were explanted beneath the panniculus carnosus muscle on the dorsum of Sprague-Dawley rats and observed for up to 8 weeks postoperative days. The fibrous capsule around silicone implants was explanted for histologic, immuno-histochemical examination, and western blotting. BellGel Micro and Motiva SilkSurface textures resulted in significant decreases in capsule thickness (P < 0.05) and collagen production (P < 0.05) at 8 weeks with respect to the BellaGel Smooth and BellaGel Textured group. Fibrous tissue formation markers (Vimentin, α-SMA, and TGF-β) were significantly reduced in BellaGel Micro and Motiva SilkSurface textures with respect to the BellaGel Smooth and BellaGel Textured group. Significant (P < 0.05) decreases in inducible nitric oxide synthase, an inflammation marker, were observed in the BellaGel Micro and Motiva SilkSurface textures. In summary, surface texture with microporographic features led to decreased fibrotic capsule formation compared with other surfaces. This finding may offer to design an improved silicone breast implant, which could alleviate capsular contracture.

Searching for an Ideal Preclinical Model to Analyze Oncologic Safety of Breast Lipofilling: Preliminary Results

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INTRODUCTION: Preclinical studies aiming to evaluate the microenvironment of breast cancer (BC) are very important for analysis of risk and the behavior of this disease to treatments proposed in humans, such as breast lipofilling. Laboratorial studies used so far for this purpose present serious methodologic problems. They are based on models that use cancer-induced carcinogens that have a residual systemic effect or through the use of nonluminal human BC implanted in immunosuppressed murine hosts. This article, although, presents preliminary results of a big project aiming to develop a preclinical studies capable of assessing risks. The primary objective here was to analyze the effectiveness of cafeteria diet (CD)—a known risk factor for BC in humans—to stimulate the mammary gland and the time required for this to trigger some effect over the murine breast tissue.

METHODS: Eighteen Sprague-Dawley rats with 28 days of life were randomly divided into 4 groups: 2 controls (C1 and C2), where rats were fed with standard diet, and 2 groups that received CD (D1 and D2). CD was introduced at rats’ age of 6 weeks, what is similar to the human age (HA) of 7 years old. The following variables were collected...