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 \(\alpha\)-gal (Gal\(\alpha\)-1,3Gal\(\beta\)-1-[3]4GlcNAc-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, \(\alpha\)-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-\(\alpha\)-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 knockout 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, \(\approx 63\%\) of all \(\alpha\)-gal–treated wounds were completely healed as opposed to only \(\approx 17\%\) 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