with 2 million nucleated bone-derived cells from donor NSG (NOD.CB17-Prkdcsck/J) mice via retro-orbital sinus injection. The success of reconstitution and immunodepletion was assessed by fluorescence-activated cell sorting (FACS) analysis of peripheral blood. After 4 weeks, 30 Gy was delivered to the right hindlimb in five fractionated doses to generate limb contracture. The irradiated, contracted limb was then grafted with 200 μl fresh human liposaprate and limb extension was measured over the subsequent 8 weeks, at which point skin was harvested for assessment of fibroblast subtypes for FACS and immunofluorescence. A group of mice with radiation-induced groin contracture did not undergo fat grafting and served as the control group.

Results: FACS analysis indicated successful immunodepletion and engraftment by 3 weeks post bone marrow transplantation. At one month following groin irradiation, mice had developed significant right hind limb contracture with significantly reduced limb extension (****p≤0.0001). Histologically this was paralleled by thickening of the dermis, and substantial expansion of the fibrogenic Prdx-1-positive fibroblast subpopulation. While human fat graft volume retention was reduced over 8 weeks following implantation, this was associated with significantly improved in limb extension. The skin overlying the grafted fat showed reduced collagen density, as indicated by trichrome staining, as well as a reduction in the fibrogenic Prdx-1-positive fibroblast subpopulation by immunofluorescence imaging, as compared to the control mice.

Conclusion: Here we show that fat grafting improves the extensibility of irradiated and contracted hind limbs and reverses radiation-induced skin fibrosis by both reducing the collagen content and by altering the composition of dermal fibroblast subpopulations. Specifically, fat grafting results in a depletion of the Prdx-1-positive fibroblast subpopulation. Further elucidating how this profibrotic fibroblast subpopulation is involved in ventral surface soft tissue fibrosis will facilitate development of novel strategies to treat/prevent debilitating late side-effect of radiotherapy.

Morphological Changes Of Skin Related To Acellular Dermal Matrix Incorporation In Tissue Expansion

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Purpose: Acellular dermal matrix (ADM) is used to create an inferolateral sling nearly three-quarters of the time in breast reconstruction and has proven a valuable alternative to total submuscular coverage of the implant. Previous work has demonstrated decreased inflammation and fibrosis of the pocket lining the ADM sling; however there has been minimal investigation into the role of ADM in skin growth and regeneration. The present study evaluates morphologic and molecular changes mediated by use of ADM in tissue expansion.

Methods: Two tissue expanders, one wrapped in ADM, were placed subcutaneously on the back of Yucatan mini-pigs. All expanders were inflated with two weekly fills of 60cc of normal saline and skin biopsies were harvested after two weeks of expansion from each condition: control, tissue expansion (TE), and tissue expansion with ADM (TE+ADM). Three biopsies per condition were embedded in paraffin or OCT medium and stained with Russell Movat Pentachrome and Immunofluorescence of CD31, respectively. Collagen in the papillary dermis of pentachrome-stained images were analyzed using an ImageJ plug-in, Fibril Tool, that applies circular statistics to estimate average fibril orientation as the direction angle from -90 to 90 with respect to the x-axis. One-way ANOVA evaluated seventy-two measurements per condition and post-hoc analysis with Tukey’s HSD test identified significant comparisons between the groups. Number of fluorescent cells expressing CD31 (a marker of endothelial cells) were counted on 12 photographs per condition. P-values ≤ .05 were considered significant. Total deformation was calculated using a computational model and isogeometric analysis.

Results: The mean fibril orientation of TE and TE+ADM underwent -85% change (P < .001) and -15% change (P = .65), respectively, compared to control. Three times more CD31+ cells were observed in TE+ADM compared to control (P < .001), but no significant changes were detected in TE alone. Histogram of total deformation revealed more even distribution of forces in TE+ADM compared to TE and control.

Conclusions: The use of ADM in a porcine tissue expansion model appears to mitigate disarray of the collagen network in adjacent tissue, thereby creating a more extensive, yet even, distribution of stretched skin. This observation, combined with the finding of increased angiogenesis, suggests it is the incorporation of ADM that confers these protective benefits. Future studies will evaluate whether the protective

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effects of ADM can serve to improve TE in compromised tissue beds, as seen in patients undergoing TE concurrent with perioperative radiation therapy.

FRIDAY, JUNE 11, 2021: BREAST/AESTHETIC/GENDER AFFIRMATION TOP SCORED ABSTRACTS

1

Iqgap1 Signaling Promotes Foreign Body Response To Biomedical Implants

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Purpose: The longevity of biomedical implants is limited by adverse implant-tissue interactions leading to implant failure. In almost all cases, implant failure occurs due to a phenomenon known as the foreign body response (FBR). FBR is characterized by fibrous capsule formation around implanted devices, leading to implant malfunction as well as distortion of the surrounding tissue. In the context of breast implants, FBR leads to capsular contracture, which is the cause of a significant proportion of all breast implant failures. Despite the high prevalence of FBR-mediated implant failure, the underlying mechanisms of FBR are incompletely understood. Our work utilizing mass spectrometry has demonstrated that when compared to healthy subcutaneous tissue, foreign body capsules in mice and humans display an up-regulation of IQ Motif Containing GTPase Activating Protein 1 (IQGAP1), a scaffolding protein involved in multiple mechanotransduction pathways. Based on these findings, we sought to investigate which cellular subpopulations express IQGAP1 as well as its role in mechanotransduction pathways mediating the development of FBR.

Methods: To verify the importance of IQGAP1-mediated signaling in FBR, we employed a murine model of mechanically stimulated silicone implants (MSI), which were implanted subcutaneously in wildtype (WT) and IQGAP1+-/- haplo-insufficient mice to compare the effect of human levels of mechanical stress on FBR. Homozygous IQGAP1 KO mice have been previously reported to harbor a fragile phenotype, more prone to pulmonary vascular damage and gastric pathologies. Haplo-insufficient mice were utilized in these experiments in order to prevent potential systemic complications from elevated levels of mechanical stimulation produced by the MSI model. We explanted the foreign body capsules from IQGAP1+-/- haplo-insufficient and WT mice and performed single-cell RNA sequencing (sc-RNA-seq) on cells isolated from the capsules. We histologically assessed the quantity as well as maturity of collagen deposition using Masson’s Trichrome and Herovici staining of tissue sections from explanted foreign body capsules. Moreover, immunostaining for the mechanotransduction related proteins alpha-smooth muscle actin (α-SMA), phosphorylated focal adhesion kinase (p-FAK), phosphorylated cell division control protein 42 (p-cdc42), and phosphorylated extracellular signal-regulated kinase (p-ERK1/2) was performed to assess the impact of IQGAP1-deficiency on the protein level.

Results: We found that IQGAP1-deficient mice displayed a significantly reduced FBR as evidenced by thinner capsules, lower levels of collagen deposition, collagen maturity, and myofibroblast activation. Our scRNA-seq analysis revealed a depletion of mechanoresponsive myeloid cells in IQGAP1-deficient mice. This was confirmed on the protein level by a significantly reduced expression of α-SMA, p-FAK, p-cdc42, and p-ERK1/2 in foreign body capsule tissue from IQGAP1-deficient mice compared to WT mice.

Conclusion: Our results highlight the important role of IQGAP1 as a critical early stage mediator of mechanotransduction pathways contributing to the development of FBR. Further, we show that IQGAP1 plays a role in modulating the innate immune response to synthetic implants. Therefore, IQGAP1 may be a promising target for the development of novel therapeutics to limit the development of FBR around biomedical implants.

2

Tranexamic Acid Is Associated With Decreased Intraoperative Blood Loss And Wound Healing Complication Rate In Penile Inversion Vaginoplasty

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