malfonction as well as distortion of the surrounding tissues. Currently, there are no FDA-approved therapies that effectively prevent debilitating fibrotic capsule formation and the resulting functional complications around biomedical devices.

METHODS: We compared human breast implant tissue and a novel murine model of FBR (mechanically stimulating implant or MSI model) to identify the key signaling pathways associated with pathological FBR. Subsequently, we utilized pathway analyses to identify potential molecular targets that are central to the signaling associated with pathological FBR. Finally, we employed small molecule inhibitors of mechanotransduction signaling in our mouse model as a proof of concept for a pharmacological strategy to target FBR and analyzed its effect on FBR capsule formation using immunostaining and histopathology.

RESULTS: We first identified that Rac2, a hematopoietic-specific Rho-GTPase, was differentially upregulated in Baker IV compared to Baker I breast implant capsule tissue. Additionally, single cell sequencing of murine capsule tissue from our MSI model of FBR revealed significant differences in the activation of Rac2 and associated inflammatory markers relative to standard murine implants. Finally, we demonstrated that pharmacologically blocking Rac2 signaling in our MSI model significantly reduced the degree of FBR capsule formation as measured by decreased capsule thickness, total collagen deposition, percent mature collagen, and myofibroblast activation.

CONCLUSION: Our results highlight the important role of Rac2 as a mediator of pathologic foreign body response in both mice and humans. We demonstrate that pharmacological inhibition of Rac2 may potentially serve as an effective therapy to reduce FBR in patients receiving biomedical implants, thereby increasing patient quality of life and reducing implant failure rates. Further, these findings provide novel insights into the molecular mechanisms underlying fibrotic responses to implanted devices.

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PURPOSE: Developing new therapies to promote wound healing and mitigate scarring has the potential to significantly impact patient morbidity, particularly for those who suffer from chronic non-healing wounds and burns. The primary objectives for any therapy that aims to improve wound healing are to provide protection against external factors and to sustain optimal moisture levels within the wound bed. Biologic scaffolds such as hydrogels provide an ideal, physio-mimetic of native ECM that can improve wound healing outcomes after cutaneous injury. While most studies have focused on the benefits of hydrogels in accelerating wound healing, there is minimal data directly comparing the relative efficacies among different hydrogel material compositions.

METHODS: In this study we utilized a splinted excisional wound model that recapitulates human-like wound healing in mice, and treated wounds with three different collagen hydrogel dressings. The first dressing was composed of 90% collagen and 10% alginate. The second dressing was composed of 55% collagen and 44% cellulose. Finally, the third dressing was composed of 5% collagen and 95% pullulan. We assessed the feasibility of applying each dressing during standard dressing changes and measured wound areas over time to determine the relative rate of wound closure. We then performed histologic and histopathologic analysis on the explanted scar tissues to assess the effects each hydrogel dressing on collagen architecture, fiber alignment, and cellular response.

RESULTS: The days to closure of wounds treated the collagen-pullulan hydrogel (~11.2 days) was significantly shorter than the collagen-cellulose treated (~13.2 days; *p<0.05) and control (~13.8 days; *p<0.01) wounds. Quantitative analysis of collagen architecture demonstrated that collagen-pullulan treated wounds had a lower proportion of mature collagen within the healed scar and significantly more randomly aligned collagen fibers compared to collagen-cellulose treated wounds. Furthermore, we found that collagen-pullulan hydrogel treated wounds...
displayed significantly shorter fiber length and greater tissue porosity compared to the other wound groups. Finally, histopathologic analysis revealed lower levels of immune cell infiltration and overall tissue response in collagen-pullulan hydrogel treated wounds relative to other groups.

CONCLUSION: Our data indicate that the material composition of hydrogel dressings can significantly influence healing time, cellular response, and the resulting architecture of healed scars. Collagen-pullulan hydrogel therapy accelerated wound closure and promoted tissue with less dense, more randomly aligned, and shorter collagen fibers with lower collagen intensity, similar to the natural ‘basket-weave’ architecture of unwounded skin. Further understanding of how specific hydrogel properties affect healing and the resulting tissue architecture of wounds may lead to novel insights and further optimization of the material properties of wound dressings.

TRACK: HAND AND UPPER EXTREMITY
The Novel Use of a Nanofiber Hydrogel Composite for Perineural Adhesion Prevention in a Rodent Model

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INTRODUCTION: Perineural adhesions can form after any surgical intervention involving peripheral nerves. Adhesion formation may then lead to nerve entrapment and compressive neuropathy, which can result in a wide variety of symptoms ranging from sensory deficits to motor weakness. Previously, we created a novel poly(ε-caprolactone) (PCL) nanofiber/ hyaluronic acid hydrogel composite that was shown to mimic the microarchitecture and mechanical properties of soft tissue extracellular matrix.1 We hypothesize that the use of this novel nanofiber hydrogel composite (NHC) will reduce perineural adhesion formation in a rodent hindlimb model.

METHODS: This study was performed with Institutional Animal Care and Use Committee approval. Male Lewis rats underwent bilateral circumferential mechanical irritation of the sciatic nerve to induce adhesion formation with subsequent primary closure. Animals then underwent a secondary neurolysis 8 weeks post-operatively. At the time of neurolysis, the experimental group (n=6) were treated with circumferentially application of NHC around the sciatic nerve before closure and the control group were closed without treatment (n=6). Both groups were sacrificed 8 weeks after their secondary surgery. At the time of euthanasia, all rodents underwent unilateral biomechanical force testing to assess the breaking point of the perineural adhesions surrounding the sciatic nerve (measured in Newtons). In the contralateral limb, the sciatic nerve, surrounding muscle, and NHC in experimental animals was harvested to assess perineural collagen deposition using hematoxylin and eosin (H&E) and Masson’s Trichrome staining.

RESULTS: Significant perineural adhesions were visually apparent after sciatic nerve irritation in the control group. In the experimental group, the sciatic nerve was grossly encapsulated by the NHC which closely resembled subcutaneous fat with visible neovascularization. Biomechanical testing demonstrated the average force required to remove the nerve from the wound bed in the experimental group was 2.02±0.43 N. In the control group, the sciatic nerve could not be removed from the wound bed and the average force prior to failure was 2.77±0.18 N. Collagen deposition, a measure of scar formation around the sciatic nerve, was assessed via H&E and MT staining. Minimal collagen deposition was seen in the experimental group compared to control, indicating a decrease in scar formation in the animals treated with perineural application of the NHC.

CONCLUSION: We found that the use of a novel PCL nanofiber/hyaluronic acid hydrogel composite resulted in a decrease in perineural adhesion and scar formation in a rat model. 1. Li X, Cho B, Martin R, Seu M, Zhang C, Zhou Z, Choi JS, Jiang X, Chen L, Walia G, Yan J, Callanan M, Liu H, Colbert K, Morissette-McAlmon J, Grayson W, Reddy S, Sacks JM, Mao HQ. Nanofiber-hydrogel composite-mediated angiogenesis for soft tissue reconstruction. Sci Transl Med. 2019 May 1;11(490):eaau6210. doi: 10.1126/scitranslmed.aau6210. PMID: 31043572.