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"Testing the role of Calcitonin Gene Related Peptide (CGRP) in scar formation after multiple tissue injury"

In the case of traumatic injury, nerves release specific neurotrophic factors that either promote regeneration or scar tissue formation. However, the difference in the type of neurotrophic factors released in a regenerating system versus a non-regenerating system is not fully understood. While most mammals do not have an ability to regenerate entire limbs, certain rodents do have the ability to regenerate complex tissues. The African Spiny Mouse (*Acomys cahirinus*) can regenerate tissue (cartilage, hair follicles, muscle, adipose tissue, nerves, and supporting dermal tissues) of the ear after a 4 mm biopsy punch. Because of these abilities, this species is the focus of the comparative mammalian model of tissue regeneration versus scar formation in a common lab mouse (*Mus musculus*).

Previous RNA sequencing reveals that several neurotrophic factors are upregulated during scar formation in *Mus* and downregulated or unchanged during regeneration in *Acomys*. One notable gene, the Calcitonin Gene Related Peptide (CGRP), is not expressed in regeneration in *Acomys* but expressed in scar formation in *Mus*. CGRP is a known component of pain transduction and migraine onset, but there is still uncertainty around its role in wound healing and scar formation. This study evaluates the direct role CGRP plays in scar formation.

To first test for response of ear fibroblasts to CGRP, fibroblasts are isolated from the external ear pinna of the mouse. These harvested fibroblasts are exposed to graded concentrations of CGRP for 10 minutes and changes in cyclic AMP levels (the downstream effector of CGRP signaling) are measured. An increase of cAMP levels after ten minutes of exposure is expected if fibroblasts are responsive to CGRP. To determine the pro-fibrotic potential of CGRP, ear fibroblasts are exposed to graded concentrations of CGRP for 24 hours. The expression of collagen and matrix metalloproteinase 9 (MMP9), a collagen degrading enzyme, using Quantitative polymerase chain reaction (qPCR). If pro-fibrotic, there is an expected increase in collagen production along with a decrease in MMP9 expression.

Suppose pro-fibrotic effects of CGRP are observed in vitro. In that case, future research efforts plan to use FDA-approved CGRP inhibitors to test the effects of CGRP inhibition on scar formation both in vitro and in vivo. The findings of these studies will contribute to efforts to target an effective treatment plan for explosion accidents in military personnel. This work is supported by the Office of Assistant Secretary of Defense for Health Affairs through the Orthopedic Research Program under Award No. W81XWH2110503.