IMPRS Award Finalists

The Role of the Integrated Stress Response and the Actin Cytoskeleton during Wound Healing

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Background and Hypothesis: Chronic cutaneous wounds are a serious health concern afflicting millions of people. One of the primary factors preventing the closure of chronic wounds is the inability of keratinocytes to migrate across the wound bed. Epidermal keratinocytes migrate in a cohesive manner known as the keratinocyte collective cell migration (KCCM). Our lab has demonstrated that the integrated stress response (ISR) plays a key role in the KCCM. The ISR is initiated by stress-sensitive kinases, such as GCN2, and results in decreased global protein synthesis while preferentially increasing the translation of mRNAs encoding cytoprotective proteins. Wound repair also relies on the actin cytoskeleton, but the crosstalk between actin and the ISR is not well established. We hypothesize that the interaction between the ISR and the actin cytoskeleton is critical for KCCM during wound healing.

Methods: Cutaneous wound healing was approximated in vitro using the KCCM-dependent scratch assay. Wild-type (WT) and GCN2-deleted (KO) keratinocytes were grown on coverslips, differentiated, scratched, and harvested at different times post-wounding. F-actin and vimentin (VIM) expression was monitored over time using fluorescent phalloidin-488 and immunofluorescence. In addition, WT keratinocytes were treated with actin-depolymerizing drugs and induction of the ISR was measured using immunoblots.

Results: Depolymerization of F-actin was observed along the leading edge of both wounded WT and GCN2-KO keratinocytes immediately following wounding. WT keratinocytes upregulated VIM expression at the leading edge whereas VIM expression remained unchanged in the GCN2-KO keratinocytes. Treatment with latrunculin B and cytochalasin D, which both result in actin depolymerization, induced GCN2 phosphorylation in the differentiated WT keratinocytes.

Conclusion and Potential Impact: F-actin depolymerization elicits a GCN2-mediated induction of the ISR. GCN2 and the ISR are critical components of the cutaneous wound repair process and their crosstalk with the actin cytoskeleton may serve as a novel therapeutic target in the treatment of chronic wounds.

Verbal Fluency, Speech-Language, and Neurocognitive Outcomes in Youth with Cochlear Implants

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Background: Cochlear implants (CIs) restore some hearing to deaf children, although some language domains such as verbal fluency (VF) are at risk for delay. VF, the ability to efficiently retrieve words from the mental lexicon, is critically important for learning, reasoning, and memory. In this study we used a novel assessment paradigm to understand how VF develops in youth with CIs and to investigate associations between VF, speech-language, and neurocognitive functioning. We hypothesized that phonemic VF (retrieving words based on sounds) would show greater delays than semantic VF (retrieving words within category) and that VF would relate to spoken language and memory outcomes.

Methods: 28 prelingually deaf, early-implanted (<4 years), long-term (≥7 years) child and adolescent users of CIs were compared with 33 age and nonverbal IQ-matched normal-hearing (NH) peers. VF measures were compared between CI and NH and were correlated with speech, language, and neurocognitive outcomes.

Results: Compared to NH peers, youth with CIs retrieved fewer words, had longer start latencies, and fewer word clusters in the phonemic VF test. Stronger phonemic VF in the CI sample was associated with better speech perception and language. Stronger VF in both samples was associated with better short-term/working memory and inhibition/concentration.

Conclusion: VF based on phonological (sound) characteristics of words is delayed in youth with CIs, whereas VF based on semantic meaning is relatively spared. Phonemic VF delays have downstream effects on speech perception and language in youth with CIs, whereas both types of VF are associated with verbal short-term/working memory and executive functioning.

Clinical Policy Impact and Implications: Study results indicate a need for assessment and intervention targeting VF (especially phonemic) in youth with CIs as a potential method for improving speech perception, language, verbal memory, and inhibition-concentration outcomes.