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The Impact of Inflammatory Mediators on the Landscape of Nascent Translation in the Dorsal Root Ganglion

Zachary Campbell is currently an assistant professor at UT-Dallas. He earned his doctorate at the University of Arizona with Thomas Baldwin. He conducted post-doctoral work at the University of Wisconsin Madison with Marv Wickens on translational control and functional genomics. He joined UT-Dallas in 2015 and has established a research program that seeks to understand RNA control in pain. The lab focuses on nociceptors. We are broadly interested in unbiased identification of transcripts that drive plasticity. We have developed a new class of mechanism based inhibitors that disrupt post-transcriptional regulons in vivo. This has led to the identification of RNA-binding factors that are required for pain associated behaviors. Our work can be found online at www.RNAcentral.com.

Abstract: Abstract: While acute pain enables injury avoidance and benefits survival, chronic pain is persistent and debilitating with very few effective treatment options. The transition from acute to chronic pain has been associated with sensitization of sensory neurons in the dorsal root ganglion. These neurons not only senses pain (i.e. nociceptors) but also innervates the response of non-neuronal cells to injury. Despite the pervasive role of translational regulation in nociception, the contribution of activity-dependent protein synthesis to inflammation is not well understood. To address this problem, we examined the landscape of nascent translation in DRG neurons treated with inflammatory mediators using ribosome profiling. We identify a remarkably small subset of transcripts that are preferentially translated in response to NGF and IL6, including the immediate early genes cFos and Arc. cFos translation is regulated by the ribosomal protein S6 kinase (S6K1). Antagonism of either S6K1 or cFos by DG2 and T5224, respectively, blocks mechanical and thermal hyperalgesia induced by inflammatory mediators, suggesting that S6K1 mediated translation of cFos is required for inflammation-related pain sensitization. Arc is locally translated in the skin. Arc deficient mice display exaggerated paw temperatures and vasodilation in response to an inflammatory challenge. Since Arc has recently been shown to be released from neurons in extracellular vesicles, we hypothesized that intercellular Arc signaling regulates the inflammatory response in skin. We found that the aberrant phenotype

observed in Arc defective mice are rescued by injection of Arc-containing extracellular vesicles into the skin, suggesting that Arc regulates neurogenic inflammation through intercellular signaling. Together, our findings expand our understanding of how dynamic translation of a specific subset of mRNAs contribute to inflammation and nociception and have clear implications for the development of novel pain therapeutics.