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Targeting Tiam1: a promising therapy for neuropathic pain

Aim: This study explores the contribution of Tiam1, a Rac1 guanine nucleotide exchange factor (GEF), in the central sensitization of spinal excitatory neurons during neuropathic pain development. This study also evaluates the potential of targeting spinal Tiam1 as a viable therapeutic strategy for alleviating neuropathic pain.

Methods: The authors of this study determined the role of Tiam1 in neuropathic pain, using various neuropathic pain mouse models and Tiam1 tissue-specific deletion strategies, and ultimately explored the potential of using spinal-targeted Tiam1 antisense oligonucleotide (ASO) as a therapeutic approach to alleviate neuropathic pain sensitivity in these mice. All the mouse models underwent painful neuropathy phenotyping using different behavioral, electrophysiological, biochemical, and morphological analyses.

Results: This study discovered that Tiam1, exclusively in spinal excitatory neurons, mediates neuropathic pain by promoting maladaptive spinal synaptic structural and functional changes. Tiam1 causes local Rac1 activation and actin polymerization, leading to dendritic spine remodeling and N-methyl-D aspartate receptor (NMDAR) stabilization, thus facilitating the initiation, transition, and maintenance of neuropathic pain. The study also demonstrated that ASO targeting spinal Tiam1 can effectively reduce neuropathic pain sensitivity.

Conclusion: This study identifies Tiam1 as a promising therapeutic target in neuropathic pain management and provides insights into its underlying mechanisms.

Comments. New therapeutic targets are urgently needed for neuropathic pain as current treatment options are limited in efficacy and have undesirable side effects. With this current preclinical study, the authors elegantly established a pathophysiological mechanism for neuropathic pain. They identified Tiam1 as a key factor in mediating unfavorable synaptic structural and functional alterations in excitatory spinal dorsal horn neurons, ultimately leading to neuropathic pain. The outcomes of this research are encouraging and support the notion of targeting Tiam1 and dendritic spines as a prospective therapeutic approach for the management of neuropathic pain. Interestingly, The relationship between spine reorganization, maturation, and synapse pruning represents an important pain circuitry dynamic to be taken into consideration when it comes to neuropathic pain especially, with a recently discovered mechanism connecting microglial activity to excitatory synapse pruning in the spinal cord (Yousefpour N et al *Cell Rep. 2023;42(1):112010*.). Additionally, exploring the plausible impact of combining Tiam1-targeted therapies with other existing treatments for neuropathic pain could also be a viable avenue for future studies. Overall, this study provides an exciting opportunity to understand how synapse growth contributes to the circuit-level changes involved in neuropathic pain and suggests promising therapeutic approaches for neuropathic pain management. However, further experimentation on murine models is necessary before we extrapolate these findings to human clinical settings.

Ali Jaafar

Reference. Li L, Ru Q, Lu Y, Fang X, Chen G, Saifullah AB, Yao C, Tolias KF. Tiam1 coordinates synaptic structural and functional plasticity underpinning the pathophysiology of neuropathic pain. Neuron. 2023 Jul 5;111(13):2038-2050.e6. doi: 10.1016/j.neuron.2023.04.010. Epub 2023 May 4. PMID: 37146610; PMCID: PMC10330505. https://www.cell.com/neuron/fulltext/S0896-6273(23)00282-9