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Unraveling the role of 4E-BP1 and TRIM32 in mechanical pain hypersensitivity

Aims: The study aimed to investigate the role of the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), a downstream effector of mammalian target of rapamycin complex 1 (mTORC1), in the mTORC1 induced development of chronic pain.

Methods: A series of behavioral sensory tests were conducted to assess mechanical and thermal hypersensitivity in a mouse model lacking nociceptor-specific 4E-BP1. Using the translating ribosome affinity purification (TRAP) method, the authors defined the translational landscape in nociceptors lacking 4E-BP1 and identified up-regulated mRNAs. The authors also employed a methodology involving the administration of adeno-associated virus (AAV) carrying shRNAmir targeting TRIM32, in a Cre-dependent manner. They also used an antibody that neutralizes the interferon alpha and beta receptor subunit 1.

Results: Deletion of 4E-BP1, a downstream effector of mTORC1, increased TRIM32 translation and type I Interferon (IFN) signaling, leading to mechanical hypersensitivity in mice. Down-regulation of TRIM32 or inhibition of type I IFN signaling reversed mechanical hypersensitivity in 4E-BP1 deficient mice, suggesting a role for type I IFN in nociceptor excitability. Peripheral nerve injury-induced mechanical hypersensitivity was not affected by the down-regulation of TRIM32 in nociceptors but was alleviated in an inflammatory pain model.

Conclusions: These findings highlight the role of the mTORC1-4E-BP1 axis in regulating interferon signaling in the pain pathway and identify TRIM32 as a potential therapeutic target for inflammatory pain.

Comments. The authors of this well-designed preclinical study generated mice with specific ablation of 4E-BP1 in DRG nociceptors, thereby mimicking the hyperactivation of the mTORC1 pathway. They demonstrated in nociceptors of these mice an elevation in TRIM32 mRNA translation and established that TRIM32 promotes the production of type I IFN and amplifies the excitability of nociceptors, leading to mechanical hypersensitivity. The authors also elegantly showed that targeting TRIM32/type I IFN alleviates mechanical hypersensitivity in a model of inflammation-induced pain (and not neuropathic pain). Collectively, this study enhances our understanding of the mechanisms by which mTORC1 promotes pain hypersensitivity and reveals the role of the mTORC1–4E-BP1–IFN axis in regulating inflammatory mechanical pain. Additionally, it proposes TRIM32 as a potential therapeutic target for conditions characterized by inflammation-induced mechanical hypersensitivity. Unfortunately, this study does not fully elucidate the specific downstream targets and signaling pathways of TRIM32 and type I interferon signaling in nociceptors. Furthermore, this study does not investigate the potential side effects or limitations of targeting TRIM32 as a therapeutic strategy for inflammatory pain nor the long-term effects of nociceptor-specific deletion of 4E-BP1 or TRIM32 ablation on pain behavior or nociceptor function. Lastly, the study is conducted in mice, and further research is needed to determine if the findings can be translated to human pain conditions.

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Reference. Wong C, Tavares-Ferreira D, Thörn Perez C, Sharif B, Uttam S, Amiri M, Lister KC, Hooshmandi M, Nguyen V, Séguéla P, Sonenberg N, Price TJ, Gkogkas CG, Khoutorsky A. 4E-BP1-dependent translation in nociceptors controls mechanical hypersensitivity via TRIM32/type I interferon signaling. Sci Adv. 2023 Nov 3;9(44):eadh9603. doi: 10.1126/sciadv.adh9603. Epub 2023 Nov 3. PMID: 37922363; PMCID: PMC10624345.

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