Cap-dependent Translation Modulates Inflammatory Pain in Aging

Natalia L. Dos Santos, Prapti H. Mody, Luz R. Barron, Theodore J. Price, Michael D. Burton

School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, TX

Abstract

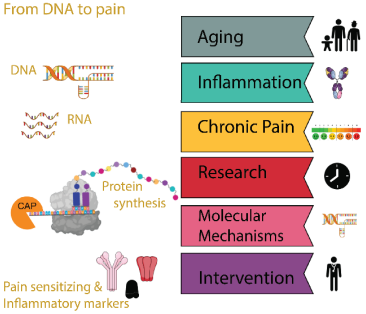
Background: The elderly population are at higher risk for injury and immune challenges and inflammatory responses that accompany these insults are aggravated in this population. Cap-dependent translation has been previously demonstrated to regulate the development of chronic pain in the young. However, its importance in the initiation and persistence of pain and inflammatory states in the aged population has never been reported.

Goal: We aim to identify age-dependent modulation of pain and inflammation by cap-dependent translation regulation.

Methods: Aged (22-24 mo) and young (3-5 mo) mice lacking the functional cap-dependent initiation site on eukaryotic initiation factor 4E (eIF4ES290A) and wild-type counterparts were subject to an intraplantar injection of complete Freund's adjuvant (CFA) to induce local inflammation and pain. Spontaneous and evoked measures of pain as well as paw temperature and inflammation were measured at 1, 2, 3, 5, and 7 days after the injection.

Results: Interestingly, aged but not young eIF4ES290A mice exhibited robust changes in acute peripheral inflammation, spontaneous, and evoked pain measures. Aged eIF4ES290A showed reduced mechanical and thermal hypersensitivity, as well as faster resolution of acute inflammation following CFA injection.

Background



Materials & Methods

Inflammatory Pain Model

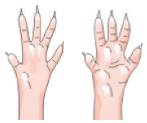
CFA injection

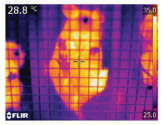
Animals

Genotype: WT, eIF4ES209A

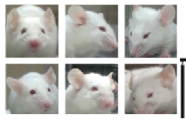
Age: YOUNG (3-5mo), AGED (22-24mo)

Inflammation





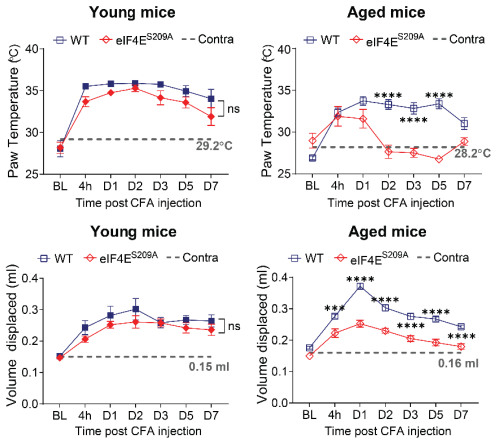
Spontaneous Pain



Evoked Pain

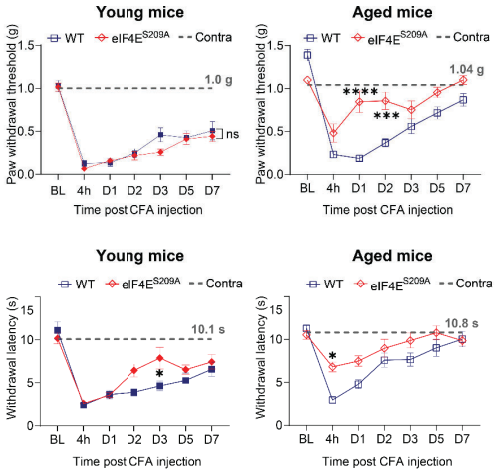
Inflammation

Intraplantar injection of Complete Freud's Adjuvant (CFA) induced less aggravated inflammatory phenotype on hind paw on aged 4eki mice.



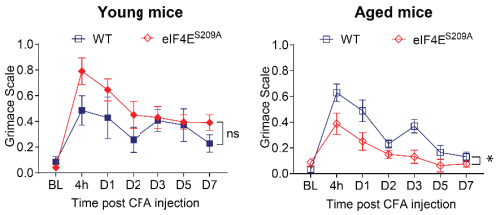
Evoked Pain

Aged animals resolve pain faster than young animals. Evoked pain is reduced in 4eki post insult in an age-dependent manner.



Spontaneous Pain

Phosphorylaticn of eIF4E modulates grimace following CFA injection in the aged.

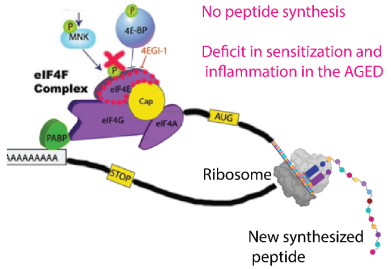


Future Direction

There is a disconnect between aggravated inflammation and pain in aging. This study starts revealing possible mechanisms that contribute to an aging phenotype and orients us to investigate cap-dependent translation as a possible target for aged specific therapeutics.

Conclusion

Aging affects function of different levels of the organism and that includes protein translation. This study is the first to demonstrate the pivotal role of functional cap-dependent translation in the development of evoked and spontaneous pain as well and peripheral inflammation in aging, demonstrating a marked age-dependent role of eIF4E in sustaining inflammatory pain.



References

Mody, P. H., Dos Santos, N. L., Barron, L. R., Price, T. J., & Burton, M. D. (2020) eIF4E phosphorylation modulates pain and neuroinflammation in the aged. GeroScience

Khoutorsky A, Price TJ (2018) Translational Control Mechanisms in Persistent Pain. Trends Neurosci 41:100-114.

Moy JK, Kuhn JL, Szabo-Pardi TA, Pradhan G, Price TJ (2018b) eIF4E phosphorylation regulates ongoing pain, independently of inflammation, and hyperalgesic priming in the mouse CFA model. Neurobiol Pain 4:45- 50

Acknowlegments

This research research support grant (M.D.B.), the A.P.S. Future Leaders Grant (M.D.B.), and the Rita Allen Foundation Grant (M.D.B.). was funded by the NINDS: K22NS096030 (M.D.B.), the U.T. System STARS

CONTACT: natalialucia.dossantos@utdallas.edu

Center for Advanced Pain Studies