Investigating The Role of AEG-1 in Mouse Models of Pain

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Introduction

• Astrocyte Elevated Gene 1 (AEG-1) was first identified as an upregulated gene in primary human fetal astrocytes infected with HIV-1 and has since been observed to have elevated expression levels in various CNS diseases.
• AEG-1 acts as a scaffold protein and mediates inflammation via direct protein-protein interaction with NF-κB.
• AEG-1 global knockout mice have been shown to be more resistant to inflammation compared to wild type littermates.
• Chemotherapy Induced Peripheral Neuropathy (CIPN) may develop in cancer patients undergoing treatment and may result in them having to switch to less effective drug regimens or causing treatment entirely.
• Current FDA approved drugs for chronic pain and neuropathy show modest efficacy and have severe side effects such as drug misuse and addiction.

Hypothesis

• AEG-1 acts as a mediator of inflammation via a NF-κB-dependent molecular mechanism. Therefore, making it a potential target for treatment in inflammatory pain.
• Therefore, we decided explore the role of AEG-1 in mouse models of Chronic Inflammatory Pain and Chemotherapy Induced Peripheral Neuropathy (CIPN).
• We hypothesized that deletion of AEG-1 gene would result in protection from noceception in our chosen mouse models of pain.

Methods

Animals:
• C57Bl6/J male and female mice, 8-14 weeks old (n = 5).
• AEG-1 WT or global knockout male and female mice on C57Bl6/J background, 8-14 weeks old (n = 6).

Models:
• Chronic Inflammatory Pain was induced via Freund’s Complete Adjuvant (CFA). Mice received 20 μl, i.pl. injections of 50% CFA or vehicle.
• Chemotherapy Induced Peripheral Neuropathy was induced via Paclitaxel (Taxol®). Mice received 8 mg/kg, i.p, injections of 50% Paclitaxel or Control at 3 days post injection cycle.

AEG-1 WT and global KO mice were given 4 periodic intraperitoneal injections of Paclitaxel in a Kolliphore solution (8 mg/kg) to model chemotherapy-induced peripheral neuropathy. AEG-1 KO mice displayed enhanced recovery from Paclitaxel-induced edema.

Results

AEG-1 WT and global KO mice were given a single intraplantar injection of 50% CFA in mineral oil to model chronic inflammatory pain. (a) AEG-1 WT mice displayed a higher degree of mechanical hypersensitivity at all time points, post injection, compared to AEG-1 KO mice. (b) AEG-1 WT mice displayed a higher degree of thermal sensitivity on day 4, post injection, compared to AEG-1 KO. (c) AEG-1 WT mice appear to show higher paw edema, measured 3 days following CFA injection, compared to AEG-1 KO mice.

Conclusion / Future

• Transgenic global knockout of AEG-1 appears to provide protection from CFA-induced mechanical hypersensitivity, thermal sensitivity, and paw edema.
• AEG-1 expression levels do not differ between C57Bl6/J mice treated with CFA or Control at 3 days post injection.
• Transgenic global knockout of AEG-1 appears to provide enhanced recovery from paclitaxel induced mechanical hypersensitivity and cold sensitivity.
• AEG-1 expression levels do not differ between C57Bl6/J mice treated with 8mg/Kg paclitaxel or Control at 3 days post injection cycle.

Future:
• Optimized IHC studies to assess AEG-1 and NF-κB protein localization in mice PAG, SpC, and DRG of various pain models.
• Performing a time course and collecting tissues at earlier time points to assess potential changes in AEG-1 expression in neuronal tissues.
• Assess the effects of analgesic drugs (such as morphine and gabapentin) on the anti-nociceptive phenotype displayed by AEG-1 KO mice.

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References


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