Publication News 101 - 18 December 2023

Spinal astrocytes are implicated in painful diabetic neuropathy via the Hdac5-Stat3 axis

***Aim*:** In the current study, Fan and colleagues examined the mechanisms by which spinal astrocytes contribute to painful diabetic neuropathy. Particularly, they interrogated the role of the signal transducer and activator of transcription-3 (Stat3), a key player in astrocyte development and astrogliosis, in pain processing.
***Methods*:** Pain behaviors were first assessed in a rat model rendered diabetic via a single dose of streptozotocin (STZ). Next, the authors used a combination of immunostaining, microarray, western blotting, and qPCR methods to characterize different cell populations within the spinal dorsal horn with major focus on astrocytes. Additionally, Stat3 cellular localization as well as gene and protein levels were determined in the STZ model. To further characterize the role of Stat3 in astrocyte degeneration and pain development, the authors either overexpressed *Stat3* or knocked it down *in vivo*. Mechanistically, the authors determined the mechanisms by which histone deacetylase 5 (Hdac5), which can regulate protein expression, downregulates Stat3 using co-immunoprecipitation and co-staining with/without siRNA targeting *Hdac5*.
***Results*:** Astrocyte degeneration during pain onset was associated with Stat3 downregulation in the spinal dorsal horn of type 1 diabetic rats. Interestingly, *Stat3* overexpression using a lentiviral-based transduction approach restored astrocytic markers, increased astrocyte number and alleviated pain symptoms in diabetic animals. Conversely, Stat3 knockdown in normal rats induced astrocyte loss and pain sensation, providing direct evidence for the importance of Stat3 in mediating pain pathology. The underlying mechanism implicated Hdac5, which was increased in spinal astrocytes and induced Stat3 deacetylation and downregulation.
***Conclusions*:** These findings shed new light onto the role of astrocytic Stat3 and its acetylation status in maintaining astrocyte health and normal sensation. Under diabetic conditions, Stat3 downregulation, secondary to Hdac5 deacetylation may contribute to astrocyte degeneration and central sensitization.

Comments. While previous studies have mostly focused on neurons in mediating pain pathology in diabetes, accumulating data suggest that glia also have a role in pain signaling. Specifically, astrocytes are the most abundant glial cell type which primarily regulate central nervous system blood flow, neuronal activity, and synaptic transmission. It is also becoming evident that astrocytes are implicated in neuropathic pain regulation. This study extends the current state of knowledge by demonstrating that astrocytes degenerate during painful diabetic neuropathy. Moreover, the authors identify Hdac5-Stat3 as a potential axis linking spinal astrocyte damage to pain mechanisms in diabetes. Together, these results enhance our understanding of painful diabetic neuropathy pathogenesis, astrocyte-specific contributions to central sensitization and disease development and provide valuable groundwork for the development of mechanism-based targeted therapies for painful neuropathy in type 1 diabetes.

Stéphanie Eid

Reference. Fan T, Yu Y, Chen YL, Gu P, Wong S, Xia ZY, Liu JA, Cheung CW. Histone deacetylase 5-induced deficiency of signal transducer and activator of transcription-3 acetylation contributes to spinal astrocytes degeneration in painful diabetic neuropathy. Glia. 2023 Apr;71(4):1099-1119. doi: 10.1002/glia.24328. Epub 2022 Dec 29. PMID: 36579750.
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