A Potential New Target for REST-mediated Chronic Pain

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Abstract

Chronic neuropathic pain originates from the damaged sensory nervous system and remains a major clinical challenge despite multiple clinical studies. Existing literature suggests an altered expression of pain associated genes (PAGs) following nerve injury and involves epigenetic modifications in dorsal root ganglion (DRG). The protein arginine methyltransferase 5 (PRMT5) is predominantly expressed in neuronal cells and catalyzes arginine methylation of histones and many non-histone proteins. However, it remains unclear if such methylation events also occur after nerve injury and pain sensation. Earlier reports suggest an increased expression of the repressor element-1 silencing transcription factor (REST) in DRGs after nerve injury—which contributes to transcriptional repression of various genes and results in the development of chronic pain.

We hypothesize that spared nerve injury (SNI)-induced chronic pain involves REST-mediated silencing of PRMT5. As a first step of this mechanism, we asked whether PRMT5 expression inversely correlates with REST in mice DRG after SNI. We used wild-type and Rest conditional knock-out (cKO) mice with various biochemical techniques.

Methods

The L3-L4 DRGs and spinal cord tissues obtained from wild type (WT) and Rest cKO mice before and after SNI on the left limb were used for quantitative real time PCR (qRT-PCR) and western blotting. No SNI (sham) was performed on the right limb of the mice. The REST binding site on the PRMT5 promoter was bioinformatically predicted by MatInspector (Genomatix).

Results

The initial qPCR results suggested an above 3.5-fold increase of REST mRNA with concurrent reduction in PRMT5 mRNA levels in the SNI compared to uninjured DRGs. The reduction of PRMT5 expression with increased levels of REST in DRGs after SNI was also confirmed by western blotting. In the Rest cKO mice, SNI did not affect PRMT5 protein levels, suggesting REST plays a role in regulating PRMT5. The predicted binding site of REST in the mouse PRMT5 promoter was located at the -369 to -339 region proximal to the transcription start site.

Conclusions

Our findings suggest a potential role of REST in negatively regulating PRMT5 expression in the DRGs after SNI. A potential binding site of REST is observed in the PRMT5 promoter; however, further validation of this binding is needed. Overall, elucidating the role of PRMT5 downregulation in epigenetic alteration of PAGs could unravel a novel mechanism of arginine methylation in chronic pain development.

References

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