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### Oxidative stress abrogates the degradation of KMT2D to promote degeneration in nucleus pulposus

**N**ucleus pulposus (NP) degeneration plays pivotal roles in intervertebral disc degeneration. The effect and mechanism of oxidative stress and epigenetics in NP degeneration is still unclear. We performed this study to evaluate the function of oxidative stress in NP and to explore the potential mechanism of ROS induced expression of matrix metalloproteinases (MMPs). We tested four methyltransferases, KMT2A, KMT2B, KMT2C and KMT2D in human NP samples, only KMT2D was significantly up-regulated in the severe degeneration samples. Knockdown of Kmt2d by siRNA significantly down-regulated the expression levels of catabolic enzymes including Mmp3, Mmp9 and Mmp13. Moreover, an interaction between KMT2D and ubiquitination was confirmed, and the application of H<sub>2</sub>O<sub>2</sub> abrogated this process. Co-IP assay confirmed that H<sub>2</sub>O<sub>2</sub> induced the phosphorylation of KMT2D to block the ubiquitination degradation, which was mainly mediated by phosphorylation of p38/MAPK. Further investigation suggested that ROS induced the alteration in levels of methylation is linked to H3K4me1 and H3K4me2, but not me3. However, usage of OICR-9429 (OICR) also suppressed the expression levels of Mmp3, Mmp9 and Mmp13. In an ex vivo model, application

of OICR-9429 (OICR) also attenuated the degeneration of NP according to the H&E and Safranin-O/Fast Green staining assay, and the protein levels of MMP3, MMP9 and MMP13 were down-regulated, as well. In conclusion, we approved that oxidative stress induced ROS production promote the process of NP degeneration by enhancing KMT2D mediated transcriptional regulation of matrix degeneration related genes during NP degeneration.

#### Biography

Wenbin Xu works as Deputy chief physician in the Department of Orthopedics at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. He is the Deputy Secretary of Youth League Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. He is also the English editor of Chinese Journal of Orthopedics. He is Member of the youth working group of the first committee of osteoporosis prevention and rehabilitation professional committee of China Rehabilitation Medical Association, Member of spinal minimally invasive group of osteoporosis Professional Committee of Zhejiang Rehabilitation Medical Association and Member of bone and joint rehabilitation group of the 10th Committee of physical medicine and Rehabilitation Branch of Zhejiang Medical Association. He is committed to the minimally invasive diagnosis and treatment of cervical spondylosis, lumbar disc herniation, osteoporotic fractures and other spinal surgery.

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