1. LSD1-Mediated Demethylation of Histone H3 Lysine 9 Contributes to Interleukin 1-Induced Microsomal Prostaglandin E Synthase-1 Expression in Human Osteoarthritic Chondrocytes.

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Objective: Microsomal prostaglandin E synthase-1 (mPGES-1) catalyzes the terminal step in the biosynthesis of PGE2, a critical mediator in the pathophysiology of osteoarthritis (OA). Histone methylation plays an important role in epigenetic gene regulation. In this study, we investigated the roles of histone H3 (H3K9) methylation in interleukin-1 (IL-1)-induced mPGES-1 expression in human chondrocytes.

Methods: Chondrocytes were stimulated with IL-1 and the expression of mPGES-1 mRNA was evaluated using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). H3K9 methylation and the recruitment of the histone demethylase LSD1 to the mPGES-1 promoter were evaluated using chromatin immunoprecipitation (ChIP) assays. The role of LSD1 was further evaluated using the pharmacological inhibitors, tranylcypromine and pargyline, and siRNA-mediated gene silencing. The LSD1 level in cartilage was determined using RT-PCR and immunohistochemistry.

Results: The induction of mPGES-1 expression by IL-1 correlated with decreased levels of mono- and dimethylated H3K9 at the mPGES-1 promoter. These changes were concomitant with the recruitment of the histone demethylase LSD1. Treatment with tranylcypromine and pargyline, potent inhibitors of LSD1, prevented IL-1-induced H3K9 demethylation at the mPGES-1 promoter and mPGES-1 expression. Consistently, LSD1 gene silencing with siRNA prevented IL-1-induced H3K9 demethylation and mPGES-1 expression, suggesting that LSD1 mediates IL-1-induced mPGES-1 expression via H3K9 demethylation. Finally, we showed that the level of LSD1 was elevated in OA compared to normal cartilage.

Conclusion: These results indicate that H3K9 demethylation by LSD1 contributes to IL-1-induced mPGES-1 expression and suggest that this pathway could be a potential target for pharmacological intervention in the treatment of OA and possibly other arthritic conditions.