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Interleukin-1-induced cyclooxygenase-2 and inducible nitric oxide synthase expression in human OA chondrocytes is associated with histone H3K4 methylation

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Objective

Increased expression of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 plays a key role in the pathogenesis of osteoarthritis (OA) disease. Methylation of lysine 4 on histone H3 (H3K4) was shown to be of fundamental importance in the regulation of gene expression. In the present study, we investigated the role of H3K4 methylation in interleukin-1β (IL-1)-induced COX-2 and iNOS expression in human OA chondrocytes.

Methods

Chondrocytes were stimulated with IL-1 for various time periods and the expression of iNOS and COX-2 mRNAs and proteins were evaluated using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blotting, respectively. H3K4 methylation at the iNOS and COX-2 promoters was evaluated using chromatin immunoprecipitation (ChIP) assays. The role of histone methylation was further evaluated using the methyltransferase inhibitor, 5'-deoxy-5'(methylthio) adenosine (MTA).

Results

IL-1 induced iNOS and COX-2 mRNA and protein in a dose- and time-dependent manner. The induction of iNOS and COX-2 expression by IL-1 was associated with H3K4 di- and trimethylation at the iNOS and COX-2 promoters, whereas the levels of H3K4 monomethylation remained unchanged. Treatment with MTA inhibited IL-1-induced H3K4 methylation as well as IL-1-induced iNOS and COX-2 expression.

Conclusion

These results indicate that H3K4 methylation contributes to IL-1-induced iNOS and COX-2 expression and suggest that this pathway could be a potential target for pharmacological intervention in the treatment of OA disease.

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