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Activation of Transforming Growth Factor β(TGFβ)by interaction of Matrix Metalloproteinase 13 (MMP-13) with the large latent complex

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ABSTRACT

Dysregulated TGFβ activation has been indicated in the pathology of osteoarthritis. We have reported that hypertrophic chondrocytes produce large quantities of activated TGFβ and a large latent complex of TGFβ that contains MMP-13 in non-covalent association. Bioinformatics revealed that the hemopexin domains of MMP-13 can non-covalently interact with the calcium-EGF-like domains of Latent TGF Binding Protein (LTBP1), the extracellular matrix anchor protein for the TGFβ large latent complex. The catalytic domain of MMP-13 is in alignment with the protease-sensitive hinge region of LTBP1, the site of release of this molecule from the extracellular matrix, suggesting a novel mechanism of TGFβ large latent complex release. To test this proposed interaction, we designed peptides of the MMP-13 hemopexin domain that are most likely to interact with LTBP1. Tissue extract of avian hypertrophic cartilage bound five times more MMP-13 peptide than extracts from resting zone cartilage. In addition, rat tibial growth plate cartilage immunoprecipitated with antibody to LTBP1 demonstrated four times more binding affinity for MMP-13 peptide than the scrambled peptide control. These data support the specific interaction between MMP-13 and LTBP1 predicted in our bioinformatics model and our proposed model of the mechanism of release of the TGFβ large latent complex by MMP-13. Sponsored in part by a grant from the CCDA.

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