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Current Topics in Bone Metabolism Pharmacological Research: The Molecular Basis of Mechanical Stress-Induced Ectopic Bone Formation

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DESCRIPTION

Ectopic Bone Formation (EBF) is common in many tissues and has an impact on the prognosis of diseases associated with EBF. Several local factors that influence the progression of EBF have been proposed, despite the fact that the mechanism of EBF remains unknown. We have been studying the role of mechanical stress as a local factor in EBF in spinal ligament tissues, specifically Ossification of the Posterior Longitudinal Ligament (OPLL), which causes severe neurological deficits. Transcriptome analyses revealed that the expression of several bone remodelling marker genes was increased after exposing OPLL cells to cyclic stretching as a type of mechanical stress. However, no significant changes in gene expression were observed after cyclic stretching of ligament cells derived from non-OPLL patients. OPLL cells exposed to cyclic stretching released several autocrine/paracrine factors known to mediate bone remodelling. These findings suggest that OPLL cells have been transformed into cells that are highly sensitive to mechanical stress, which may cause OPLL progression. These findings shed light on the role of mechanical stress in the EBF process.

Ossification of the Posterior Longitudinal Ligament (OPLL) of the spine is characterised by ectopic bone formation in the spinal ligament. It is a common disease in Japan and throughout Asia. OPLL compresses the spinal cord and its roots, resulting in a range of neurological symptoms ranging from discomfort to severe myelopathy. OPLL patients frequently receive surgical treatment as an established therapy, despite the fact that it is still associated with issues such as an increased risk of neurological complications. As a result, the development of a safe and effective drug therapy is required. However, the mechanism involved in promoting ossification is still unknown. From a molecular standpoint, we will discuss a potential role for mechanical stress in the progression of OPLL in this review.

When compared to normal spinal ligament cells, spinal ligament cells derived from OPLL patients (OPLL cells) have several phenotypic

characteristics of osteoblasts, including *in vitro* calcification and high Alkaline Phosphatase (ALP) activity in cultures. OPLL cells respond to Transforming Growth Factor (TGF-1), Bone Morphogenetic Protein-2 (BMP-2), insulin-like growth factor-I, connective tissue growth factor, Prostaglandin I2 (PGI2), and Parathyroid Hormone (PTH). An immune histochemical study of OPLL patients' ossified ligament tissues revealed increased expressions of osteogenic protein1/BMP-7 and its receptors (type-IA, -IB, and -II receptors).

To confirm the distinct differences between OPLL and non-OPLL cells, we examined whether these cells mineralized when cultured in osteogenic medium. Within 4 weeks of being exposed to osteogenic medium, the matrix surrounding the OPLL cells began to mineralize, and crystals appeared on the collagen fibres, accompanied by high ALP activity. Non OPLL cells, on the other hand, did not exhibit these morphological changes. These findings support the hypothesis that OPLL cells have been transformed into osteoprogenitor cells.

OPLL is frequently associated with ossification of other spinal ligaments. It has been identified as a manifestation of Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Ankylosing Spinal Hyperostosis (ASH). As a result, systemic factors are thought to play a role in the pathogenesis of OPLL. Several lines of clinical evidence, on the other hand, have suggested that mechanical stress acting on the ligaments is important as a local factor in the progression of OPLL. To investigate the latter possibility, we used a variety of methods, including Deoxyribonucleic acid (DNA) microarray and differential display Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test, to examine the effect of mechanical stress on ligament cells. Cyclic stretching was applied to ligament cells attached to the ligament as a mechanical stress that may act on ligament tissues.

Mechanical stress is thought to play an important role in the progression of OPLL, at least in part by promoting the autocrine/paracrine mechanism of several cytokines involved in the disease. Mechanical stress's effects on OPLL cells are thought to be the first step in mechanically-induced ossification processes. These findings may shed light on the role of mechanical stress in ectopic bone formation in other tissues.