学位論文内容の要旨

Abstract of the dissertation

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学位論文題名

The title of the doctoral dissertation

Structure-related Effects of Pentosan Polysulfate Sodium: Modulation on Phenotypic Change and Chondrogenic Properties in Canine Chondrocyte *in-vitro* Cultures

（ポリ硫酸ペントサンの構造と効果発現に関する研究：培養軟骨細胞における形質維持と軟骨分化能の調節）

Abstract of the Dissertation

Hyaline cartilage is a specialized connective tissue on the joint surface that supports normal joint movements and protects the subchondral bone. Chondrocytes are the only cellular components in the cartilage, which are physiologically responsible for maintaining a balance between the synthesis and degradation of the extracellular matrix (ECM). Osteoarthritis (OA) is the most common degenerative joint disease that progressively destroys the joint structures, including cartilages. During OA pathogenesis, chondrocytes undergo a dedifferentiated phenotypic change that leads to transiently increased proliferation, downregulated ECM biosynthesis, and activated production of biochemical mediators associated with OA progression. These changes of chondrocytes disturbed cartilage homeostasis, which pharmacological interventions of chondrocytes dedifferentiation could be beneficial for OA treatment.

Pentosan polysulfate sodium (PPS) is a semi-synthetic polysaccharide, which has been found to relieve OA symptoms in animals. Although the underlying mechanisms are not fully understood, PPS has shown effects in promoting the redifferentiation and ECM production of articular chondrocytes. On the other hand, the structure similarity between PPS and glycosaminoglycans has been identified. Since glycosaminoglycans achieve their biological properties mainly through the interaction with proteins, modifying their molecular weights or sulfate levels could alter their effects. However, the structure-effect relation of PPS is rarely discussed. To improve the therapeutic effects of PPS, more information is need.

Therefore, the present study was conducted with two major objectives: 1. To check the effects on the phenotypic changes and ECM production of dedifferentiated canine chondrocytes and the underlying molecular mechanisms of these effects. 2. To explore how the variations in molecular weights and sulfate levels of PPS affect these treatment effects.

This dissertation contains two sections: Section one investigated the effects of different sulfate levels PPS on the proliferation and cell cycle in dedifferentiated

chondrocytes and the related phenotypic change in monolayer cultures. In the second section, the effects in promoting the redifferentiation and ECM production of canine chondrocytes were further investigated in micro-mass cultures using PPS with different molecular weights.

The results of this study provide evidence that PPS exerts inhibitory effects on cell cycle progression while promotes the redifferentiation of dedifferentiated canine articular chondrocytes in monolayer cultures, which involves the suppression of PI3K/Akt signaling pathway. The improvement in the phenotype and ECM production of chondrocytes with PPS treatment was further confirmed under a micro-mass cultured condition. Relations between the structure and the anabolic effects of PPS was also confirm in this study, which larger PPS molecules (5,000 and 7,000 Da) exert stronger effects in promoting chondrocyte redifferentiation and ECM synthesis. Furthermore, the full sulfate level of PPS seems to be necessary to achieve these effects.

In conclusion, this dissertation provided further information on the therapeutic effects of PPS in canine articular chondrocytes and their underlying mechanisms, which could be a potential target for developing pharmaceutical treatments for OA. In addition, the information about structure-effects relation of PPS could deepen the understanding of its interaction with the body and help to improve the treatment effects of PPS, which would have a positive impact to solve OA problems in animals.