学位論文内容の要旨
Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）　　氏名：Ekkapol Akaraphutiporn
Name

学位論文題名
The title of the doctoral dissertation

The Cellular Physiology of Canine Chondrocytes: an *in-vitro* Study on Phenotype Regulation and Characteristics of Cell Death
（犬軟骨細胞の細胞生物学的態度：培養環境における分化調節と細胞死に関する研究）

Articular cartilage is a thin layer of highly specialized connective tissue that covers the ends of the bones where they articulate with each other and form a joint. The structure of articular cartilage is regulated by chondrocytes, which responsible for cartilage homeostasis by maintaining the extracellular matrix (ECM) components through the formation and degradation process. Alteration in metabolic activities of chondrocytes could lead to homeostasis imbalance and resulting in a degenerative condition of articular cartilage.

Osteoarthritis (OA), which is also referred to as degenerative joint disease, is the most common form of arthritis characterized by the progressive breakdown of articular cartilage. During OA progression, resting chondrocytes undergo a phenotypic shift and become activated chondrocytes, which results in a transient increase in proliferative activity, phenotypic instability and upregulation of several biochemical mediators associated with disease progression. A comprehensive investigation of chondrocyte responses in OA conditions will be beneficial for cartilage degenerative disease treatment.

Therefore, the present study was constructed to investigate the cellular biology of canine articular chondrocytes based on two major purposes. The first objective was to identify the effect of cell metabolic activity and extracellular microenvironment on the phenotypic stability of chondrocytes. The second objective was to investigate the molecular mechanisms regulating programmed cell death on chondrocytes stimulated by a particular biochemical mediator.

The dissertation is structured into three experimental sections: First, the unconventional cell culture model was established and used to observe the influence of proliferative activity and microenvironment conditions on the phenotypic stability of chondrocytes during the expansion process. Second, the effects of disease modifying osteoarthritic drugs (DMOADs) named pentosan polysulfate (PPS) was evaluated on the

phenotypic stability and proliferative activity of chondrocytes, particularly in cell cycle modulation. In the last section, the molecular mechanisms regulating apoptosis and autophagy in nitric oxide (NO) -induced chondrocyte cell death were investigated.

Findings of the current study provide evidence that the metabolic state of chondrocytes and the extracellular microenvironment condition exert a considerable influence on phenotypic stability and differentiation process. These results were supported by the inhibitory effect of PPS on cell cycle progression while maintaining the phenotypic stability of chondrocytes. In cartilage, both forms of programmed cell death, apoptosis and autophagy are essential cellular degradation mechanisms that influence the homeostasis and survivability of chondrocytes. The results of the current study confirmed that NO inhibits autophagy and induces chondrocyte apoptosis, while autophagy is a protective mechanism of chondrocytes in the pathogenesis of OA and could be proposed as a valuable therapeutic target for the treatment of degenerative joint diseases.

The main conclusions drawn from this research were that the metabolic state of chondrocytes would be a key to maintain phenotypic stability, which could be applied for cartilage tissue regeneration and used as a prospective therapeutic target in joint diseases. Furthermore, by revealing the molecular mechanism of biochemical mediators induced programmed cell death on chondrocytes, the findings in this study will undoubtedly provide useful information on both research and clinical aspects for the treatment of joint diseases.