氏　　名	Abdellatif　Elseoudi　Abdellatif　Abouelseoud
授与した学位	博　士
専攻分野の名称	歯　学
学位授与番号	博甲第５９３２号
学位授与の日付	平成３１年３月２５日
学位授与の要件	医歯薬学総合研究科機能再生・再建科学専攻 （学位規則第４条第１項該当）
学位論文の題目	Catabolic effects of FGF-1 on chondrocytes and its possible role in osteoarthritis. （軟骨細胞に対するFGF-1 の異化促進効果とその変形性関節症における役割）
論文審査委員	松本　卓也　教授　　中野　敬介　准教授　　川邉　紀章　准教授

学位論文内容の要旨

論文内容の要旨（2000字程度）

Fibroblast growth factor 1 (FGF-1) is a classical member of the FGF family and is produced by chondrocytes cultured from osteoarthritic patients. Also, this growth factor was shown to bind to CCN family protein 2 (CCN2), which regenerates damaged articular cartilage and counteracts osteoarthritis (OA) in an animal model. However, the pathophysiological role of FGF-1 in cartilage has not been well investigated. In this study, we evaluated the effects of FGF-1 in vitro and its production in vivo by use of an OA model. Treatment of human chondrocytic cells with FGF-1 resulted in marked repression of genes for cartilaginous extracellular matrix components, whereas it strongly induced MMP-13 (matrix metalloproteinase 13), representing its catabolic effects on cartilage. Interestingly, expression of the CCN2 gene was dramatically repressed by FGF-1, which repression eventually caused the reduced production of CCN2 protein from the chondrocytic cells. The results of a reporter gene assay revealed that this repression could be ascribed, at least in part, to transcriptional regulation. In contrast, the gene expression of FGF-1 was enhanced by exogenous FGF-1, indicating a positive feedback system in these cells. Of note, induction of FGF-1 was observed in the articular cartilage of a rat OA model. These results collectively indicate a pathological role of FGF-1 in OA development, which includes an insufficient cartilage regeneration response caused by CCN2 down-regulation.

論文審査結果の要旨

Fibroblast growth factor 1 (FGF-1) is a classical member of the FGF family and is produced by chondrocytes cultured from osteoarthritic patients. Also, this growth factor was shown to bind to CCN family protein 2 (CCN2), which regenerates damaged articular cartilage and counteracts osteoarthritis (OA) in an animal model. However, the pathophysiological role of FGF-1 in cartilage has not been well investigated. In this study, we evaluated the effects of FGF-1 *in vitro* and its production *in vivo* by use of an OA model. Treatment of human chondrocytic cells with FGF-1 resulted in marked repression of genes for cartilaginous extracellular matrix components, whereas it strongly induced matrix metalloproteinase 13 (MMP-13), representing its catabolic effects on cartilage. Interestingly, expression of the CCN2 gene was dramatically repressed by FGF-1, which repression eventually caused the reduced production of CCN2 protein from the chondrocytic cells. The results of a reporter gene assay revealed that this repression could be ascribed, at least in part, to transcriptional regulation. In contrast, the gene expression of FGF-1 was enhanced by exogenous FGF-1, indicating a positive feedback system in these cells. Of note, induction of FGF-1 was observed in the articular cartilage of a rat OA model induced by mono-iodo acetic acid (MIA) exposure.

This study sheds a light on FGF-1 involvement in OA process. FGF-1 can be induced by initial cartilage damage leading to OA, which is well represented in the rat model. Once FGF-1 is produced, the production is amplified through the auto-induction feedback loop of FGF1 expression. The FGF-1 molecule overproduced in articular cartilage strongly activates the MMP13 gene, which encodes a proteinase to destroy cartilaginous Extracellular matrix (ECM). The destroyed ECM could be restored by production of cartilaginous components including type II collagen and aggrecan, which are strongly restrained by FGF-1 at the gene expression level. FGF-1 also inhibits the gene expression and protein production of CCN2, a molecule that promotes cartilage repair. These results collectively indicate a pathological role of FGF-1 in OA development, which includes an insufficient cartilage regeneration response caused by CCN2 down regulation. Such molecular functions of FGF-1 have not reported previously. Therefore, this study is of significant scientific value and may lead to the development of novel OA therapeutics, and thus the committee here approves this study as a Ph. D thesis in dentistry.