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学位論文題目	The distribution of vascular endothelial growth factor in human meniscus and meniscal injury model (半月板における VEGF の局在と役割)
論文審査委員	教授 木股敬裕 教授 大橋俊孝 准教授 寶田剛志

学 位 論 文 内 容 の 要 旨

Meniscus injury is very common in the knee joint. Some studies displayed that vascularization is a key factor for healing an injured meniscus, and that the outer meniscus has a better healing capacity than the inner meniscus because of vascularization. Vascular endothelial growth factor (VEGF) has important roles in promoting vascularization of various tissues. VEGF-mediated neovascularization is beneficial to the healing of injured tissues. However, the distribution and angiogenic role of VEGF remains unclear in the meniscus and injured meniscus. In the current study, we investigated the localization of VEGF in human native meniscus and in an ex vivo model of meniscal injury. Macroscopically intact lateral menisci were obtained at total knee arthroplasty in patients with knee osteoarthritis. Full-thickness, radial, 5-mm-long lesions in both the inner and outer meniscal area were created with a microsurgical blade. VEGF mRNA and protein expression were detected by the polymerase chain reaction and immunohistochemical analyses, respectively. In native meniscal tissue (obtained from freshly isolated meniscus) and cultured meniscal tissue, the expression of VEGF and HIF-1 α mRNAs could not be detected. However, VEGF and HIF-1 α mRNAs were found in cultured meniscal cells (VEGF: outer > inner; HIF-1 α : outer $\frac{1}{4}$ inner). In the other hand, we observed that injury increased mRNA levels of both VEGF and HIF-1 α , with the increase being greatest in the outer meniscus. Similarly, quantitative real time PCR results were similar to the PCR data. Immunohistochemical analyses revealed that VEGF protein was detected mainly in the outer region and around injured areas of the meniscus. However, VEGF concentrations were similar between inner and outer menisci-derived media. Our study demonstrated that meniscus contains VEGF in both the inner and outer regions. However, only outer meniscal tissue is vascular area, we consider that anti-angiogenic factors may prevent the function of VEGF in the inner meniscus. Besides, HIF-1 α expression was elevated and VEGF deposition increased in injured meniscus. Our results suggest that injury stimulates the expression of HIF-1 α and VEGF that may be preserved in the extracellular matrix as the healing stimulator of damaged meniscus, especially in the outer meniscus.

論 文 審 査 結 果 の 要 旨

膝関節の軟骨損傷は一般的疾患で、その修復過程の鍵となるのが血管新生である。そして、内側関節軟骨と比較し外側関節軟骨の方が高い修復能力を有すると言われている。しかし、血管新生に関わる各種成長因子と膝関節における局在などに関しては不明な点が多い。

申請者は、血管新生に重要な役割を有する VEGF に着目し外側関節軟骨と内側関節軟骨における局在を検討した。6 例の患者さんから得られた関節軟骨を、外側と内側に分け、さらに意図的に切れ目を入れた障害軟骨と正常の軟骨に分け、組織ならびに細胞培養を行い、遺伝子発現状況と VEGF の局在を研究した。その結果、外側軟骨に優位に局在していること、また障害軟骨に優位に VEGF 関連遺伝子が発現し、VEGF が局在していることを明らかにした。

今後さらなる研究が必要であるが、障害された軟骨を効果的に再生修復させる治療に結び付く可能性がある成果である。

よって、本研究者は博士（医学）の学位を得る資格があると認める。