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研究課題名（和文）関節軟骨に対するテネイシンCの修復促進・変性抑制の分子機構解明と治療への応用

研究課題名（英文）Mechanism of articular cartilage repair and prevention of cartilage degeneration with tenascin C and application for treatment

研究代表者

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研究成果の概要（和文）：テネイシンC(TNC)の軟骨修復効果をみるため、家兎膝に骨軟骨欠損を作製し、硫酸化ジェラン固定化ジェランスポンジを担体としたTNCを投与したところ、良好な軟骨修復を認めた。マウスの膝に骨軟骨欠損を作製し、TNCを欠損部に直接投与しても良好な軟骨修復を認めた。軟骨変性抑制作用を調べるために、マウスの靱帯切離による変形性関節症モデルを作製し、TNCを投与すると6週まで軟骨変性が抑制されていた。すなわち、TNCは軟骨修復作用、軟骨変性抑制作用があることが示された。培養軟骨細胞にTNCを添加すると、ADAMTS4は発現量が増加したが、ADAMTS5は減少した。

研究成果の概要（英文）：We implanted Gellan-GS soaked in TNC into full-thickness osteochondral defects of the patellar groove of rabbits. Histologically as well as macroscopically, we found satisfactory repair of cartilage. Using mice, full-thickness osteochondral defects were created and the defects were filled with TNC. Histologic study showed satisfactory repair of cartilage. In posttraumatic osteoarthritis model with transection of anterior cruciate ligament and medial collateral ligament, we performed intra-articular injection of TNC. TNC administration markedly protected the articular cartilage from proteoglycan depletion for 6 weeks. These studies indicated that TNC could promote cartilage repair and protect cartilage degeneration in vivo. Although TNC upregulated the expression of ADAMTS4, TNC downregulated the expression of ADAMTS5.

研究分野：　医歯薬学

キーワード：　関節軟骨　テネイシン

１．研究開始当初の背景

軟骨損傷や変性に対する新しい治療法に利用する候補分子として、テネイシン C（TNC）に着目した。TNC はマトリックス細胞タンパクの一つであり、軟骨培養細胞を用いた研究や、TNC ノックアウトマウスの検討から、TNC が軟骨修復を促進していることを明らかとした。

２．研究の目的

TNC の担体となる硫酸化ジェラン固定化ジェランを用いた徐放実験と TNC の家兎関節軟骨欠損修復効果の検討、TNC のマウス関節軟骨欠損修復効果、軟骨変性抑制の効果の検討を行う。さらに TNC の軟骨に対する作用の分子メカニズムを検討する。

３．研究の方法

TNC の徐放性を検討するために、硫酸化ジェラン固定化ジェランに TNC を含浸させ、PBS 入りのチューブに入れ、TNC 濃度を ELISA キットを用いて測定した。

関節軟骨修復効果をみるため、家兎大腿骨関節面に大きさ 4㎜ 径の軟骨下骨を貫く骨軟骨欠損を作製した。担体として硫酸化ジェラン固定化ジェランスポンジを用い、TNC 濃度は 10μg/ml、100μg/ml とした。コントロールとして、TNC を含浸させず、生食を含浸させたものを作製した。軟骨欠損修復効果を組織学的に評価した。

マウスの大腿骨関節面に大きさ 0.3㎜ 径で、軟骨下骨を貫く骨軟骨欠損を作製し、TNC を欠損部に直接投与した。TNC 濃度は 10μg/ml、100μg/ml とし TNC を投与しないコントロール群も作製し、組織学的に検討した。

関節軟骨変性抑制作用を調べるために、マウスの前十字靱帯および内側側副靱帯切離して、変形性関節症モデルを作製し、TNC（10μg/ml、100μg/ml）を投与し、組織学的に評価した。

培養軟骨細胞の TNC 添加の有無による遺伝子発現の変化を real-time PCR を用いて炎症性サイトカイン(TNFα,IL1-β,NFκB)，軟骨細胞に対する anabolic factor (bFGF, TGFβ, TIMP3)，catabolic factor (ADAMTS4,ADAMTS5,MMP3,MMP13) の各群において検討した。

４．研究成果

徐放実験において、4 日以降、硫酸化ジェラン固定化ジェランスポンジから徐放される TNC の濃度は、コラーゲンスポンジと比較して有意に高値であった。（図１）。

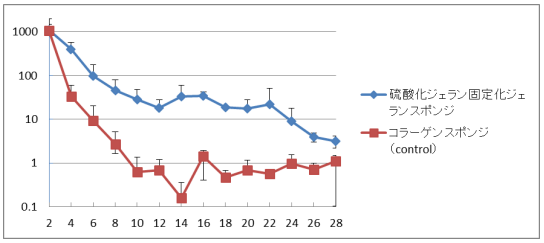
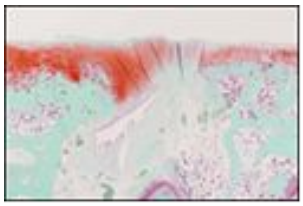


図１． 徐放実験

家兎関節軟骨欠損修復効果の検討において、TNC 10μg/ml 投与群は TNC 100μg/ml 投与群、生食群より有意に良好な結果であった（図２）。



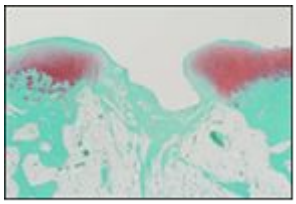
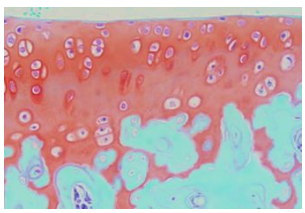


図 2. 組織像（サフラニン O 染色）
家兎軟骨欠損に TNC 含浸硫酸化ジェラン埋植後 12 週．TNC 10 μg/ml 投与（上）はコントロール（下）より軟骨修復良好．

マウス関節軟骨欠損修復効果の検討において、TNC 100μg/ml 投与群は良好な軟骨修復を認めた。

マウス関節軟骨変性抑制効果の検討において、TNC の投与は 10μg/ml、100μg/ml ともに 6 週までの軟骨変性抑制に有効であった（図 3)。



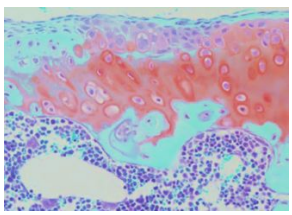


図 3. 組織像（サフラニン O 染色）
マウス OA モデル 6 週．TNC 投与（上）はコントロール（下）より軟骨変性を抑制．

TNFα,IL1-β,NFκB は TNC 投与により有意に発現量の増加を認めた。TGFβ,TIMP3 も有意に発現量の増加を認めた．ADAMTS4,MMP3,MMP13 は有意に発現量の増加を認めたが、軟骨変性に最も関与しているとされる ADAMTS5 では発現量の減少を認めた。

５．主な発表論文等
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〔その他〕
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