Conclusions: Chondrocyte survival signals are transmitted via the α5131 fibronectin receptor. Integrin survival signals may work synergistically with growth factor signals including IGF-1, but unlike cells from normal cartilage the cells from OA cartilage lacked a survival response to IGF-1, when α5-integrin was blocked.

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EPIGALLOCATECHTN-3-GALLATE (EGCG) INHTBITS INTERLEUKIN-1b-INDUCED ACTIVATION OF MITOGEN ACTIVATED PROTEIN KINASES (p-38MAPK, JNK/SAPK) NUCLEAR FACTOR-kB (NF-kB), EXPRESSION OF NITRIC OXIDE SYNTHASE, PRODUCTION OF NITRIC OXIDE AND IL-6 IN HUMAN OSTEOARTHRITIS CHONDROCYTES

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Aim: The aim of this study was to assess the effect of green tea polyphenol epigallocatechin-3-gallate (EGCG) on IL-1β-induced inflammatory stimuli in human chondrocytes.

Methods: Human chondrocytes were prepared by enzymatic digestion of cartilage samples from OA patients and treated with IL-1β and EGCG. Production of NO, PGE2 and IL-6 was assayed in culture supernatants and expression of NO synthase (iNOS), cyclooxygenase-2 (Cox-2) and MAPKinases was analyzed by western blotting and RT-PCR.

Results: EGCG was non-toxic to human chondrocytes and inhibited IL-1b-induced expression of iNOS mRNA and protein and suppressed the NO production in dose-dependent manner. Our results also show that EGCG only weakly suppressed COX-2 expression but prostaglandin E2 (PGE2) production was not affected. In contrast, co-treatment of chondrocytes with EGCG resulted in almost complete inhibition of IL-6 production in human OA chondrocytes. EGCG also inhibited the activation of NF-kB, mitogen activated protein kinase (p38-MAPK) and c-jun N-terminal kinases / stress activated protein kinases (JNK/SAPK).The inhibitory effect was more pronounced on the JNK/SAPK p46 isoform. Similar treatments had no effect on IL-1β-induced phosphorylation of the extracellular-signal related kinase (ERK p44/42) in human OA chondrocytes. Total non-phosphorylated levels of the kinases were not affected by treatment with IL-1β or EGCG indicating that EGCG or IL-1β did not alter or induce the production of MAPK protein in human OA chondrocytes.

Conclusion: These results suggest that the green tea polyphenol EGCG may be of value in the treatment and of prevention of OA.

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THE EFFECFS OF MMP INHIBITOR ON ARTICULAR CARTILAGE DEGENERA11ON IN AN ANIMAL MODEL OF OSTEOARTHRITIS

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Aim: The aim of this study was to examine preventive effect of MMP inhibitor on articular cartilage degeneration.

Methods: Anterior cruciate ligament transection models (ACLT) of 27 New Zealand White female rabbits were used for this study. At 4 weeks after operation, oral administration of 5.0mg/kg, 10mg/kg of MMP inhibitor (MMI-8I, Shionogi Japan) and vehicle were started once a day and continued for 5 weeks. Rabbits were killed at 9 weeks after operation and their knees were taken out. We compared morphological, chemical and histological status of the cartilage of each group.

Results: In histological status, we observed the significant difference as followings. In control group (7 rabbits), the cartilage surfaces were almost normal. In vehicle group (7), 5 samples had the formation of erosion both femoral and tibial articular cartilage. In the high dose group (7), 5 samples showed minimum degeneration in comparison with the vehicle group. In the low dose group (6), the result was almost similar to the high dose group. Histological evaluation was performed by Mankin score, and statistical significance of intergroup differences was analyzed by Mann-Whitney u test In high dose group, total Mankin score was significantly lower than vehicle group.

Conclusion: In this study, we demonstrated that high dose MMI-81 suppressed degenerative changes of articular cartilage effectively. As a new starting point examinations should be started to clarify about the cartilage degeneration mechanism more precisely. Among new strategies for the treatment of osteoarthritis, including gene therapy, artificial regulation of cytokine productions and chondrocyte transplantation, MMP inhibitor might be one of the choices.

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DIFFERENTIAL REGULATION OF SYNDECAN EXPRESSION BY INTERLEUKIN-I AND TRANSFORMING GROWTH FACTOR-b1 IN HUMAN ARTICULAR CHONDROCYTES

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Aim: The aim of this study was to determine the effect of IL-1 and TGF-β, as major cytokines implicated in OA cartilage metabolism, on the mRNA levels of syndecans 1, 2 and 4 in cultured human articular chondrocytes.

Methods: Human chondrocytes from the patella of healthy donors (postmortem) were cultured in monolayers, at a seeding density of 10^5 cells/cm^2, in 10% FCS-containing medium. Primary confluent cultures were treated with IL-Iβ (2, 10, 20 ng/ml) during 48 h (Dose-dependency experiment) or 10 ng/ml for 24, 48 and 72 h (Time-dependency experiment). Similar experiments were performed with TGF-β1 (0.5, 2, 5 ng/ml) for 48 h and 2 ng/ml for 24, 48 and 72 h. Total RNA was extracted and used in semi-quantitative RT-PCR to determine the mRNA steady-state levels of syndecans 1, 2 and 4.

Results: IL-1 was found to decrease the expression of syndecans 1 and 2, whereas it stimulated that of syndecan 4. This data correlates with our previous finding showing that osteoarthritic cartilage has similar pattern of syndecan expression, compared with normal tissue. TGF-b1 had no significant effect on syndecan 1 and 2 mRNA levels whereas it clearly decreased the amount of mRNA for syndecan 4. It has therefore an opposing effect to IL-1 on syndecan 4 expression.

Conclusions: It is interesting to note that IL-1 induces an alteration in the pattern of syndecan expression by chondrocytes. This may play a role in the modulation of chondrocyte phenotype in OA. Interesting enough is the finding that syndecan 4, which is known to be associated with focal adhesions in fibroblastic cells and can induce PKC activation, is differentially regulated by IL-1 and TGF-b1. Chondrocytes start to divide in early OA events, forming clusters, and are likely to develop focal adhesions. IL-1-induced increase of syndecan 4 may have great importance at this stage.