The **COLL2-1** Peptide of **Collagen Type II** : A **New Actor** of Synovitis in Osteoarthritis

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P U R P O S E . Osteoarthritis (OA) is characterized by degradation of the extracellular matrix associated with inadequate repair responses including pro-inflammatory pathways of nonspecific natural immune response. We evaluated the inflammatory effect of Coll2-1 peptide in osteoarthritic synoviocytes and rats by comparing peptide-induced inflammatory reaction with the one induced by bovine type II collagen or streptococcal cell wall.

M E T H O D S . Human synoviocytes from knee OA patients (n=10) were pre-treated with AS0619 or CLI-095 (500nM, 1 and 2.5µM) before a 24 hours treatment with Coll2-1 peptide ([108]HRGYPGLDG[116]; 0.45 or 4.5nmol). Expression of Interleukin (IL)-8, Vascular Endothelium Growth Factor (VEGF) and phosphorylation of the IκB-α and p65 were evaluated. Either Coll2-1 peptide, bovine type II collagen (CIA), streptococcal cell wall (SCW) or saline solution (100µl SC or 50µl IA) were injected into Lewis rats (n = 108). The Coll2-1 peptide was subcutaneously injected (SC; 20 and 200µg/100µl/animal) or intra-articular (IA; 0.5 and 5µg/50µl/animal). The bovine type II collagen was SC injected (200µg/100µl/animal), the streptococcal cell wall in IA (5µg/50µl/animal). The animals were injected on day 10 and monitored for 21 or 28 days. Visual evaluation of the severity of arthritis and histological lesions were performed.

R E S U L T S .

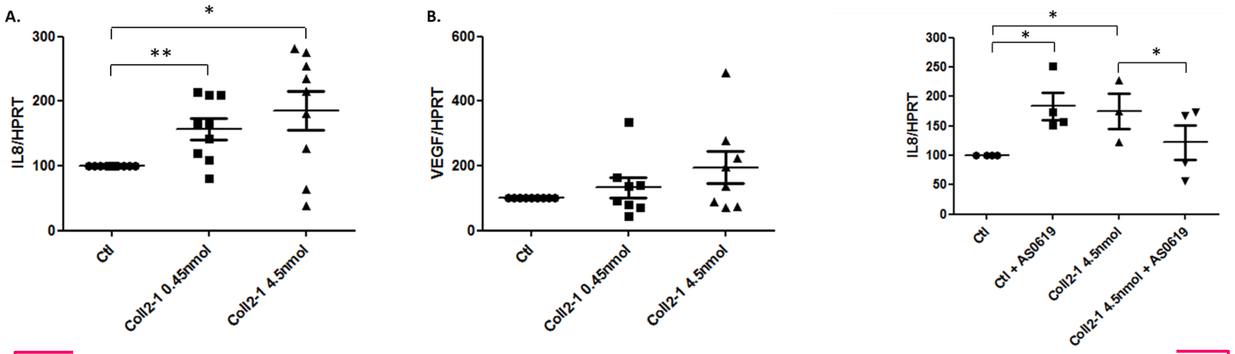

Fig. 1
Coll2-1 peptide increases IL-8 and VEGF expression by OA synovial fibroblast cells. Results are expressed as mean ± SEM (n=10). * P<0.05 and ** P<0.01.

Fig 2
AS0619, a specific Coll2-1 IgG reverses the effect of Coll2-1 peptide on IL-8 expression. Results are expressed as mean ± SEM (n=10). * P<0.05.

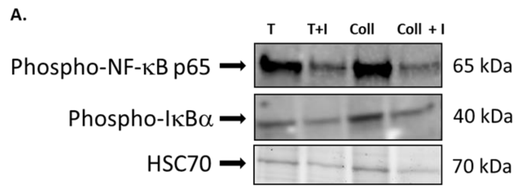

Fig. 3
Coll2-1 peptide activates the nuclear factor NF-κB. The protein extracts are probed for phospho NF-κB p65, phospho IκBα and HSC70 (control) by Western blot analysis using specific antibodies. I: apocynine (0.2mM) and diphenyleneiodonium (6.35 10^{-2}mM).

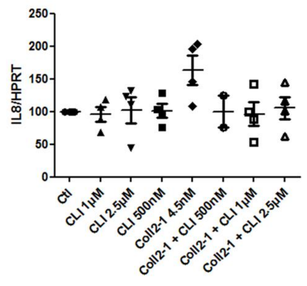

Fig 4
Coll2-1 peptide acts through TLR-4 receptors. Results are expressed as mean ± SEM (n=4). * P<0.05.

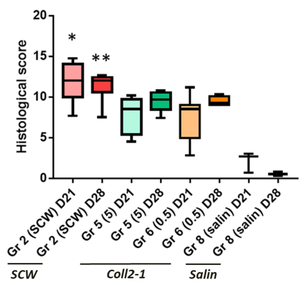

Fig. 5
Coll2-1 peptide induces an increase of the global histological score of right knees after I.A. injection. Peptide injection was compared to SCW (KW; p<0,0001). *P* values on graphs are given versus respective controls.

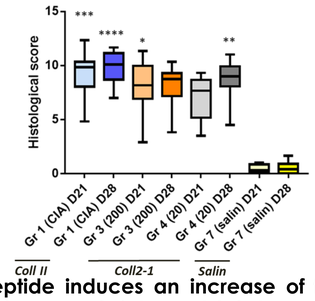

Fig 7
Coll2-1 peptide induces an increase of the global histological score of right and left knees after S.C. injection. Peptide injection was compared to CIA (KW; p<0,0001). *P* values on graphs are given versus respective controls.

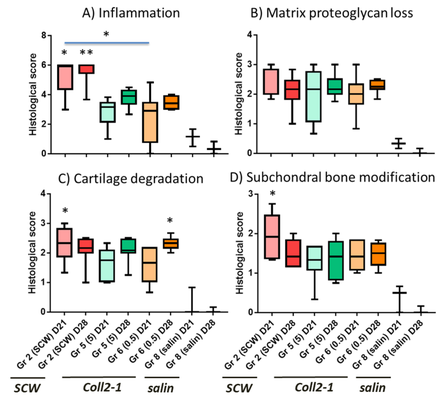

Fig. 6
Detailed criteria of evaluation for the right knee of the histological score after I.A. injection. Peptide injection was compared to SCW. A) Inflammation (0-6) (KW, p<0,0001); B) Cartilage matrix proteoglycan loss (0-3) (KW; p=0,0145); C) Cartilage degradation (0-3) (KW, p=0,0004); and D) Subchondral bone modification (0-3) (KW, p=0,0038). P values on graphs are given versus respective controls.

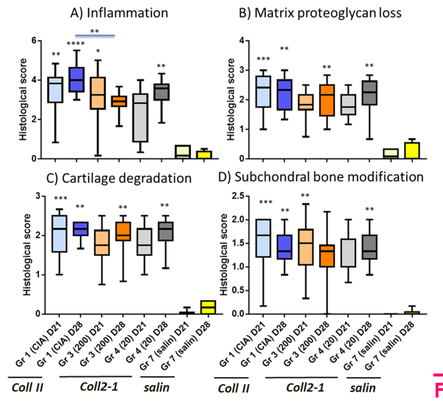

Fig 8
Detailed criteria of evaluation of the histological score after S.C. injection. Peptide injection was compared to CIA. A) Inflammation (0-6) (KW; p<0,0001); B) Cartilage matrix proteoglycan loss (0-3) (KW; p<0,0001); C) Cartilage degradation (0-3) (KW; p<0,0001) and D) Subchondral bone modification (0-3) (KW; p<0,0001). *P* values on graphs are given versus respective controls.

C O N C L U S I O N S . **Coll2-1 peptide is able to induce an inflammatory reaction and structural changes in articular cartilage and subchondral bone comparable but in a lesser extent than those induced by SCW and bovine type II collagen. Coll2-1 may initiate non-specific natural immunity and therefore is a therapeutic target for biotherapy.**