IL-18 DRIVES CARTILAGE DESTRUCTION IN MURINE OSTEOARTHRITIS

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Introduction
Interleukin-18 (IL-18) is a member of the IL-1 family of proteins that exerts proinflammatory effects. It was formally known as interferon gamma inducing factor (IGIF) and is a pivotal cytokine for the development of Th1 responses (1,2). IL-18 is structurally related to IL-1β both cytokines need interleukin-1β converting enzyme (ICE or caspase-1) for cleavage of the precursor to release the bioactive molecules for IL-1β and IL-18 (3,4). Apart from immune-stimulatory activity, IL-18 induces production of pro-inflammatory cytokines such as TNFα and IL-1 in vitro. IL-18 synthesis is found in both articular chondrocytes and osteoblasts and, with respect to cartilage, IL-18 promotes gene expression of nitric oxide synthase, inducible cyclooxygenase, IL-6 and stromelysin (5). Recently, it was shown that IL-18 levels were enhanced in synovial fluid of OA patients and that OA chondrocytes expressed IL-18, indicating a possible role of IL-18 in the pathogenesis of OA (7,8). Experimental osteoarthritis can be induced in larger animals by cutting the anterior cruciate ligament (ACL), causing defined joint instability. In the mouse this method would lead to uncontrolled damage to other tissues. However, joint instability can be induced by local injection of bacterial collagenase as has been shown previously (9). After 6 weeks major osteophytes and focal cartilage lesions in the tibia-femoral area are found, which are compatible with a biomechanical origin. The collagenase-induced OA model allows analysis of the pathogenetic mechanism in cytokine deficient mice. The goal of the present study was to investigate whether IL-18 is involved in OA pathology using IL-18 deficient mice.

Methods
Osteoarthritis was induced by intraarticular injection of 1U highly purified bacterial collagenase at days 0 and day 2 in the right knee joint. IL-18 deficient (n=30) and the control littermates (n=28) mice were used in this study and care was taken to house the IL-18 deficient and control mice under identical conditions. IL-18 deficient breeder pairs were kindly provided by Prof. Dr. S. Akira, Department of Host Defense, Osaka University, Japan. At six weeks the mice were sacrificed and knee joints were processed for histology. Cartilage lesions were scored, on a scale from 0 -30 ranging from no abnormalities to fully destroyed pathology, lateral femur, medial femur, lateral tibia and medial tibia site. Four joints were processed for histology. Cartilage lesions were scored, indicating a possible role of IL-18 in the pathogenesis of OA (7,8). Experimental osteoarthritis can be induced in larger animals by cutting the anterior cruciate ligament (ACL), causing defined joint instability. In the mouse this method would lead to uncontrolled damage to other tissues. However, joint instability can be induced by local injection of bacterial collagenase as has been shown previously (9). After 6 weeks major osteophytes and focal cartilage lesions in the tibia-femoral area are found, which are compatible with a biomechanical origin. The collagenase-induced OA model allows analysis of the pathogenetic mechanism in cytokine deficient mice. The goal of the present study was to investigate whether IL-18 is involved in OA pathology using IL-18 deficient mice.

Results
In the control group all animals (28/28) developed mild to severe form of OA, with marked cartilage lesions in the tibia-femoral plateau and pronounced osteophyte formation. Both IL-18 and ICE could be detected in the wild type animals at the sites of cartilage destruction (figure 1). IL-18 and ICE were also expressed in cartilage layers with minor destruction and in the synovial membrane of osteoarthritic joints.

IL-18

ICE

Figure 1. IL-18 and ICE protein expression in murine OA lesions

Discussion
Our results suggest a role of IL-18 in the induction of OA cartilage pathology in the mouse. Clear reduction of cartilage destruction was noted in IL-18 deficient mice. Furthermore, wild type mice expressed high levels of IL-18 and ICE, which is needed for cleavage of pro-IL-18, at the sites of cartilage destruction. This is in line with previous reports that showed IL-18 and ICE expression in human OA cartilage (7). Of high interest, IL-18 gene ablation did not reduce osteophyte formation in the murine OA joints, both IL-18 deficient and control mice develop pronounced osteophytes. This lack of effect on osteophyte formation suggest that IL-18 is not a crucial factor in this process and seems compatible with our previous research showing that TGFβ is the dominant mediator. Osteophyte formation could be blocked with TGFβ soluble receptor (10). Previous studies already identified a pivotal role of IL-18 in cartilage destruction in autoimmune arthritis (11). This is the first paper to show that IL-18 is involved in cartilage pathology in OA models. Inhibition of IL-18 generation by specific ICE inhibitors might be a cartilage protective therapy in OA.

References

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