INTRODUCTION: Increasing evidence suggests that oxidative stress may play a key role in joint destruction due to rheumatoid arthritis (RA) (1). Recent studies revealed that oxidative stress leads for example to an increase of catabolic growth factors like vascular endothelial growth factor (VEGF) (2). Several studies could show that Nrf2 is participated in the pathogenesis of different diseases like preeclampsia (3). The aim of this study was to elucidate the role of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that maintains the cellular defence against oxidative stress, in RA and in antibody induced arthritis (AIA).

METHODS: Activation status of Nrf2 was assessed in synovial tissue from RA- patients using immunohistochemistry. Antibody induced arthritis (AIA) was induced in Nrf2-knockout and wild-type control mice. The severity of cartilage destruction was evaluated via an arthritis score. The extent of oxidative stress, the activation state of Nrf2, and the expression level of Nrf2-target genes were analyzed via immunhistological staining. In addition, we used a Xenogen imaging system to measure Nrf2-activity in an ARE-luciferase transgenic mouse during AIA.

RESULTS: Nrf2 was activated both in joints of arthritic mice and of RA patients. Nrf2-knockout mice show more severe cartilage injuries and more oxidative damage, and the expression of Nrf2-target genes were enhanced in Nrf2 wild type but not in knockout mice during AIA. Both VEGF-A mRNA and protein expression was upregulated in Nrf2-knockout mice during AIA. An unexpected finding was the number of spontaneously-fractured bones in the AIA-treated Nrf2-knockout mice.

DISCUSSION: These results provide strong evidence that oxidative stress is significantly involved in the cartilage degradation in experimental arthritis and indicate that the presence of a functional Nrf2 gene is a major requirement for limiting cartilage destruction.

References