6 PERIODONTAL PATHOGENS AMPLIFY ARTHRITIC BONE EROSION BY REDUCING THE TH2 RESPONSE AND PROMOTING A TOLL-LIKE RECEPTOR 2-DEPENDENT TH17 PHENOTYPE

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Background and objectives Increased incidence of periodontal disease and association with development of anticitrullinated peptide antibodies (ACPA) in patients with rheumatoid arthritis suggest a possible pathologic link between the two diseases. The aim of the present study was to investigate the influence of periodontal pathogens on T helper cell phenotype and disease severity during experimental arthritis.

Materials and methods The effect of periodontal bacteria *Porphyromonas gingivalis* and *Prevotella nigrescens* on T cell differentiation and the involvement of toll-like receptors (TLRs) were studied using cells from wild-type and interleukin-1 (IL-1) receptor antagonist deficient mice. Invivo, mice with collagen-induced arthritis received five oral inoculations of either *P gingivalis* or *P nigrescens* every other day starting from day 14 after immunisation. Joint histopathology, gene expression in synovium, T cell phenotype and presence of ACPA were analysed on day 30.

Results *P gingivalis* and *P nigrescens* strongly induced Th17 differentiation in a co-culture of splenic antigen-presenting cells (APCs) with $CD4^+$ T cells, as measured by fluorescence-activated cell sorting analysis and IL-17 production. This effect was enormously increased in the absence of IL-1 receptor antagonist. In addition, both bacteria significantly lowered the Th2 differentiation, but were weak inducers of Th1. Using IL-$1Ra^{-/-}$ cells derived from TLR knockouts, Th17 induction was found to depend on TLR2, but not TLR4, expression on APCs; whereas the minor Th1 induction was dependent on TLR2 expression directly on T cells. Invivo, oral inoculation with *P gingivalis* and *P nigrescens* significantly increased the clinical scores of arthritis. Although no antibodies against CCP2 and citrullinated fibrinogen, α-enolase and vimentin could be detected under this condition, both bacteria substantially increased the intensity of bone erosion specifically, without influencing cartilage destruction. Analysis of T helper cell phenotype in draining lymph nodes upon pan-T cell as well as collagen II stimulations revealed a significant increase of IL-17 production, but not interferon γ. The level of IL-17 induced by periodontal bacteria strongly correlated with the intensity of bone erosion. While *P gingivalis* was the main inducer of local IL-1β, tumour necrosis factor α and cathepsin K in synovium, only *P nigrescens* caused a marked reduction of Th2/IL-4 phenotype invivo.

Conclusions This study reveals the modulation of T cell phenotype, in particular Th17 induction, as a relevant pathogenic characteristic of periodontal pathogens irrespective of ACPA induction or possession of citrullinating enzymes (present in *P gingivalis*, but not *P nigrescens*). The data further support the relevance of periodontal bacteria in pathogenesis of arthritis, especially with respect to bone erosion.

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