Publication

A crucial role for tumor necrosis factor receptor 1 in synovial lining cells and the reticuloendothelial system in mediating experimental arthritis

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INTRODUCTION: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that mainly affects synovial joints. Biologics directed against tumor-necrosis-factor (TNF)-alpha are efficacious in the treatment of RA. However, the role of TNF receptor-1 (TNFR1) in mediating the TNFalpha effects in RA has not been elucidated and conflicting data exist in experimental arthritis models. The objective is to investigate the role of TNFR1 in the synovial lining cells (SLC) and the reticuloendothelial system (RES) during experimental arthritis. METHODS: Third generation of adenovirus serotype 5 were either injected locally in the knee joint cavity or systemically by intravenous injection into the retro-orbital venous sinus to specifically target SLC and RES, respectively. Transduction of organs was detected by immunohistochemistry of the eGFP transgene. An adenoviral vector containing a short hairpin (sh) RNA directed against TNFR1 (HpTNFR1) was constructed and functionally evaluated in vitro using a nuclear factor-kappaB (NF-kappaB) reporter assay and in vivo in streptococcal cell wall-induced arthritis (SCW) and collagen-induced arthritis (CIA). Adenoviruses were administered before onset of CIA, and the effect of TNFR1 targeting on the clinical development of arthritis, histology, quantitative polymerase chain reaction (qPCR), cytokine analyses and T-cell assays was evaluated. RESULTS: Systemic delivery of Ad5.CMV-eGFP predominantly transduced the RES in liver and spleen. Local delivery transduced the synovium and not the RES in liver, spleen and draining lymph nodes. In vitro, HpTNFR1 reduced the TNFR1 mRNA expression by three-fold resulting in a 70% reduction of TNFalpha-induced NF-kappaB activation. Local treatment with HpTNFR1 markedly reduced mRNA and protein levels of interleukin (IL)-1beta and IL-6 in SLC during SCW arthritis and ameliorated CIA. Systemic targeting of TNFR1 in RES of liver and spleen by systemic delivery of Ad5 virus encoding for a small hairpin RNA against TNFR1 markedly ameliorated CIA and simultaneously reduced the mRNA expression of IL-1beta, IL-6 and Saa1 (75%), in the liver and that of Th1/2/17-specific transcription factors T-bet, GATA-3 and RORgammaT in the spleen. Flow cytometry confirmed that HpTNFR1 reduced the numbers of interferon (IFN)gamma (Th1)-, IL-4 (Th2)- and IL-17 (Th17)-producing cells in spleen. CONCLUSIONS: TNFR1-mediated signaling in both synovial lining cells and the reticuloendothelial system independently played a major

pro-inflammatory and immunoregulatory role in the development of experimental arthritis.
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