LYMPTOTOXIN α STIMULATES PROLIFERATION AND PROINFLAMMATORY CYTOKINE SECRETION OF RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES

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10.1136/ard.2010.129650e

Background and Purpose  Lymphotoxin α (LTα) is a proinflammatory cytokine with structural homology with tumour necrosis factor α (TNFα). Both cytokines bind to the receptors TNFRI and TNFRII, and LTα also binds to the herpes virus entry mediator (HVEM). Increased LTα levels have been detected in patients with rheumatoid arthritis (RA), but its role in RA is poorly characterised. To elucidate its role in comparison with TNFα, we analysed the effect of LTα in cultured RA fibroblast-like synoviocytes (FLS).

Methods  RA FLS were extracted from synovial tissues of patients who met the ACR criteria for RA (revised 1987). Surface expression of receptors was analysed by FACS. Cells were stimulated with 0.5 nM LTα or TNFα for 24h and apoptosis was measured by annexin-V/TOPRO-3. After 72h of stimulation, proliferation was evaluated by measuring DNA synthesis through incorporation of tritiated [3H] thymidine and secretion of inflammatory cytokines by ELISA. Activation of MAP kinases and Akt was analysed by western blotting and nuclear translocation of NF-κB by immunofluorescence. Differences between experimental groups were evaluated by ANOVA followed by Tukey post-test.

Results  60–80% and 30–50% of the RA FLS tested expressed TNFRI and TNFRII, respectively, and 7–10% expressed HVEM. In comparison with non-stimulated cells, LTα induced proliferation 4-fold, such as TNFα. LTα- and TNFα-induced proliferation was significantly blocked by etanercept. Both LTα and TNFα induced phosphorylation, thus activation of MAP kinases ERK 1/2 and p38 as well as Akt. Specific inhibitors for the MAP and PI3 kinases blocked proliferation induced by LTα and TNFα. 95–98% of RA FLS showed nuclear translocation of NF-κB after stimulation with either cytokine. Both LTα and TNFα were potent to induce secretion of interleukin (IL)6, IL8 and metalloproteinase-3 in RA FLS.

Conclusions  LTα is as effective as TNFα in stimulating RA FLS. Blocking both cytokines might allow a better control of inflammation and synovial proliferation observed in RA.

This work was supported by Wyeth and GERIR.
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*Ann Rheum Dis* 2010 69: A61
doi: 10.1136/ard.2010.129650e

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