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A78 MECHANISMS AND CLINICAL RELEVANCE OF TRAIL-TRIGGERED RESPONSES IN SYNOVIAL FIBROBLASTS OF RHEUMATOID ARTHRITIS PATIENTS

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Objective We have shown that TRAIL induces apoptosis only in a portion of RA fibroblast-like synoviocytes (RAFLS) and that in the surviving cells, TRAIL induced proliferation. In the present study, we compared RAFLS-resistant and RAFLS-sensible to TRAIL-induced apoptosis including levels of the TRAIL receptors (TRAIL-R) and clinical features of respective patient. We evaluated TRAIL and its soluble decoy receptor osteoprotegerin (OPG) levels in RA patients, osteoarthritis (OA), spondylarthritis (SpA).

Methods FLS were extracted from synovial tissues of RA patients (n=30) and analysed by FACS for TRAIL-receptors expression. We obtained DAS28 within the 3 months of surgery for 13 patients. TRAIL-responses of FLS were analysed by AnnexinV for apoptosis, thymidine-incorporation for proliferation. TRAIL receptor activity was assessed by RNA silencing. HIC were performed to evaluate TRAIL level in synovial tissues from RA (n=7) and OA patients (n=4). ELISA was used to determine TRAIL-levels in synovial fluid of OA; n=20), SpA; (n=20) and establish RA patients (n=30). Serum levels of TRAIL and OPG were measured in 72 patients fulfilling the ACR criteria (1987) with recent (<2 years) and active (>3 swollen joints) RA that were not treated or had a stable background treatment for at least 1 month. 48 of the RA patients were followed up at 6 months.

Results Disease severity of RA patients inversely correlated with susceptibility of FLS to TRAIL-induced apoptosis ($r=0.753$, $p=0.011$). TRAIL-sensitive cells expressed significantly lower levels of the decoy TRAIL-R4 ($p=0.008$) and surprisingly also of TRAIL-R1 ($p=0.014$), one of the described death receptor. Silencing of these two receptors increased TRAIL-induced apoptosis in RAFLS. TRAIL levels were elevated in the arthritic joints of patients with established RA compared to other patients ($p<0.001$). A low ratio OPG/TRAIL in sera of early RA patients at baseline was associated with a better evolution of disease activity ($p=0.028$), but high serum levels of TRAIL at follow-up were associated with joint damages ($p=0.0063$).

Conclusion Surprisingly, TRAIL-R1 seems to be a survival factor protecting RAFLS against TRAIL-induced apoptosis.

The negative correlation between TRAIL sensitivity in vitro and RA activity suggests that RAFLS develop resistance to escape TRAIL protective role. Indeed, in early RA patients, a low OPG/TRAIL ratio at baseline was associated with remission at 6 months but persistent TRAIL serum levels are associated with joint damage. These findings suggest a dual role for TRAIL in RA and resistance of RAFLS to TRAIL-induced apoptosis is associated with a disease promoting activity of TRAIL in RA.

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