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T CELL PROLIFERATIVE RESPONSE TO TYPE II COLLAGEN IS MORE PREVALENT AND STRONGER IN EARLY STAGE OF RHEUMATOID ARTHRITIS.

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Objective: We previously demonstrated that T cell responses to type II collagen (CII) were enhanced in rheumatoid arthritis (RA) (Arthritis Rheum, S164, 1998). To further characterize the pathologic role of T cell responses to CII in patients with RA, we analyzed the association of T cell responses to CII with clinical and laboratory features of RA.

Methods: T cell proliferative responses to bovine native CII were assayed in peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC) obtained from RA patients by mixed lymphocyte culture. The clinical and laboratory variables were investigated at the time of sampling.

Results: In PBMC (n=95), patients with positive T cell response to CII (defined as stimulation index: SI≥2, n=35) often had a shorter disease duration than those (n=60) with negative responses (median months 84 [range, 12-331] versus 103.5 [range, 4-359] months, p=0.021). Positive T cell responses and median SI in PBMC were significantly higher in early RA (<3 years, n=19) than late RA (>3 years, n=76) (68.4% and 2.12 for T cell responsiveness and median SI for the early group versus 28.9% and 1.62 for the late group, p=0.001 and 0.021, respectively). There is a trend for positive T cell responses to decrease over time (72.7% [8/11] in < 2 years, 47.4% [9/19] in 2-5 years, 27.7% [18/65] in >5 years). In SFMC (n=42), positive T cell responses and median SI also tended to be higher in early RA (n=8) than in late RA (n=34) (62.5% and 2.27 versus 50.0% and 1.93, p=NS). The positive responses and SI with CII were significantly higher in SFMC than PBMC in late RA (p=0.03, p=0.004, respectively). However, no differences were found in age, sex, levels of ESR and CRP, rheumatoid factor positivity, HLA-DR1 (+) and/or HLA-DR 4 (+), the presence of erosion within early or late RA patients, and extraarticular manifestations such as vasculitis, rheumatoid nodule and sicca symptom between patients with positive T cell response to CII and those with negative responses.

Conclusion: T cell proliferative responses to CII were more prevalent and stronger in early RA. T cell responses to CII in SFMC were more potent than PBMC responses in late RA. These findings suggest that autoimmune T cell responses may be intrinsic to the pathogenesis of RA yet may also involve in perpetuating immune reaction in the joints of long standing RA patients.

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THE ROLE OF INTERLEUKIN-12 IN INFLAMMATORY ACTIVITY OF PATIENTS WITH RHEUMATOID ARTHRITIS.

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Objective: To investigate the role of interleukin-12 (IL-12) in patients with rheumatoid arthrtis (RA).

Methods: Levels of IL-12 (p70) and associated TH1/TH2 cytokines were measured in sera and synovial fluid (SF) by enzyme-linked immunosorbent method. Seven ACR core set measures as well as IL-12 levels were sequentially monitored at baseline and 4 months after treatment.

Results: In the sera, sixty four (42.2%) of 152 RA patients had detectable concentration of IL-12 (p70), whereas one (1.4%) of 69 OA patient and 5 (10%) of 50 healthy control had detectable IL-12 (p<0.001). The median level of circulating IL-12 was also higher in RA patients (p<0.001). In the SF, the number of patients with detectable IL-12 and the median IL-12 level were significantly higher in RA patients (n=53) than in OA patients (n=22) (p=0.001 and p<0.001). In paired samples (n=53) of the serum and SF from RA, IL-12 levels were higher in the SF compared to the sera (p<0.001). Patients with detectable IL-12 (n=51) in sera had higher tender joints score (p=0.003), swollen joints score (p<0.001) and CRP (p=0.036) compared to those without (n=55). Levels of circulating IL-12 correlated well with tender joint (r=0.469, p<0.001), swollen joint count (r=0.453, p<0.001), visual analogue pain scale (r=0.279, p=0.005), physician's global assessment (r=0.267, p=0.008), patient's global assessment (r=0.231, p=0.02) and CRP (r=0.238, p=0.014). Four months after treatment, improved group had a higher degree of IL-12 decrease compared to non-improved group along with clinical improvement (p=0.017). Circulating IL-12 positively correlated with IL-6 (r=0.432, p<0.001) and TNF-α (r=0.315, p=0.002), but inversely correlated with IL-10 (r= -0.323, p=0.002). In the SF, patients (n=23) with detectable IL-12 had higher levels of IL-2 (p=0.011), INF-γ (p<0.001), TNF-α (p=0.007) and IL-6 (p=0.002) compared to those (n=30) without. The levels of IL-12 in the SF correlated well with IL-6 (r=0.449, p=0.001), TNF-α (r=0.481, p<0.001) and INF-γ (r=0.369, p=0.007).

Conclusion: Our results suggest that IL-12 reflect disease activity of RA and is involved in the production of proinflammatory cytokines and in a shift T cells with TH1 cytokines. IL-12 blockade could be useful for the treatment of RA.