

INCREASE OF CYCLOOXYGENASE-2 EXPRESSION BY IL-15 IN RHEUMATOID SYNOVIOCYTES.

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Objective: To determine the effect of IL-15 on the expression of cyclooxygenase-2 (COX-2) in rheumatoid synoviocytes.

Methods: Fibroblast-like synoviocytes (FLS) were prepared from the synovial tissues of rheumatoid arthritis (RA) patients and cultured in the presence of IL-15. The expression of COX-2 mRNA and protein was determined by RT-PCR and Western blot analysis, respectively. The production of IL-15 by FLS was measured in culture supernatant by ELISA.

Results: IL-15 (0.1 to 10 ng/ml) dose-dependently increased COX-2 mRNA expression in FLS, but not COX-1 mRNA level. COX-2 protein in FLS was also specifically induced by IL-15. Both IL-1 (10 ng/ml) and TNF- (10 ng/ml) up-regulated COX-2 mRNA comparable to 10 ng/ml of IL-15, whereas neither IL-2 nor IFN- had effect on it. Treatment with anti-IL-1 or anti-TNF- monoclonal antibodies partially reduced IL-15-stimulated COX-2 mRNA expression, suggesting that these cytokines may partake in the modulation of COX-2 by IL-15. Dexamethasone and pyrrolidine dithiocarbamate, but not curcumin, completely blocked IL-15-induced up-regulation of COX-2, indicating that NF-B is the major signal to mediate the COX-2 induction by IL-15. In addition, selective COX-2 inhibitor, NS-398 and rofecoxib, strongly inhibited the production of IL-15 by FLS stimulated by IL-1.

Conclusion: Our data demonstrate IL-15 strongly increases the COX-2 expression, which may be involved in IL-15 production, constructing a positive feedback loop in rheumatoid inflammation.

FUNCTIONAL PROMTER POLYMORPHISM IN MATRIX METALLOPROTEINASE-1 AND RHEUMATOID ARTHRITIS

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Purpose: To investigate whether the functional promoter polymorphism in matrix metalloproteinase-1(MMP-1) is associated with susceptibility to rheumatoid arthritis(RA) and its clinical features.

Methods: The MMP-1 1G/2G polymorphism was determined by polymerase chain reaction-restriction fragment length polymorphism in 116 RA patients and 68 healthy control subjects. Clinical manifestations were analyzed in each patient and correlated with the genotypes.

Results: The genotype distribution of the MMP-1 promoter did not differ between RA patients and control subjects(1G/1G, 1G/2G, 2G/2G genotypes 11, 36, 69 vs. 10, 23, 35 controls respectively, chi-squared = 1.62, 2 df, $p = 0.45$). Clinically there was no significant difference in physician global assessment, severity, functional class, CRP, RF titer, WBC, Hb except for ESR, platelet(Plat) count in RA patients according to the MMP-1 promoter genotypes. In 2G/2G genotype, ESR and Plat were the most highest in comparison with 1G/1G and 1G/2G genotypes (ESR(mm/hr) 47 ± 28 vs. 27 ± 16 , 35 ± 22 , Plat($10^3/\mu\text{L}$) 331 ± 130 vs. 270 ± 70 , 271 ± 84 , $p < 0.05$).

Conclusions: Our data show that the functional polymorphism in the MMP-1 promoter may not play an important role in the susceptibility of RA, but the polymorphism may be related to clinical phenotypes, such as ESR or Plat in RA.