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PPAR-? ligands suppress arthritis in rats

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Keywords

Adjuvant-induced arthritis, apoptosis, PPAR-? ligands

Context

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcriptional factors of nuclear hormone receptor super family with some immunomodulatory properties. Various lipid or prostaglandin molecules have been proposed as natural PPAR-? ligands. Recent studies have shown that the PPAR-? ligands 15d-PGJ_2, and troglitazone (a synthetic anti-diabetic) induce apoptosis in various cell types and inhibit nitric oxide (NO), tumor necrosis factor (TNF)-a, interleukin (IL)-1?, and IL-6 synthesis by antagonizing the activities of AP-1 and NF- B transcription factors. Therefore, the authors investigated the expression of PPAR-? in synovial tissues and in cultured synoviocytes of rheumatoid arthritis (RA) patients.

Significant findings

PPAR-? expression was detected in synovial tissues of all RA and OA patients in RA patients the expression was marked in macrophages and moderate in synovial cells , endothelial cells, and fibroblasts. The expression was lower in cells from OA patients. Untreated cultured synoviocytes showed both cytoplasmic and nuclear expression but 15d-PGJ_2 treated cells showed nuclear translocation of PPAR-?. PPAR? mRNA and protein were produced by synoviocytes of RA patients and detected using RT-PCR and western blot analysis. PPAR-? ligands, troglitazone and 15d-PGJ_2 effectively inhibited synoviocyte proliferation and induced classic apoptotic changes in these cells. Intraperitoneal administration of 15d-PGJ_2 and troglitazone ameliorated AIA in Lewis Rats, suggesting that PPAR-? ligands have ani-inflammatory and growth-inhibitory effects on synovial cells without obvious side effects.

Comments

Several inflammatory mediators (prostaglandin E2, cytokines, and nitric oxide) are involved in the pathogenesis of rheumatoid arthritis (RA). Understanding the molecular mechanisms by which these inflammatory molecules mediate the pathogenic process is important for designing therapeutic interventions. The present study elegantly demonstrates the presence of PPAR-? in the synovial tissues from RA patients. More importantly they show that the PPAR-? ligands 15-deoxy-?^{12,14}-prostaglandin J_2 (15d-PGJ_2) and thiazolidinedione (troglitazone) induce apoptosis in RA synoviocytes *in vitro*. Furthermore, treatment with 15d-PGJ_2 and thiazolidinedione significantly improves symptoms in an adjuvant-induced arthritis (AIA) Lewis rat model without significant side effects. The precise mechanism of action of these agents needs to be studied in more detail.

Methods

Synovial tissues from RA and osteoarthritis (OA) patients were used. Synovial tissues and cultured cells from these tissues were immunostained with anti-human PPAR- and the extent and intensity of staining was graded on various cell types. The PPAR- mRNA and protein expression was studied by RT-PCR and Western blotting. The cell proliferation and growth-inhibitory activities were studies by MTT assay. Apoptosis in cultured synovial cells was detected by Hoechst staining and propidium iodide. Female Lewis rats were used for arthritis induction and 15d-PGJ_2or troglitazone treatment.

References

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