The role of TCDD and AhR in RA pathogenesis
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Introduction: Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis, characterized by chronic inflammation of the synovial tissues in joint and causes progressive joint destruction and disability. Although the pathogenesis of RA is still unknown, it is widely believed that both genetic factors and environmental factors are involved in the pathogenesis of RA. Recently, epidemiological studies have suggested that smoking is an environmental risk factor for RA (1-3), but the mechanism of smoking effect on RA is still not understood. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is one of the major toxic components in cigarettes. It is known that exogenous TCDD binds to the aryl hydrocarbon receptor (AhR) in the cytoplasm and then translocates it into the nucleus ultimately resulting in carcinogenesis, teratogenesis and immune system impairment (4-7). TCDD have been reported to regulate expression of several pro-inflammatory cytokines in various cells, such as macrophage (8, 9), B cells (10), keratinocytes (11, 12), splenocytes (13), A549 cells (14), but association between TCDD and RA synovialcyte is not well understood. We investigated the role of TCDD and AhR in the pathogenesis of RA.

Materials and Methods: Human synovial tissues were obtained from RA and OA patients who were undergoing total knee replacement. AhR expression in synovial tissues from RA and OA patients were evaluated using immunohistochemistry and real time PCR. Expression of various cytokines were measured by ELISA and real time PCR following stimulation of RA synoviocytes with different concentrations of TCDD (0.01-100nM). To study the role of AhR, we treated RA synoviocytes with alpha naphthoflavone, a known AhR antagonist. Towards an understanding of the signal transduction pathways stimulated by the TCDD-AhR interaction, we used inhibitors of NF-κB and ERK. In order to study the effect of cytokines on AhR expression, we stimulated RA synoviocytes with various cytokines and measured AhR expression using a real time PCR assay.

Results: Higher AhR mRNA and protein levels were observed in RA synovial tissues than in OA tissues. TCDD up-regulated the expression of IL-1β, IL-6 and IL-8 at both the mRNA and protein levels. The stimulatory effect of TCDD was mediated through binding to AhR, and this effect was transmitted to the NF-κB and ERK signaling cascades. AhR expression in synovial cells was up-regulated by TNFα.

Discussion: TNFα plays an important role in the pathogenesis of RA and clinical use of a TNFα inhibition strategy has been shown to be beneficial for the treatment of RA. Our study indicates that TNFα activates expression of AhR in RA synovial tissues. Cigarette smoking and exposure to TCDD enhances the inflammatory process of RA. TCDD induces inflammatory cytokines via its association with AhR resulting in the stimulation of the NF-κB and ERK signaling cascades. Our data suggests that smoking or TCDD exposure exacerbates RA pathophysiology via its receptor AhR.