HISTONE DEACETYLASE INHIBITORS PREVENT INTERLEUKIN-1-INDUCED MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 EXPRESSION IN HUMAN CHONDROCYTES: ROLE OF EGR-1

Montreal Univ., Montreal, QC, Canada

Purpose: Microsomal prostaglandin E synthase-1 (mPGES-1), an inducible enzyme, catalyzes the terminal step in the biosynthesis of PGE2, which plays a critical role in the pathogenesis of osteoarthritis (OA). mPGES-1 is strongly induced by inflammatory cytokines and is upregulated in OA cartilage. Egr-1 is a key transcription factor in inducible mPGES-1 expression. In the present study, we examined the effect of three histone deacetylase (HDAC) inhibitors, trichostatin A (TSA), valproic acid (VA), and butyric acid (BA) on IL-1-induced mPGES-1 expression. Egr-1 expression and Egr-1 DNA-binding activity in human OA chondrocytes.

Methods: Chondrocytes were stimulated with IL-1 in the absence or presence of increasing concentrations of TSA, VA or BA. The expression of mPGES-1 and Egr-1 proteins and mRNAs was evaluated using Western blotting and real-time reverse transcriptase-polymerase chain reaction (RT-PCR), respectively. Electrophoretic mobility shift assay (EMSA) was utilized to analyze the DNA-binding activity of Egr-1 in vitro, and Chromatin Immunoprecipitation (ChIP) was used to evaluate the recruitment of Egr-1 to the mPGES-1 promoter in vivo.

Results: Treatment with each of the HDAC inhibitors (TSA, VA and BA) reduced IL-1-induced mPGES-1 protein expression in a dose-dependent manner. The induction of mPGES-1 mRNA expression was also dose-dependently inhibited. Treatment with HDAC inhibitors did not alter IL-1-induced Egr-1 expression. Finally, we demonstrate that the HDAC inhibitors did not affect the DNA-binding activity of Egr-1 nor its binding to the endogenous mPGES-1 promoter.

Conclusions: These data indicate that HDAC inhibitors suppress IL-1-induced mPGES-1 expression. The suppressive effect of HDAC inhibitors is not due to impaired expression of Egr-1 nor to its DNA-binding activity. These findings also suggest that HDAC inhibitors may be of potential therapeutic value in the treatment of OA.

ASSOCIATION OF LEPTIN GENE (LEP) WITH KNEE OSTEOARTHRITIS SUSCEPTIBILITY IN HAN CHINESE

Q. Jiang, J. Qin, J. Dai, L. Zhu, D. Shi
Ctr. of Diagnosis and Treatment for joint disease, Nanjing, China

Purpose: Former studies suggested that leptin worked as a key regulator in the pathogenesis of osteoarthritis (OA). This study assessed the contribution of leptin gene polymorphism to knee OA in Chinese Han population.

Methods: 3 tag SNPs of LEP were selected by haploviewwer software from Hapmap database. They cover all the SNPs of LEP whose heterozygosity rate are over 10%. We genotyped the selected SNPs in 719 patients who had symptomatic knee OA with radiographic confirmation and 699 age matched controls, compared allelic and genotypic frequencies and haplotype distribution.

Results: Statistical difference was observed in body mass index (BMI) (P<0.0001) but not in age between case and control groups in Chinese Han populations (P=0.257). After stratification by gender, associations were observed with allele frequency (T vs. C, P=0.037) and genotype (CC vs. others, P=0.046) in rs2071045, and haplotype AGT shows a significant difference (P=0.010) in fe-

VARIATION IN THE GENE ENCODING CYTOSOLIC GROUP IVA PHOSPHOLIPASE A2 IS ASSOCIATED WITH BOTH SYSTEMIC LUPUS ERYTHEMATOSUS AND OSTEOARTHRITIS

1Dept Genetics and Pathology, Uppsala Univ., Uppsala, Sweden; 2Academic Rheumatology, Univ Nottingham, Nottingham, United Kingdom; 3Kings Coll. London, London, United Kingdom; 4Inst Parasitología y Biomedicina Lopez Neyra, CSIC, Granada, Spain; 5Oklahoma Med. Res. Fndn., Oklahoma City, OK; 6Dept Genetics and Pathology, Uppsala Univ, Uppsala, Sweden

Purpose: Cytosolic group IVA phospholipase A2 (cPLA2a), encoded by PLA2G4A, catalyzes the rate-limiting step in the production of pro-inflammatory eicosanoids and free radicals. This enzyme is involved in receptor-activated signalling cascades, in particular MAPK/p38 and has been shown to play pivotal roles in several physiological processes. We hypothesized that variation in this gene could affect susceptibility to systemic lupus erythematosus (SLE), a systemic autoimmune and inflammatory disease characterized by autoantibody production and involvement of multiple organ systems and a variety of symptoms, including arthropathy. Variants near the PLA2G4A gene have also been implicated in risk of osteoarthritis (OA), the most common form of arthritis in the elderly. We assessed the role of genetic variation in the PLA2G4A gene in susceptibility to SLE, knee OA and hip OA.

Methods: We genotyped 18 variants in the PLA2G4A gene and identified 3 markers significantly associated with SLE in 1781 cases and 2254 controls from Argentina, Belgium, Germany, Hungary, Italy, Portugal, Spain and Sweden. The four PLA2G4A markers showing the strongest association with SLE were subsequently typed in 2190 OA cases and 1535 controls from the UK.

Results: Three markers in the PLA2G4A were found to be nominally significantly associated (p<0.05) with SLE. All three of them and an additional marker with p<0.20 with SLE were typed in OA samples and were found to be significantly associated with risk of knee OA. Two of the markers were also significantly associated with risk of total hip replacement. Overall the strongest association with SLE was seen at rs17591814 (ORsLE = 0.87 95%CI 0.79-0.95 p<0.0078 ORkneeOA = 0.87 95%CI 0.72-0.93 p<0.034 ORhipOA = 0.82 95%CI 0.73-0.91 p=0.20) with SLE were typed in OA samples and were found to be significantly associated with risk of knee OA. Two of the markers were also significantly associated with risk of total hip replacement. Overall the strongest association with SLE was seen at rs17591814 (ORsLE = 0.87 95%CI 0.79-0.95 p<0.0078 ORkneeOA = 0.87 95%CI 0.77-0.98 p<0.025; ORhipOA = 0.95 95% CI 0.83-1.09 n.s.) and the strongest association with OA was seen at rs726706 (ORsLE = 0.90 95%CI 0.81-0.98 p=0.034 ORkneeOA = 0.82 95%CI 0.73-0.91 p<2.4×10^-4; ORhipOA = 0.82 95% CI 0.72-0.93 p<0.0016).

Conclusions: Our data indicate that genetic variation in this key enzyme regulating immunoinflammatory reactions is involved in susceptibility to both SLE and OA, in spite of the fact that these arthropathies have extremely different manifestations. This work was supported by the Arthritis and Research Campaign and by the EU FP7 large collaborative project grant 200800 TREAT-OA, the Swedish Research Council of Medicine and the Torsten and Ragnar Söderbergs Foundation, the EU FP6 grant CVDIMMUNE, and grants SAF2006-00398 and CTS1180.