Session: Disease & Treatment

15 GENOME-WIDE INTERACTION ANALYSIS BETWEEN MITOCHONDRIAL SNPs AND NUCLEAR SNPs ON OSTEOPOROSIS
Ya-Qian Hu a, Liu Yang b, Yan Guo a,b
Xijing Hospital, The Fourth Military Medical University, China
Xian Jiaotong University, China

Osteoporosis is a typical complex disease of reduced bone mineral density (BMD). Previous studies demonstrated that mitochondrial single nucleotide polymorphisms (mtSNPs) and nuclear SNPs (nSNPs) are involved in the pathogenesis. However, possible mtSNP-nSNP interactions of most non-significant SNPs were usually ignored and led to missing heritability. In this study, we performed a genome-wide association study (GWAS) to explore potential mtSNP-nSNP interactions contributing to osteoporosis susceptibility in a sample of 2,286 Caucasian subjects. Correlation analysis was carried out for 44 mtSNPs and 562,011 nSNPs on spine and hip BMD. Eventually, we found interactions involving 5 mtSNPs and 26 nSNPs that correlated with BMD (without interaction analysis, these SNPs did not show any significant correlation with BMD). Four pairs of the most significant interaction SNPs with BMD were: mtSNP ND5-rs3135030 and nSNP RORB-rs950058 (P = 8.05 x 10^-14, spine BMD), mtSNP Cytb-rs28357375 and nSNP TOMM20-rs4920161 (P = 1.28 x 10^-12, spine BMD), mtSNP Cytb-rs28357375 and nSNP VRK2-rs2678919 (P = 2.61 x 10^-11, spine BMD), mtSNP Cytb-rs283573847 and nSNP CAMTA1-rs871443 (P = 3.85 x 10^-12, hip BMD). Besides, there were three newly reported genes: ZNF518B, RMST, and APPADC1A, with more than one significant nSNPs. These results provide new insights into the pathogenesis of osteoporosis.

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33 ATTENUATION OF COLLAGEN-INDUCED ARTHRITIS BY POTENTIAL ANTI-INFLAMMATORY DRUG GENISTEIN IN DBA/1 MICE
Yiping Hu, Wenxiang Cheng, Peng Zhang
Center for Translational Medicine Research and Development, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

Background: This work aimed to evaluate the effects of genistein treatment CIA in mice. The CIA model was used to observe the treatment effects of genistein. Methods: After the onset of arthritis, animals were divided into two groups according to their clinical symptom scores. The treatment group was intraperitoneally injected daily with genistein (based on the pre-experiment data and literature review, a 5 mg/kg dose was selected and tested) for 12 days, whereas phosphate buffered saline was treated as a control group. Immunohistochemical analysis was performed to investigate the expression and distribution of VEGF in joint tissues.

Results: Genistein reduced the secretions of IL-1β, IL-6 and TNF-α in the serum. Radiological results showed that bone degradation was inhibited by the treatment. Moreover, haematoxylin and eosin staining showed that the degree of inflammation was significantly alleviated. TRAP stain-positive cells were also detected in the destruction of the articular cartilage, which was significantly reduced in the treatment group compared with the control group. Micro-CT 3D images clearly exhibited that the joint adhesions and structures were destroyed in the control group. Furthermore, genistein suppressed VEGF expression and blocked angiogenesis in the synovial tissue.

Conclusion: This study provides further evidence regarding the effects of genistein as a potential treatment drug for RA, as well as the role of genistein in the anti-inflammatory pathway in RA therapy.

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36 CXCR1 KNOCKDOWN IMPROVES THE SENSITIVITY OF OSTEOSARCOMA TO CISPLATIN
Xiuguo Han, Tingting Tang
Shanghai Jiaotong University of Medicine, China

Introduction: Chemoresistance is one major cause of the poor prognosis of osteosarcoma. Cisplatin is one of the basic drugs of osteosarcoma chemotherapy, but many patients showed resistance to cisplatin in osteosarcoma treatment. Objectives: The aim of this study is to investigate if CXCR1 knockdown could improve the cisplatin sensitivity of osteosarcoma and the depth of molecular mechanisms.

Methods: 1. Comparison of the cisplatin sensitivity of the highly metastatic Saos2-lung osteosarcoma cells and its parental Saos2 cells: Two osteosarcoma cell lines, including the Saos2 and Saos2-lung, which is a highly metastatic osteosarcoma cell line derived from Saos2, were treated with cisplatin and their sensitivity to cisplatin was compared by a CXCR1 knockdown test and an apoptosis assay. The expression of CXCR1 was detected by Western Blot. 2. Sensitivity of osteosarcoma cells to cisplatin treatment and the molecular mechanisms after CXCR1 knockdown: Saos2 and Saos2-lung cells were transfected with two shRNA against CXCR1 sequences by lentivirus. The chemotherapy sensitivity to the cisplatin with or without the stimulation of IL-8 was determined and Western blot was used to test the activation of the Akt signalling pathway. 3. Cisplatin sensitivity of Saos2-lung cells after CXCR1 knockdown in vivo: The Saos2-lung with luciferase labelling with CXCR1 knockdown or control cells were injected into the bone marrow cavity of the tibia of nude mice with cisplatin treatment. The tumour size and the luciferase intensity of nude mice bearing tumours were detected. The expression of IL8, CXCR1, p-Akt, PCNA, and Cleaved-Caspase-3 were also determined by immunohistochemistry.

Results: 1. Comparison of the cisplatin sensitivity of the highly metastatic Saos2-lung osteosarcoma cells and its parental Saos2 cells: The cisplatin chemotheraphy sensitivity of Saos2 cells is stronger than Saos2-lung cells, which have higher expression of CXCR1. 2. Sensitivity of osteosarcoma cells to cisplatin treatment and the molecular mechanisms after CXCR1 knockdown: CXCR1 knockdown cell line of Saos2 and Saos2-lung cells has been established, respectively. CXCR1 knockdown improved the cell’s sensitivity to the cisplatin greatly and IL-8 could reduce the chemotheraphy sensitivity of osteosarcoma cells, which could be blocked by CXCR1 knockdown. Western Blot showed that CXCR1 knockdown suppressed the Akt signal pathway, which was activated by IL-8. 3. Cisplatin sensitivity of Saos2-lung cells after CXCR1 knockdown in vivo: Compared with the control group, the tumour size was reduced greatly, which was consistent with the luciferase intensity. The expression of IL8, CXCR1, p-Akt, and PCNA were suppressed and Cleaved-Caspase-3 was increased in CXCR1 knockdown groups under the treatment of cisplatin.

Conclusion: Knockdown of CXCR1 in osteosarcoma cells could improve its chemotheraphy sensitivity to cisplatin, which may be regulated partly by the IL-8/CXCR1/Akt signalling pathway. CXCR1 will be a new target for osteosarcoma treatment.

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