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The study on the relationship between selenium and Kashin-Beck Disease

Background: Kashin-Beck Disease (KBD) is an endemic, disabling and deforming osteoarthropathy and mainly affects children or teenagers in growth and development period. The mainly pathological changes in KBD are degeneration and necrosis in joint cartilage and epiphyseal plate cartilage. The disease has been found over 160 years, but, its etiology remains unclear. Epidemiological investigation of environmental risks has shown that selenium deficiency may contribute to the etiopathogenesis of KBD and Se supplementation could significantly decrease the incidence of KBD. However, the exact molecular mechanism for KBD treatment with Se is still obscure.

Objective: Screening of KBD susceptibility genes and related functional experiments were conducted in order to illuminate molecular mechanism of selenoprotein on cartilage cell oxidative stress, inflammation and apoptosis signaling pathway, and further search new molecular targets for the early diagnosis, warning and treatment of KBD.

Methods: Selenoprotein gene transcription level, protein expression level and enzymatic activity in KBD and normal blood and cartilage samples were detected by using qRT-PCR, ELISA and Western blot, respectively. Selenoprotein SNPs were detected by using PCR-RFLP and ARMS-PCR.

Results: The mRNA expression of GPx1, GPx4, SEPP, TrxR and DIO2 in whole blood decreased in the KBD group compared to controls, and mRNA expression of GPx1, GPx4 and DIO2 in cartilage decreased in the KBD group compared to controls. GPx1Pro198Leu, GPx4Haplotype (rs713041, rs4807542), SEPS1 (rs28665122, rs34713741), SEP15 rs5859 displayed significant differences in genotypic and allelic frequency between the KBD and control groups, while TrxR2 (rs5748469, rs1139793, rs5746841), SEPP1 (rs7579) and DIO2 (rs225014) showed no significant differences. The protein expression levels of PI3K/Akt, ERK, JNK, Nrf2-ARE, NFkB and AP1 signal molecule in KBD group were significantly higher than that in control group. In genotype subgroup analyses, GPx enzyme activity decreased in the variant genotype GPx1Pro198Leu, and PI3K/Akt signaling pathway was up-regulated in the variant genotype (AA) individual in SEPS1-105G>A (rs28665122). 300 µmol/L tBHP could induce apoptosis and suppress cell survival in human chondrocyte C28 cells, the up-regulation of protein expression levels of c-jun, p-c-jun, MEKK1, p-JNK, AP-1 and the down-regulation of Bcl-2 were observed. Pre-protection with Na₂SeO₃ (0.05 µg/mL, 0.1 µg/mL) could ameliorate the cell apoptosis, inhibit the ROS generation and regulate the protein expression of the signaling.

Conclusion: Some important SNPs of selenoprotein are associated with the risk of development of KBD, including GPX1Pro198Leu, GPx4 (rs713041, rs4807542), SEPS1G-105A, sep15rs5859, which might influence inflammation or oxidative stress signal pathways in KBD patients. Furthermore, chondrocyte apoptosis induced by oxidative stress might be mediated via up-regulation of PI3K/Akt, JNK, NFkB and AP1 signaling pathways, and Na₂SeO₃ has an effect of anti-apoptosis by down-regulating the signaling pathways.

Biography

Yongmin Xiong is the director of the Endemic Institute of Xi'an Jiaotong University, deputy director of the key laboratory of trace element and endemic diseases of national health and family planning commission, china. She is currently the committee member of society of endemic diseases of chinese medical association and chairman of trace elements branch in shaanxi province medical association. She has a particular interest in the environment and gene interactions in the molecular mechanism of endemic osteoarthritis diseases. She has published more than 30 articles in reputed journals.

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