Effects of increased cholesterol level on BK channels

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Background: The large conductance Ca^{2+}-activated K^+ (BK, or slo) channels are ubiquitously expressed in different tissues and play an important role in regulating various physiological processes such as cell excitability, hormone secretion, vascular activity, etc. The present study was designed to investigate how/whether BK channels are regulated by increased cholesterol level.

Methods: Whole-cell BK current and BK single channel current were recorded in whole-cell patch clamp mode and cell-attached single channel recording, respectively, in HEK 293 cells stably expressing Maxi-K with beta1-subunit.

Results: Whole-cell BK current was significantly suppressed in cells expressing both with α and β1 subunits with cholesterol-enrichment by cholesterol-saturated methyl-beta-cyclodextrin (MβCD), whereas cholesterol depletion by MβCD had no effect on the current amplitude. Low-density lipoprotein (LDL) also decreased BK current. Single channel recording showed that cholesterol enrichment significantly reduced the open probability of BK channels. However, in cells expressing only α-subunit of BK channels (without β1-subunit), cholesterol-saturated MβCD had no significant effect on the current amplitude of BK channels.

Conclusion: Our results demonstrate the important evidence that BK channels exhibit β1-subunit-dependent response to cholesterol. The enriched-cholesterol and LDL reduce the activity of BK channels in cells co-expressed with both α and β1 subunits, which may at least in part accounts for the occurrence of hypertension in patients with high plasma cholesterol level, since both of α and β1 subunit transcripts are abundant in vascular smooth muscle.

Association of *JAG1* gene and its variant sequence with bone mineral density and osteoporotic fractures: a genome-wide association study and follow-up replication studies

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Introduction: Bone mineral density (BMD), a diagnostic parameter for osteoporosis and a clinical predictor of fracture, is a polygenic trait with high heritability. The identified variants so far demonstrate only a small effect size on BMD variation. Many additional associated loci remain to be identified. The identification of additional genes underlying BMD variation would therefore provide insight into the pathogenetic mechanisms of osteoporosis and offer strategies for therapeutic development.

Methods: We performed a genome-wide association study (GWAS) on 800 unrelated Southern Chinese women with extreme BMD and follow-up replication studies in six independent European descent and Asian populations including 18 098 subjects. The potential biological function of the identified variant was further validated via electrophoretic mobility shift assay (EMSA) and gene expression study in human bone-derived cells (HBDCs) and peripheral blood mononuclear cells (PBMCs).

Results: In the meta-analysis, rs2273061 of the Jagged 1 (*JAG1*) gene was associated with high BMD ($P=5.27\times10^{-8}$ for lumbar spine [LS] and $P=4.15\times10^{-5}$ for femoral neck [FN], n=18 898). This SNP was also associated with the low risk of osteoporotic fracture (P=0.009, OR=0.7, 95% CI 0.57-0.93, n=1881). Furthermore, we performed an EMSA which demonstrated the binding of c-Myc to the 'G' but not 'A' allele of rs2273061. An mRNA expression study in both HBDCs and PBMCs confirmed the high BMD-related allele 'G' of rs2273061 was associated with higher JAG1 expression.

Conclusion: Our results support the *JAG1* gene as a novel candidate for BMD regulation and it is a potential key factor for fracture pathogenesis.

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