Genetic Prediction of Atherosclerosis
— Significance of Polymorphisms in Bone Morphogenetic Protein Signaling Molecule Genes —

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Being able to predict an individual’s risk of progressive disease has important prognostic and therapeutic implications. The carotid artery intima-media thickness (IMT) is a noninvasive measurement of artery wall thickness, inclusive of atherosclerotic plaque, which is associated with cardiovascular events such as myocardial infarction or stroke. The Multi-Ethnic Study of Atherosclerosis (MESA), a cohort of whites, Chinese, blacks, and Hispanics, showed that race/ethnicity IMT percentiles

Figure. Bone morphogenetic protein (BMP) signaling and BMP-regulated effectors possibly involved in the pathogenesis of cardiovascular disease. A variety of BMPs are present in the circulation. They are potent modulators of cell growth and fate in all vascular lineages. BMPs bind to a heterotetrameric complex of type I and type II receptors (BMPR1 and BMPR2, respectively). BMPR2 transphosphorylates and activates BMPR1, which further activates Smad transcriptional regulators. Smades form complexes with co-Smad4 and translocate into the nucleus to regulate transcription of target genes through interaction with transcription factors and transcriptional coactivators. The BMP-regulated effectors and possible pathogenesis are shown on the right. ER, endoplasmic reticulum; ICAM-1, intercellular adhesion molecule 1; Msx2, muscle segment homeobox2; p-eNOS, phosphorylated endothelial nitric oxide synthase; p21, cyclin-dependent kinase inhibitor 1; Pit-1, sodium-dependent phosphate transporter 1; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; VCAM-1, vascular adhesion molecule 1.
improved the prediction of coronary artery disease (CAD) when added to Framingham risk factors. It should be emphasized that the MESA study was designed to study reasonable risk factors linked to subclinical cardiovascular disease (CVD) and determine their predictive power in a population without clinical CVD at baseline. The data from the Kaplan-Meier curves for quartiles of IMT showed progressive increase in risk of CAD as the quartiles increased. All these data suggest that IMT is an independent phenotype that has different predictive values to those of the classical risk factors for CAD.

Multiple factors confer susceptibility to atherosclerosis, but it is widely accepted that genetic factors play an important role in the pathogenesis of atherosclerosis. As many candidate genes, genetic polymorphisms, and susceptibility loci associated with atherosclerotic diseases, including CAD, have been identified, CAD appears to be a complex disease with various genetic contributions from multiple loci. Recent genome-wide association studies have identified at least 56 independent loci associated with CAD, including the SLC22A3-LPAL2-LPA gene cluster, PCSK9, SORT1, ABCG5/G8, IL6R, CXCL12, NOX5, GUCY1A3, KCNK5, SCL22A4/A5, TRIB1, and UBE2Z. Their putative functions of possible relevance to CAD are related to lipid function, inflammatory response, endothelial function, transportation, cell proliferation, and apoptosis.

In this issue of the Journal, Wu et al report 2 single-nucleotide polymorphisms (SNPs) on bone morphogenetic protein receptor type I (BMPR1) B that show significantly independent correlations with thicker IMT. BMPs are implicated in the pathogenesis of atherosclerosis and BMPR1B is closely related to the pathogenesis of atherosclerosis: signaling is involved in the progression of atherosclerosis:

BMPs transduce their signals through the formation of heteromeric complexes of 2 types of receptors, BMPR1 and BMPR2. BMPR2 transphosphorylates and activates BMPR1, which further signals to the intracellular mediator, Smad transcriptional regulators. BMP signaling and BMP-regulated effectors possibly involved in the pathogenesis of CVD are summarized in the Figure. Genetic evidence implicates mutation of BMPR2 as a cause of heritable pulmonary arterial hypertension. With regard to the report by Wu et al, the possible mechanisms by which BMPR1B rs4456963 and rs3796433 variations drive IMT thickening are unknown.

Recently, a prospective study of participants without CVD at baseline by Kokubo et al showed that progression of the carotid artery thickness itself is a risk for CVD. They reported that the risk of CVD increased when plaques formed after the initial measurement of the carotid arteries without plaque. Thus, the 2 novel SNPs reported by Wu et al may be useful biomarkers in addition to traditional cardiovascular risk factors for future CVD. However, as the 2 SNPs are intron variants and have not been reported to be related with any other clinical significance, further investigation is required to determine how these SNPs influence IMT thickening.

**Disclosure**

None.

**References**

1. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. *JAMA* 2012; 308: 796–803.

2. Polak JF, O’Leary DH. Carotid intima-media thickness as surrogate for and predictor of CVD. *Glob Heart* 2016; 11: 295–312.

3. McPherson R, Tybjærg-Hansen A. Genetics of coronary artery disease. *Circ Res* 2016; 118: 564–578.

4. Wu YJ, Lee YN, Wu TW, Chou CL, Wang LY. Common genetic variants on bone morphogenetic protein receptor type II (BMPR2) for residents enrolled in an ongoing community-based cohort and verified the relationship of the SNPs with IMT. After adjustment for traditional cardiovascular risk factors, the 2 SNPs on BMPR1B, rs4456963*G* and rs3796433*C*, were significantly independent determinants of IMT thickening by multivariate analysis. Additionally, both SNPs correlated with the total number of carotid plaques. Importantly, the authors show that the 2 SNPs were common in the study population, as well as in other ethnic groups. In general, the cohort size required for sufficient power to detect the effect of a single genetic variation is highly dependent on the frequency of the minor allele in the population being studied. For polymorphisms that give a relative risk of ≤1.5, minor allele frequencies >5% are required. Thus, the study supports the possibility that BMPR1B is closely related to the pathogenesis of atherosclerosis and is a target for therapeutic development.

BMPR1B is a member of the BMP receptor family of transmembrane serine/threonine kinases. The ligands are BMPs, members of the transforming growth factor-β superfamily, which have been detected in the arteries from patients with advanced atherosclerosis. In vitro and in vivo studies suggest the potential mechanisms by which BMP signaling is involved in the progression of atherosclerosis: generation of reactive oxygen species, pro-inflammatory functions, and endothelial cell activation mediated by BMPs. BMPs transduce their signals through the formation of heteromeric complexes of 2 types of receptors, BMPR1 and BMPR2. BMPR2 transphosphorylates and activates BMPR1, which further signals to the intracellular mediator, Smad transcriptional regulators. BMP signaling and BMP-regulated effectors possibly involved in the pathogenesis of CVD are summarized in the Figure. Genetic evidence implicates mutation of BMPR2 as a cause of heritable pulmonary arterial hypertension. With regard to the report by Wu et al, the possible mechanisms by which BMPR1B rs4456963 and rs3796433 variations drive IMT thickening are unknown.

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