Functional polymorphism in the promoter region of p27/kip1 is associated to early myocardial infarction

González P, Díez-Juan A, Andres V, Álvarez V, Coto E.
Laboratorio de Genética Molecular, Hospital Central de Asturias, Oviedo, Spain

The proliferation of vascular smooth muscle cells (VSMCs) within the artery wall is a hallmark of the atherosclerotic process. The entrance of VSMCs from the resting G0-phase of the cell cycle into the G1/S proliferative phases depends on the activity of several cyclin-dependent protein kinase (CDK) haloenzymes. In resting cells, cyclin-CDK complexes are inhibited by the CDK-inhibitors (CKIs), including p27/Kip1.

In animal models, p27/Kip1 ablation in apolipoprotein E-null mice challenged with an atherogenic diet enhanced arterial cell proliferation and accelerated atherogenesis. Therefore, p27/Kip1 is a candidate-gene to modify the risk of developing atherosclerosis, such that genetic variation at p27/Kip1 could influence the individual risk to suffering coronary artery disease. A total of 180 DNAs of human patients who had suffered an episode of myocardial infarction were obtained.

All these patients were male, 55 years old or younger. Single-strand conformation analysis was used to study the entire p27/Kip1-coding sequence, as well as 1,150 nucleotides of the promoter region. For those samples showing atypical electrophoretic patterns the amplified fragment was sequenced. We identified 3 SNPs: –840 (A/C); –79 (C/T) and +326 G/T (Val109Gly).

Patients and 250 controls (males and younger than 55 years) were analysed for these polymorphisms. We found a significantly higher frequency of the -840AA genotype in patients, compared to controls (OR=1.75; 95%CI=1.08-2.82). Luciferase reporter gene assays with both alleles showed a low luciferase levels of allele A compared with allele C (p=0.04). Thus, given the important role of p27/kip1 as an inhibitor of VSMC proliferation and atheroma development, we suggest that genetic variation of the p27/kip1 gene leading to reduced promoter activity could be a genetic risk factor predisposing to myocardial infarction.