

Associations between the genetic polymorphisms which influence homocysteine metabolism and the aging related vascular and heart diseases.

A.L. Pawlak, E. Strauss

Institute of Human Genetics, Poznań, Poland

Homocysteine (Hcy) is precursor in methionine synthesis and the supply of methyl groups for this reaction requires the activity of methylene tetrahydrofolate reductase (MTHFR). In vascular tissues, because of the absence of the alternative pathways of Hcy metabolism the activity of this protein is particularly important. Therefore the low activity alleles of the common polymorphisms of the *MTHFR* gene (677 C<T and 1298 A>C) may lead to local excess of Hcy and produce many disturbances of endothelial functions. This may be due to the high reactivity of Hcy, which may lead to the posttranslational modifications of many proteins, which affect their functions. The blood components are the natural substrates to these modifications. The paraoxonase (Hcy-thiolactonase) is an important factor in the protection from these modifications. Therefore, the genetic polymorphisms of the *PON1* gene coding for this activity may also be considered to influence the Hcy-related pathology. Such effects of Hcy have been described toward the NMDA receptor, the signaling molecules, the enzymes and structural proteins. The nitrosohomocysteine produced by nitrosylation of Hcy, may be incorporated into the newly synthesized proteins hampering in this way their functions. Elastin, the main structural element in the abdominal aorta wall, is very rich in the lysine residues which are main target of the reaction of N-homocysteinylation. Therefore the modification of elastin by Hcy may contribute to development of the abdominal aortic aneurysm (AAA). The associations between the low activity genotypes of the *MTHFR* as well as the *PON1* genes and the vascular diseases such as AAA (Strauss et al., 2003) myocardial infarct and hypertension has been noted (Strauss et al., 2004). The aging related changes in frequency of the low activity polymorphic variants of *MTHFR* and *PON1* genes may indicate the higher morbidity of carriers of these alleles in the older age.