**MOLECULAR MECHANISMS OF THE BENEFICIAL CARDIOVASCULAR EFFECTS OF TRANS-RESVERATROL**

**U. Forstermann**, H. Li

Johannes Gutenberg University Medical Center, Mainz, RP, Germany

An enhanced inactivation and/or reduced synthesis of vascular nitric oxide (NO) are seen in conjunction with cardiovascular disease. This endothelial dysfunction is largely caused by vascular oxidative stress with an increased production of reactive oxygen species (ROS) and a rapid inactivation of bioactive NO. Oxidative stress results mainly from an imbalance between the activity of endogenous pro- and anti-oxidative enzymes. Increased ROS concentrations reduce bioactive NO by chemical inactivation; superoxide and NO rapidly recombine to form toxic peroxynitrite. Peroxynitrite can oxidize the essential cofactor of endothelial NO synthase

(6R-)5,6,7,8-tetrahydrobiopterin (BH4). As a consequence, oxygen reduction by endothelial NO synthase is uncoupled from NO formation, and a functional NO synthase is converted to a dysfunctional superoxide-generating enzyme. The polyphenolic phytoalexin trans-resveratrol can reduce oxidative stress and restore endothelial NO production in cultured endothelial cells in vitro and in atherosclerosis-prone apolipoprotein E knockout mice in vivo. By upregulating antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) and by suppressing the expression and activity of NADPH oxidases in endothelial cells, resveratrol inhibits superoxide-mediated inactivation of NO. By stimulating eNOS expression, eNOS phosphorylation at serine 1177 and eNOS deacetylation at lysine residues in the calmodulin-binding domain, resveratrol stimulates endothelial NO production. Resveratrol also enhances the expression of GTP cyclohydrolase I (GCH1), elevates the content of BH4 and reverts the functionality of uncoupled eNOS. Many effects of resveratrol are mediated by the NAD+-dependent class III histone deacetylase sirtuin 1 (SIRT1) or estrogen receptors, respectively. SIRT1 may represent a novel target for the treatment of cardiovascular disease.