Activating SIRT1: a new strategy to prevent atherosclerosis?

Ralf P. Brandes*

Institut für Kardiovaskuläre Physiologie, Goethe-Universität, Theodor-Stern-Kai 7, D-60596 Frankfurt am Main, Germany

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This editorial refers to ‘Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice’ by Zhang et al., pp. 191–199, this issue.

The development of atherosclerosis is a complex, multi-step process, which is at least in part controlled by the functional state of the vascular endothelium. It is generally believed that the functional state of the endothelium is influenced by a broad set of cardiovascular risk factors and that endothelial dysfunction is the stereotypic cellular response to a broad range of different stimuli on the background of a poorly defined genetic predisposition.

That such a concept represents an over-simplification has become evident through studies demonstrating maternal–foetal transmission of the atherosclerotic risk and ‘atherosclerotic programming’ of cells derived from mice with a poorly defined genetic predisposition. Such programming is the consequence of epigenetic modifications like DNA methylation or histone acetylation, processes that are controlled by several different enzyme families.

One of these enzymes, SIRT1, a class III histone deacetylase (HDAC), has gained considerable interest as a mediator of longevity induced by caloric restriction. It has been linked to aging: down-regulation of the protein-induced premature senescence and overexpression of SIRT1 protected endothelial cells against H2O2-induced senescence. SIRT1 belongs to the family of sirtuin proteins, which consists of seven family members (SIRT1–7). SIRT1, -2, -3, and -5 mediate NAD+-dependent deacetylation of ε-amino-acetylated lysine residues of proteins. This effect is not restricted to histones, and individual sirtuins have a broad spectrum of substrates and targets in the cell. Thus, functional changes mediated by SIRT1 are not necessarily the consequence of the histone deacetylase function of the protein.

SIRT1 is highly expressed in endothelial cells and controls their angiogenic function: it is involved in vascular growth of cultured endothelium, in the formation of the vascular network of the developing zebrafish, and even in ischaemia-induced neovascularization of the adult mouse.

Such a profile suggests that SIRT1 maintains normal endothelial function and that overexpression of SIRT1 might be ‘vasoprotective’.

In this issue of Cardiovascular Research, evidence to strengthen this concept comes from the elegant study by Zhang et al. The authors characterized the SIRT1 expression in endothelial cells in response to pro-atherosclerotic stimuli and determined the impact of endothelial cell-specific overexpression of the enzyme on atherosclerosis development in ApoE knockout mice treated with a high-fat diet. In cultured human umbilical vein endothelial cells (HUVEC), they observed that oxidized LDL (oxLDL) as well as hydrogen peroxide (H2O2) down-regulate SIRT1. Overexpression of SIRT1 prevented the oxLDL-induced apoptosis of HUVECs, and this effect was mediated by a marked increase in the expression of endothelial NO synthase (eNOS). Accordingly, endothelial-specific overexpression of SIRT1 in ApoE−/− mice-induced eNOS and significantly blunted the high-fat diet-induced attenuation of endothelium-dependent relaxation in isolated aortic rings. Most importantly, endothelial-specific overexpression of SIRT1 also attenuated aortic plaque development in response to the high-fat diet in ApoE−/− mice.

It is well established that NO prevents endothelial cell apoptosis and senescence. Moreover, endogenous NO is anti-atherosclerotic, as genetic deletion of eNOS promotes atherosclerosis in ApoE−/− mice. Thus, it is conceivable that most of the effects observed in the present study are mediated by the SIRT1-dependent induction of eNOS. Indeed, by using inhibitors of SIRT1 and SIRT1 siRNA, Zhang et al. demonstrate a direct dependency of eNOS protein expression on SIRT1 activity. The underlying mechanisms of how SIRT1 controls eNOS expression are, however, still uncertain.

SIRT1 has been linked to longevity in response to caloric restriction. Interestingly, caloric restriction also increases eNOS expression. Whether this effect is involved in the overall extension of lifespan is questionable, as other important proteins such as p53 and Foxo transcription factors are also targets of this deacetylase.

The activity of SIRT1 can be modulated directly by pharmacological compounds. The polyphenolic plant antioxidant resveratrol moderately increases the SIRT1 activity and has been shown to slow down the development of atherosclerosis in different mouse models (Figure 1). Recently, compounds that are 1000 times more potent...
than resveratrol have become available, and it has already been shown that these potential new drugs improve the glucose homeostasis. In the light of these beneficial effects, it could be speculated that these compounds might also be of value as a potential anti-atherosclerotic therapy.

References


Figure 1 SIRT1 prevents development of atherosclerosis. Reactive oxygen species and oxidized lipoproteins like oxLDL attenuate activity and expression of eNOS and SIRT1. A positive feedback loop exists between eNOS and SIRT1. Through this mechanism important effectors like p53 or telomerase reverse transcriptase (TERT) are modulated to prevent endothelial apoptosis and senescence. Activators of SIRT1 such as resveratrol or endothelial-specific overexpression of this sirtuin restore eNOS expression and prevent the development of atherosclerosis in mice.