Aging is considered to be a major risk factor for the development of cardiovascular diseases, the leading cause of morbidity and mortality in Western countries. Among the age-associated functional and structural changes in the vascular wall, particularly endothelial function declines during the ageing process. Impairment of endothelial function critically contributes to the pathogenesis of several cardiovascular diseases (eg, atherosclerosis) and is manifested in its earliest form as an attenuation of endothelium-dependent dilator responses as a consequence of an alteration in the expression or activity of the endothelial nitric oxide (NO) synthase (eNOS) and increased oxidative stress. Endothelial senescence appears to play a key role in the process of vascular aging, affecting vascular tone, blood vessel growth, and regeneration. Thus, identifying new molecular targets involved in senescence signaling offers opportunities to potentially improve endothelial cell function and cardiovascular disease progression.

Sirtuins, Senescence, and Aging

Cellular senescence has been used as a model for mammalian aging. This process consists of a state of permanent cell cycle arrest associated with characteristic changes in cell morphology and gene expression. Most mammalian cells undergo a limited number of divisions in culture, eventually entering a state of cellular senescence. This process, also referred to as replicative senescence, is related to the attrition of telomeres after extended propagation in culture. In addition to the shortening of telomeres ends, several cellular stressors, such as oxidative stress, induce a similar growth arrest within just a few days, referred to as stress-induced premature senescence. Although endothelial cells are rarely dividing under normal conditions and exhibit a turnover rate estimated in the range of few days, referred to as stress-induced premature senescence.

Apart from the relevance of these findings for improving the understanding of vascular endothelial senescence pathways, they point to SIRT1 as an important modulator of signaling networks critical for maintaining vascular endothelial homeostasis and suggest novel therapeutic opportunities for the treatment of cardiovascular diseases.

See accompanying article on page 1634

In a study published in the present issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Ota et al report that the PDE3 inhibitor cilostazol prevents endothelial premature senescence by a NO-dependent upregulation of SIRT1, a key regulator of ageing and longevity in lower organisms.1 Apart from the relevance of these findings for improving the understanding of vascular endothelial senescence pathways, they point to SIRT1 as an important modulator of signaling networks critical for maintaining vascular endothelial homeostasis and suggest novel therapeutic opportunities for the treatment of cardiovascular diseases.

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including histones, Foxos, NF-κB, PGC-1, LXR1, and p53. The tumor suppressor p53 was among the first nonhistone substrates shown to be functionally regulated by reversible acetylation, and SIRT1 promotes cell survival in response to cellular stress by deacetylating p53, which decreases p53 stability and activity. In fibroblasts, however, SIRT1 increases total p53 levels on conditions of chronic oxidative damage, causing cellular senescence.

The SIRT1–eNOS Axis: A Key Pathway for Maintaining Vascular Homeostasis

Ota and coworkers now report that the PDE3 inhibitor, cilostazol, a vasodilating antiplatelet drug for peripheral artery disease, inhibited oxidative stress–induced premature senescence by enhancing the expression of SIRT1 in human endothelial cells in vitro and in vivo (Figure 2). The findings are based on a previous study by this group, which demonstrated that overexpression of SIRT1 prevented oxidative stress–induced endothelial senescence, whereas inhibition of SIRT1 activity or expression induced premature senescence-like phenotypes in endothelial cells. These studies suggested that SIRT1-activating drugs might exert protective effects on the vascular endothelium. Using H2O2-induced premature senescence in cultured endothelial cells or paraquat-treated mice as models for endothelial cell senescence, Ota et al show that cilostazol leads to the activation of eNOS through a cAMP/PKA- and PI3K/Akt-dependent pathway by inducing the phosphorylation of eNOS at serine 1177. Further detailed analysis revealed that cilostazol enhances the mRNA and protein expression of SIRT1, which requires the generation of nitric oxide by the endothelial nitric oxide synthase (Figure 2). Indeed, nitric oxide has been shown to activate the SIRT1 promoter in white adipose tissue, where caloric restriction, a dietary regimen known to extend life span, induces an increase in eNOS expression, which is in turn involved in both mitochondrial biogenesis and SIRT1 expression. Moreover, SIRT1 deacetylates and activates the eNOS enzyme, indicating that a positive feedback mechanism exists between these two key signaling molecules. Thus, activating SIRT1 through small molecules may help to reset the activity of eNOS during situations of endothelial dysfunction where nitric oxide availability is limited.
How does SIRT1 exert its beneficial effects on the vascular endothelium? The authors suggest that p53 might be of utmost importance. Indeed, p53 is itself acetylated in response to oxidative stress and has been identified as a key regulator of senescence signaling in different cell types. By assessing acetylation of p53 at lysine 373/382 in response to H₂O₂ treatment, the authors show that cilostazol decreased acetylation of p53 at SIRT1-targeted lysine residues. Obviously, these findings do not exclude the possibility that the protective effect of SIRT1 is also mediated by other SIRT1 targets known to affect senescence and endothelial cell biology. Indeed, SIRT1 has been shown to associate with Foxos in an acetylation-dependent manner, eg, in response to oxidative stress, thereby “tipping” Foxo responses away from apoptosis and toward stress resistance. Although an interaction between SIRT1 and Foxos in endothelial cells has so far only been documented for Foxo1 in the context of angiogenesis, it is more than likely that the conserved SIRT1-Foxo interaction is also operational during stress-induced endothelial senescence.

In addition to its cell-intrinsic function in endothelial cells, the well known effects of SIRT1 on cholesterol metabolism, glucose homeostasis, and insulin resistance might also beneficially affect vascular homeostasis and cardiovascular disease progression. Thus, these findings point to SIRT1 as a point of convergence of several signaling pathways critical for homeostatic endothelial functions and identify the cardiovascular system as an important target tissue for the direct and indirect actions of SIRT1.

**SIRT1: A Therapeutic Target in Cardiovascular Disease**

Given the experimental observation that the effects of cilostazol were dependent on the functional activity of SIRT1, the study by Ota et al may also have implications for future design of novel cardiovascular drugs. Because SIRT1 has enzymatic activity, it has become an attractive target for drug development. Consistent with these considerations, recent studies reported that resveratrol, a polyphenolic activator of SIRT1, ameliorated insulin resistance and prolonged survival in mice fed a high-fat diet. Moreover, the finding that small molecule activators of SIRT1, which are 1000-fold more potent than resveratrol, induce many of the beneficial small molecule activators of SIRT1, which are 1000-fold more potent than resveratrol, induce many of the beneficial and Foxos in endothelial cells has so far only been shown to associate with Foxos in an acetylation-dependent manner, eg, in response to oxidative stress, thereby “tipping” Foxo responses away from apoptosis and toward stress resistance. Although an interaction between SIRT1 and Foxos in endothelial cells has so far only been documented for Foxo1 in the context of angiogenesis, it is more than likely that the conserved SIRT1-Foxo interaction is also operational during stress-induced endothelial senescence.

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**References**

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