Deacetylase SIRT6 deaccelerates endothelial senescence

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This editorial refers to ‘SIRT6 protects human endothelial cells from DNA damage, telomere dysfunction, and senescence’ by A. Cardus et al., pp. 571–579, this issue.

Vascular endothelial homeostasis is critical to health and is a significant factor in many human diseases. It is established that endothelial cell (EC) dysfunction is one of the earliest pathological steps in the initiation and progression of vascular diseases such as atherosclerosis and vascular remodelling.1–3 How to maintain a healthy or repair an injured endothelial lining of the vasculature has been a scientific mystery and a clinical challenge. In general, two theories have been proposed. On the one hand, it is thought that during their turnover, injured ECs, due to senescence, ageing, or other pathological challenges, might be replaced by circulating EC progenitors that can repopulate the damaged endothelium. Although this hypothesis has undergone rigorous investigation and achieved some promising initial results,4–6 recent studies demonstrated that circulating EC progenitors do not contribute to the regeneration of a damaged endothelium, thus significantly reducing this theory’s promise in the field.6 On the other hand, healing damaged EC areas with adjacent mature ECs through their migration and proliferation is still a viable theory.7 In order to achieve this ‘in situ healing’, however, the pre-existing mature ECs in the vasculature may have to maintain a ‘threshold’ of healthy phenotype. Unfortunately, like virtually any cells in the body, ECs are not immune to ageing and senescence, which compromise vascular homeostasis and lead to vascular pathologies.8

In the past decade, a myriad of genes or molecules have been shown to modulate the cellular ageing process, with fewer studies focused on ECs. Among all the targets, a family of mammalian proteins called sirtuins (SIRT1–SIRT7) has gained considerable attention for their impact on animal models of longevity and cellular senescence.9 Initial studies found that SIRT1, a structural homologue of yeast Sir2, is often linked to protection against the onset of various chronic disease states including atherosclerosis.10 However, transgenic mice with SIRT1 overexpression are not long-lived, meaning that the scientific mystery remains.11 Cardus et al.12 address the role of SIRT6, a less-studied sirtuin member, in human EC senescence. The authors found that SIRT6 is expressed at much higher levels in ECs from different vascular beds than in haematopoietic progenitor cells, whereas SIRT1 levels are all comparable. In addition, silencing of SIRT6 leads to a reduction of replication capacity, angiogenesis in vitro, and a senescent phenotype. Their further mechanistic studies indicate that SIRT6 is crucial for preventing nuclear DNA damage and telomere dysfunction (Figure 1).12 Although it is known that SIRT6 is cytoprotective in some other cells, its role in EC biology and vascular disease has been unclear. Thus, the study by Cardus et al.12 provides new molecular insights into our understanding of the mystery of endothelial ageing. In addition to the seminal observation of SIRT6 protection on endothelial senescence, the current study also made a surprising finding. The investigators found that although silencing of SIRT6 leads to the presentation of many known markers of cell senescence, oxidative stress was not detected. This is particularly unexpected since their data showed obvious DNA damage in response to SIRT6 knockdown, and many other studies have demonstrated that oxidative stress is a causal factor in cell senescence or ageing.10 Nonetheless, it is plausible that the observed DNA damage is a non-oxidative modification(s) of other chemical or biochemical nature after SIRT6 deletion. Future studies should determine the exact form of the observed DNA damage and address whether oxidative stress actively affects SIRT6 expression and activity.

It should be noted, however, that some of the current findings remain to be further verified. For example, a single approach, siRNA silencing, was used in this study. It would be more convincing if many of the findings could be validated in complementary approaches. These could be investigated in cultured ECs overexpressing SIRT6 and/or in ECs isolated from SIRT6-null mice, which are viable and have an ageing phenotype. In addition, like many excellent reports, the current study by Cardus et al.12 is far from complete and raises many important questions. First, it is unknown to what extent a repeated in vitro EC culture model resembles the pathology of in vivo senescent ECs linked to human cardiovascular diseases. Perhaps this challenging question will remain until we know the actual rate of EC turnover in the ageing vasculature. However, studies in in vivo animal models repeatedly showed that EC senescence is evident in atherosclerotic plaques and is associated with DNA damage and telomere dysfunction.10 Second, since SIRT6 is an enzyme, it remains unknown from this study whether the observed senescent phenotype in ECs is linked to its enzymatic activity. This is particularly important in view of the fact that SIRT6 is not just a simple protein deacetylase, it is...
also an NAD\textsuperscript{+}-dependent ADP ribosyltransferase.\textsuperscript{14} Thus, it remains to be determined which of its enzymatic functions is responsible for maintaining a ‘young’ EC phenotype or decelerating EC senescence, and which of its activities is changed in senescent ECs \textit{in vitro} and \textit{in vivo}. Third, what are the exact substrate(s) and cell signalling pathways that are targets for SIRT6, in terms of its cellular anti-ageing benefit? Identification of its substrate(s) will provide invaluable potential for drug development and optimization for the prevention of EC senescence-related vascular diseases and perhaps many other ageing-related human diseases as well. Although the current study presented some hints on how SIRT6 intervenes with endothelial ageing-associated gene expression, including inflammatory gene up-regulation, eNOS down-regulation, and p21 induction (\textit{ageing-associated gene expression, including inflammatory gene expression, presented some hints on how SIRT6 intervenes with endothelial ageing-related human diseases as well}. Although the current study presented some hints on how SIRT6 intervenes with endothelial ageing-associated gene expression, including inflammatory gene up-regulation, eNOS down-regulation, and p21 induction (\textit{Figure 1}), a much clearer picture is needed to illustrate their cause–effect relationships. Finally, a more straightforward question is whether endothelial SIRT6 plays a role in vascular pathologies \textit{in vivo}. This can be investigated in mice with endothelial targeted SIRT6 deletion or overexpression in an ApoE-null background. Indeed, mice with endothelial targeted overexpression of SIRT1 have shown an anti-atherosclerotic phenotype.\textsuperscript{15}

In summary, Cardus et al.\textsuperscript{12} made an interesting observation about SIRT6 on endothelial ageing; however, many essential questions remain. New studies that provide answers to these questions will not only be enlightening, but may also prompt the discovery of new drugs targeting SIRT6 to decelerate EC senescence and ageing-related human diseases.

**Conflict of interest:** none declared.

**Funding**

The research is supported by the American Heart Association—National SDG award (12SDG8850011 to J. S.).

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**Figure 1.** SIRT6 prevents endothelial senescence. Over-replication of ECs leads to decreased expression of SIRT6, which in turn results in a pro-inflammatory phenotype, p21 up-regulation, DNA damage, telomere dysfunction, cell-cycle arrest, and impaired angiogenesis. All are indications of EC senescence, but their cause–effect relationship is unknown.\textsuperscript{12}

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**References**


