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INVITED EDITORIAL

PCSK9 reloaded: sirtuin-1 as a post-translational checkpoint for LDL-C control

Angela Pirillo [1] **and Alberico L. Catapano** [2,3]*

[1]Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy; [2]Center for the Study of Atherosclerosis, IRCCS MultiMedica, Via Milanese 300, 20099 Sesto S. Giovanni, Milan, Italy; and [3]Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti, 9, Milan 20133, Italy

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This editorial refers to 'Sirtuin-1 directly binds and deacetylates hepatic PCSK9 thereby promoting the inhibition of LDL receptor degradation' by S. Velagapudi *et al.*, https://doi.org/10.1093/cvr/cvaf087.

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of morbidity and mortality worldwide, despite the availability of effective lipid-lowering therapies such as statins, ezetimibe, PCSK9 inhibitors, and bempedoic acid. These approaches significantly lower low density lipoprotein cholesterol (LDL-C) levels and the risk of major adverse cardiovascular events (MACE).

PCSK9 is a validated target in LDL metabolism. By binding to the LDL receptor (LDLR) on hepatocytes, PCSK9 targets it to degradation, leading to higher circulating levels of LDL-C.[1] Inhibition of circulating PCSK9 by monoclonal antibodies lowers LDL-C levels by ~60% and significantly reduces the risk of MACE.[2,3] Other approaches to inhibit PCSK9 include inclisiran, an siRNA that targets hepatic PCSK9 mRNA, and enlicitide decanoate, an oral PCSK9 inhibitor that is in advanced development, but other mechanisms that may modulate PCSK9 activity are under investigation.[4]

The PCSK9 protein undergoes several post-translational modifications, including phosphorylation, N-glycosylation, and sulphation, which modulate PCSK9 half-life/stability, protein–protein interactions, biological activity, and/or subcellular localization.[5] N-glycosylation appears to enhance the ability of PCSK9 to trigger LDLR degradation.[5] PCSK9 is also acetylated at several lysine residues, a modification that may affect the function of PCSK9 and/or its ability to bind to LDLR. Acetylation and deacetylation of protein lysines are controlled by acetyltransferases and deacetylases.

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases that are highly conserved across species and are involved in several physiological and pathological processes such as inflammation, metabolism, oxidative stress, and apoptosis and are therefore considered a potential therapeutic target for various pathologies such as cancer, cardiovascular diseases, and others.[6] Among the sirtuins, sirtuin 1 (SIRT1) is the best-studied member of this family; there is ample evidence that SIRT1 plays a beneficial role in the cardiovascular system through multiple protective activities, including antioxidant, anti-apoptotic, and anti-inflammatory effects.[6] SIRT1 is mainly localized in the nucleus, where it modulates gene transcription, but due to its ability to shuttle from the nucleus to the cytoplasm, it also modulates the activity of several proteins through deacetylation.[7]

SIRT1 has also been detected in the bloodstream, raising questions about its systemic functions and therapeutic potential. Serum SIRT1 levels are lower in patients with obesity and hepatic steatosis and correlate inversely with disease severity.[8] Plasma SIRT1 levels are also reduced in diabetes; interestingly, chronic supplementation of recombinant murine SIRT1 improved endothelial function and reduced oxidative stress in diabetic mice.[9]

The most important question is whether plasma SIRT1 is simply a product of cellular release or whether it exerts an independent biological activity. A recent study provides mechanistic insight into the functional role of systemic SIRT1. In this issue of *Cardiovascular Research*, Velagapudi and colleagues report that SIRT1 binds directly to PCSK9 and reduces its activity through deacetylation. Using apolipoprotein E-knockout ($ApoE^{-/-}$) mice fed a high-cholesterol diet, they showed that SIRT1 levels were lower than in control mice and LDL-C levels were increased.[10] Following intraperitoneal administration of recombinant murine SIRT1 (rmSIRT1) over a four-week period, hepatic LDLR increased and LDL-C levels decreased. Importantly, this effect occurred without changes in PCSK9 mRNA expression. Recombinant Sirt1 also reduced inflammation and plaque size. Mechanistically, SIRT1 was found to bind directly to PCSK9 and promote its deacetylation at three lysine residues (Lys243, Lys421, and Lys506). This deacetylation led to reduced PCSK9 activity and thus to a reduced ability to target LDLR for degradation. Circulating SIRT1 (and not intracellular SIRT1) was responsible for the inactivation of PCSK9 and the resulting reduction in LDL-C levels. To investigate these mechanistic findings in humans, the study included a clinical correlative analysis in patients with acute coronary syndromes. Analysis of plasma showed an inverse correlation between SIRT1 and PCSK9 levels. Patients with higher plasma SIRT1 levels had a significantly lower risk of MACE, suggesting a prognostic value.

These preliminary results suggest that plasma SIRT1 is not only a potential biomarker but also a potential therapeutic target in ASCVD. The ability to modulate LDL-C and plaque burden by SIRT1 may provide an additional approach to modulate lipid metabolism and atherosclerosis. While most current therapies target PCSK9 transcription or promote its inhibition by monoclonal antibodies, SIRT1 modifies PCSK9 post-translationally, offering a new pathway of PCSK9 regulation.

The integrative approach of this study, using mouse models, molecular biology, and human translational data, supports this observation. In addition, the identification of specific acetylation sites on PCSK9 is particularly relevant and emphasizes the hypothesis that circulating SIRT1 is biologically active. However, there are some open questions that need to be addressed to substantiate these findings. First, due to the small sample size of animals and patients used in this study, cautious interpretation is warranted. Certainly,

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* Corresponding author. Tel: +39 0249637591, E-mail: alberico.catapano@unimi.it

larger cohort studies are needed to confirm the correlation between plasma SIRT1 and cardiovascular outcomes. Secondly, administration of recombinant SIRT1 in mice by intraperitoneal injection is not directly translatable to humans. Thirdly, questions remain about the stability/half-life of SIRT1, tissue distribution, and immunogenicity. The development of stable, bioavailable forms of SIRT1 should be the first approach to continue this research in humans. Fourthly, the 4-week intervention used in this study may not capture the long-term benefits or risks in humans, emphasizing the need for studies to evaluate the effects of chronic administration of SIRT1. Prospective studies investigating the effects of SIRT1 modulation on LDL-C levels and plaque burden in humans would be crucial. In addition, it would be interesting to explore whether a synergistic effect between SIRT1 and existing lipid-lowering therapies, such as statins or PCSK9 inhibitors, could enhance the therapeutic effect. Finally, a better understanding and quantification of the acetylated/deacetylated status of PCSK9 in individuals with cardiovascular disease is warranted.

The identification of circulating SIRT1 as an active modulator of lipid metabolism may represent a paradigm shift in the field of cardiovascular therapeutics. By regulating PCSK9 activity through deacetylation, systemic SIRT1 provides a novel mechanism to improve LDLR function and promote LDL-C lowering. If confirmed in larger studies, therapeutic modulation of extracellular SIRT1 could redefine strategies for the treatment of ASCVD. This study paves the way for a new direction in atherosclerosis research, in which SIRT1 could become a new molecular target in clinical practice.

Conflict of interest: none declared.

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