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EDITORIAL

High-Density Lipoprotein: a Molecule-Modulating Angiogenesis

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Coronary artery disease (CAD), also known as ischemic heart disease, is a fatal cardiovascular condition primarily caused by myocardial ischemia and infarction. In CAD, angiogenesis plays a vital role in constructing collateral circulation, which is essential for restoring blood flow in myocardial tissues. Despite numerous clinical trials conducted over the past two decades to promote coronary artery growth for CAD treatment, these efforts have largely been unsuccessful [1]. Currently, there is no effective method to enhance coronary artery growth in patients with CAD. While there are several factors related to CAD, one often overlooked factor is dysfunctional high-density lipoprotein (dHDL). Normal HDL (nHDL) can effectively induce angiogenesis. However, during CAD, the composition of HDL changes and it loses its angiogenic capability, referred to as dHDL. The mechanism behind the impaired vascular growth–regulating functionality of dHDL remains elusive so far.

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Non-coding RNAs (ncRNAs) are a special class of transcripts that do not get translated to form functional proteins. ncRNAs have been recognized as high-quality biomarkers for risk stratification, diagnosis, and prognosis of various cardiovascular diseases. Recent reports suggest that HDL serves as a significant carrier of ncRNAs in the plasma, delivering them to target cells and inducing essential cellular actions in angiogenesis. Among ncRNAs, the functions of long non-coding RNAs (lncRNAs) are more complex including the regulation of endothelial function, vessel growth, and cell cycle. However, little is known about HDL and lncRNAs. Investigating whether HDL modulates lncRNAs is crucial for understanding the HDL-mediated angiogenic mechanisms. In a previous study, researchers identified lncRNAs differentially expressed in endothelial cells treated with nHDL or dHDL [2]. However, the roles of these lncRNAs in nHDL and dHDL-regulated angiogenesis remain unclear.

Recently, Ou et al. published a research paper entitled "High-density lipoprotein regulates angiogenesis by long non-coding RNA HDRACA" in the journal of Signal Transduction and Targeted Therapy. This study was the first to discover that nHDL promotes angiogenesis by suppressing the expression of high-density lipoprotein-regulated angiogenesis in coronary artery disease lncRNA (HDRACA) in vascular endothelial cells. However, under CAD conditions, the suppression of HDRACA by dHDL was weakened, causing dHDL to lose its angiogenesis-promoting function [3].

Initially, to identify the lncRNAs involved in the regulation of angiogenesis by nHDL and dHDL, the researchers analyzed previous lncRNA sequencing data, pinpointed those that regulate angiogenesis. They found that HDRACA, which was a 553nt lncRNA localized in the cytoplasm of endothelial cells, modulated vascular endothelial cell proliferation and tube formation. Meanwhile, nHDL could reduce the expression of HDRACA in various endothelial cells, while dHDL had a diminished effect.

The researchers then investigated the mechanisms of differential regulation of nHDL and dHDL of HDRACA. They found that sphingosine 1-phosphate (S1P) carried by nHDL

could interact with the S1P receptor 1 (S1P1) in vascular endothelial cells, activating the E3 ubiquitin-protein ligase 2 (WWP2). This activation led to the ubiquitination degradation of the transcription factor KLF5, which, in turn, suppressed HDRACA transcription. In contrast, dHDL contained a reduced amount of S1P, which could not significantly affect Kruppel-like factor 5 (KLF5) ubiquitination, weakening its inhibitory effect on HDRACA expression. Most S1P was bound to apolipoprotein M (ApoM) in HDL. The researchers found that although ApoM levels were not significantly different between nHDL and dHDL, ApoM could enhance the inhibitory effect of S1P on HDRACA.

Subsequently, the team explored how the regulation of HDRACA expression by nHDL and dHDL affected angiogenesis. They found that HDRACA bound to a crucial angiogenesis regulatory protein-Ras-interacting protein 1 (RAIN), inhibiting the interaction between RAIN and Vigilin. This inhibition subsequently promoted the mRNA instability-induced degradation of proliferating cell nuclear antigen (PCNA) by Vigilin. The suppression of PCNA expression inhibited angiogenesis in human and mouse endothelial vessels. Lastly, staining arterial tissue samples revealed elevated levels of KLF5 and HDRACA, and reduced PCNA levels in atherosclerotic occlusive disease. Additionally, the S1P content of HDL was found to be negatively correlated with HDRACA levels in vascular endothelial cells. These findings verify the changes in the S1P-KLF5-HDRACA-PCNA signaling pathway in atherosclerotic occlusive disease.

In summary, this study uncovers that nHDL, through the interaction between S1P and S1P receptor, activates WW domain-containing E3 ubiquitin-protein ligase 2 (WWP2), which leads to the ubiquitin degradation of KLF5, subsequently suppressing HDRACA transcription. This, in turn, increases the interaction between RAIN and Vigilin, inhibiting Vigilin-induced mRNA instability degradation of PCNA, promoting PCNA-mediated endothelial cell proliferation and tube formation, ultimately promoting angiogenesis. However, under CAD conditions, due to the loss of S1P, dHDL cannot suppress the transcription of HDRACA induced by KLF5 through the S1P1-WWP2 signaling pathway. As a result, dHDL cannot promote angiogenesis through increasing PCNA expression. This research elucidates the roles and a novel mechanism of HDRACA in nHDL-induced angiogenic functions and the inability of dHDL to effectively induce angiogenesis, offering new avenues and targets for therapeutic angiogenesis in patients with CAD.

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Declarations

Consent to Participate This article does not contain any studies with human participants.

Conflict of Interest The authors declare no competing interests.

Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any authors.

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