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Blood Flow Patterns Regulate PCSK9 Secretion via MyD88 Mediated Proinflammatory Cytokines

Shijie Liu [1 2], Xiaoyan Deng [3 4], Peng Zhang [3], Xianwei Wang [2], Yubo Fan [3 4], Sichang Zhou [5], Shengyu Mu [6], Jawahar L Mehta [2], Zufeng Ding [1 2]
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Affiliations

- [1] Henan Key Laboratory of Medical Tissue Regeneration, Xinxiang Medical University, Xinxiang, China.
- [2] Central Arkansas Veterans Healthcare System and University of Arkansas for Medical Sciences, Little Rock, AR.
- [3] Key Laboratory for Biomechanics and Mechanobiology of Ministry of Education, School of Biological Science and Medical Engineering, Beihang University, Beijing, China.
- [4] Beijing Advanced Innovation Center for Biomedical Engineering; Beihang University, Beijing, China.
- [5] Department of Neurological Surgery, Weill Cornell Medicine, New York.
- [6] Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock.

Abstract

Aims: Blood flow patterns play an important role in the localization of atherosclerosis in the sense that low-flow state is pro-atherogenic, and helical flow is protective against atherosclerosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates cholesterol metabolism via LDL receptor degradation and is highly expressed in the atherosclerotic tissues. This study was designed to investigate the role of different blood flow patterns in the regulation of PCSK9 expression.

Methods and results: We designed an experimental model guider to generate stable helical flow. Our data showed that compared with normal flow, low flow state induces while helical flow inhibits PCSK9 expression in the rabbit thoracic aorta in an inflammatory state. Our data also identified that TLR4-MyD88-NF-κB signaling plays an important role in PCSK9 expression. On the other hand, TRIF pathway had almost no effect. Further studies showed that the signals downstream of NF-κB, such as proinflammatory cytokines (IL-1β, IL-18, MCP-1, IL-6, TNF-α, IL-12, IFNγ and GM-CSF) directly influence PCSK9 expression. Interestingly, high fat diet further enhanced PCSK9 expression in an inflammatory milieu.

Conclusions: These observations suggest a link between abnormal flow patterns and PCSK9 expression in inflammatory states, which may qualify helical flow and proinflammatory cytokines as potential targets to treat PCSK9 related cardiovascular diseases.

Translational perspective: PCSK9 regulates LDL receptor degradation and plays key roles in hypercholesterolemia and related cardiovascular diseases. In this study, we show that helical flow which is associated with atherosclerosis induces more PCSK9 than linear flow. Further proinflammatory cytokines directly determine PCSK9 levels. As upstream pathway, TLR4-MyD88-NF-κB signaling plays an important role in the regulation of PCSK9 expression. TRIF has almost no effect in this signaling. Thus, inhibition of TLR4-MyD88-NF-κB signaling may be a novel strategy to attenuate PCSK9 release associated with helical flow.

Keywords: PCSK9; TLR4; helical flow; proinflammatory cytokines.