Korean Circ J. 2025 May;55(5):456-458
https://doi.org/10.4070/kcj.2025.0006
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Epigenetic Regulation of Endothelial-Mesenchymal Transition in Vascular Atherosclerosis Development

JaeHyuk Jang, MD, and Hun-Jun Park, MD, PhD

Division of Cardiology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, Korea

▸ See the article "LncRNA uc003pxg.1 Interacts With miR-339-5p Promote Vascular Endothelial Cell Proliferation, Migration and Angiogenesis" in volume 55 on page 440.

Received: Jan 7, 2025
Revised: Mar 3, 2025
Accepted: Mar 9, 2025
Published online: Apr 7, 2025

Correspondence to
Hun-Jun Park, MD, PhD
Division of Cardiology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, 271, Cheonbo-ro, Uijeongbu 11765, Korea.
Email: cardioman@catholic.ac.kr

ORCID iDs
JaeHyuk Jang
https://orcid.org/0000-0002-2153-2810
Hun-Jun Park
https://orcid.org/0000-0001-8009-9546

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
The authors have no financial conflicts of interest.

Atherosclerosis is a progressive disease characterized by the pathological remodeling of the vessel wall due to the accumulation of lipids and intimal mesenchymal cells, which lead to the formation of atheromatous plaques. In this process, endothelial dysfunction plays a pivotal initiating role in the development of atherosclerosis.[1] The endothelium, a thin layer of cells lining the interior surface of blood vessels, plays a central role in maintaining vascular homeostasis in healthy individuals. Its primary function acts as a selective barrier, regulating the exchange of molecules and cells between the bloodstream and the vessel wall. Beyond this, the endothelium is highly responsive to chemical and biomechanical signals, releasing factors influencing vascular tone, smooth muscle cell proliferation and migration, immune cell adhesion, and inflammation. However, when activated, the endothelium transitions to a pro-inflammatory state, becoming more permeable. This change facilitates the infiltration of leukocytes and lipids into the arterial intima, setting the stage for foam cell formation and the development of fatty streaks—key hallmarks of atherosclerosis.[2]

Recent studies indicate another role for the endothelium in atherosclerosis development and progression through a specialized process known as endothelial-to-mesenchymal transition (EndMT). During EndMT, endothelial cells lose their characteristic marker proteins and functional properties, transitioning to express mesenchymal markers and adopting mesenchymal-like behaviors. This transformation involves the breakdown of cell-cell adhesion and polarity, alongside the acquisition of migratory and invasive phenotypes. These altered cells secrete proinflammatory molecules and increase extracellular matrix production, thereby contributing to plaque formation and influencing plaque stability.[3] Excessive EndMT could lead to plaque instability and rupture, increasing the risk of cardiovascular events. Notably, the extent of EndMT observed in human atherosclerotic plaques strongly correlates with disease severity, underscoring its clinical significance.[4] Deciphering this multi-step, sequential process of cellular reprogramming holds the potential to monitor endothelial cell behavior and prevent the generation of harmful cell population in atheroma plaque. Therefore, EndMT can serve both as a biomarker for early diagnosis of atherosclerosis development and as a therapeutic target for preventing atherosclerosis progression.

kcj
Korean Circulation Journal

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Supervision: Park HJ; Writing - original draft: Jang J; Writing - review & editing: Park HJ.

Non-coding RNAs, such as microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs, play pivotal roles in regulating both physiological development and disease progression.[5] LncRNAs are non-coding RNAs with a length of more than 200 nucleotides that have recently emerged as important regulators in the process of EndMT. For instance, lncRNA H19, found elevated in aortic tissues, has been shown to upregulate transforming growth factor (TGF)-β receptor 2 and thrombospondin 1 through the let-7/TET1 axis, influencing EndMT markers such as Slug, SM22-α, Vimentin, and Fibronectin 1. Similarly, Li et al.[6] reported increased lncRNA MALAT1 expression in both atherosclerotic mice and oxidized low-density lipoprotein (ox-LDL)-treated human umbilical vein endothelial cells (HUVECs). This was accompanied by the downregulation of endothelial markers CD31 and von Willebrand factor, alongside overexpression of mesenchymal markers α-smooth muscle actin (α-SMA) and Vimentin. MALAT1 promoted β-catenin nuclear translocation and exacerbated ox-LDL-induced EndMT via the MALAT1/Wnt/β-catenin pathway. Another lncRNA, LINC00657, was found to be upregulated in the serum of atherosclerosis patients, acting as a sponge for miRNA-30c-5p and activating Wnt7b/β-catenin signaling to drive EndMT in ox-LDL-treated HUVECs. Additionally, lncRNA ZFAS1 facilitated EndMT by inhibiting miR-150-5p, leading to increased expression of Notch3, a known EndMT regulator.[7] In this study, Li and colleagues[6] identified significant upregulation of uc003pxg.1 and downregulation of miR-339-5p in peripheral blood mononuclear cells of coronary heart disease patients. Functional studies revealed that silencing uc003pxg.1 or mimicking miR-339-5p reduced HUVEC proliferation, migration, and the expression of TGF-β1 and α-SMA. Conversely, upregulation of uc003pxg.1 and suppression of miR-339-5p had the opposite effect, promoting cell proliferation and migration by upregulating the expression of TGF-β1 and α-SMA. High-throughput sequencing and dual-luciferase assays further confirmed miR-339-5p as a downstream target of uc003pxg.1, elucidating a novel regulatory mechanism in EndMT and its implications in atherosclerosis.[6]

Canonical TGF-β signaling is considered the driving force of EndMT. In brief, the TGF-β family ligands bind to type I receptors and type II receptors, phosphorylating and thereby activating the transducer SMAD. These complexes translocate to the nucleus, where they collaborate with transcription factors and enhancers to regulate gene expression.[8] In patients with coronary artery disease, a strong correlation has been observed between the extent of EndMT and TGF-β activation in the luminal endothelium.[3] This suggests that endothelial TGF-β signaling actively contributes to plaque progression through the induction of EndMT. Subsequently, miR-339-5p can interact with TGF-β1. Zhang et al.[9] reported that NEAT1 induced osteosarcoma development by modulating the miR-339-5p/TGF-β1 pathway. However, while TGF-β is considered a primary regulator of this process, studies show that inhibiting TGF-β signaling in endothelial cells only partially suppresses EndMT. This indicates the involvement of additional signaling pathways in driving EndMT during atherosclerosis, such as Notch and Wnt/β-catenin signaling. Despite their established roles in developmental EndMT, the contributions of Notch and Wnt/β-catenin pathways to EndMT in atherosclerosis remain unexplored.[10] Further research is essential to unravel the interplay of signaling pathways in EndMT and their implications for atherosclerosis.

Targeting EndMT,—either by reversing or inhibiting it—shows great potential for reducing plaque formation and progression, offering innovative therapeutic strategies against atherosclerosis. Certain compounds, such as Icariin, and clinical drugs like Simvastatin, have demonstrated protective effects against atherosclerosis by inhibiting EndMT. However, effective drugs capable of reversing EndMT remain unavailable. Advancements in single-cell

https://doi.org/10.4070/kcj.2025.0006

and high-throughput sequencing technologies could provide valuable insights into identifying EndMT-related targets for atherosclerosis treatment.

REFERENCES

1. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004;109:III27-32. PUBMED | CROSSREF
2. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007;115:1285-95. PUBMED | CROSSREF
3. Chen PY, Qin L, Baeyens N, et al. Endothelial-to-mesenchymal transition drives atherosclerosis progression. *J Clin Invest* 2015;125:4514-28. PUBMED | CROSSREF
4. Evrard SM, Lecce L, Michelis KC, et al. Endothelial to mesenchymal transition is common in atherosclerotic lesions and is associated with plaque instability. *Nat Commun* 2016;7:11853. PUBMED | CROSSREF
5. Hulshoff MS, Del Monte-Nieto G, Kovacic J, Krenning G. Non-coding RNA in endothelial-to-mesenchymal transition. *Cardiovasc Res* 2019;115:1716-31. PUBMED | CROSSREF
6. Li P, Wang F, Yue A, et al. LncRNA uc003pxg.1 interacts with miR-339-5p promote vascular endothelial cell proliferation, migration and angiogenesis. *Korean Circ J* 2025;55:440-55. PUBMED | CROSSREF
7. Huang Q, Gan Y, Yu Z, Wu H, Zhong Z. Endothelial to mesenchymal transition: an insight in atherosclerosis. *Front Cardiovasc Med* 2021;8:734550. PUBMED | CROSSREF
8. Hata A, Chen YG. TGF-β signaling from receptors to Smads. *Cold Spring Harb Perspect Biol* 2016;8:a022061. PUBMED | CROSSREF
9. Zhang L, Lu XQ, Zhou XQ, Liu QB, Chen L, Cai F. NEAT1 induces osteosarcoma development by modulating the miR-339-5p/TGF-β1 pathway. *J Cell Physiol* 2019;234:5097-105. PUBMED | CROSSREF
10. Souilhol C, Harmsen MC, Evans PC, Krenning G. Endothelial-mesenchymal transition in atherosclerosis. *Cardiovasc Res* 2018;114:565-77. PUBMED | CROSSREF