UTJMS 2025 October 9, **14**(S2):e1-e1 doi:10.46570/utjms-2025-1557

Cysteinyl Leukotriene Receptors Mediate Macrophage-Endothelial Cell Crosstalk and Contributing to Atherosclerosis Progression

Somayeh Darzi[1], Lakshminarayan Teegala[1], Emma Elizabeth Sabu Kattuman[1], Charles Thodeti[2], Sailaja Paruchuri[2*]

[1]College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[2]Professor, Department of Physiology and Pharmacology, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: sailaja.paruchuri@utoledo.edu

Received: 1/10/2025

Accepted: 2/7/2025

Published: 10/9/2025

Introduction: Atherosclerosis a leading cause of cardiovascular disease, occurs when cholesterol-rich plaques accumulate in arteries, narrowing their lumen. This chronic inflammatory disease involves dysfunction of endothelial cells (ECs) and macrophages (M?s), which can lead to increased uptake of oxidized low-density lipoprotein (ox-LDL) by M?. Cysteinyl leukotrienes (cys-LTs; LTC4, LTD4, LTE4) are inflammatory molecules that act through their receptors, CysLT1R and CysLT2R. Few studies have examined cys-LTs in ECs or M?s individually, and their effects on EC-M? interactions are unclear. Therefore, we investigated the role of CysLTR signaling in EC-M? interactions using an *in vitro* co-culture system and an *in vivo* PCSK9-induced atherosclerosis model employing CysLTR knockout mice.

Objectives: To uncover how CysLTRs modulate EC-M? function in atherosclerosis progression.

Methods: *In vivo*, atherosclerosis was induced in WT, *Cysltr1-/-* and *Cysltr2-/-* mice by ip injections of PCSK9 followed by high-fat diet (HFD) for 12 weeks. Aortic plaques were examined to analyze plaques and their composition using Oil-red O staining and immunofluorescence. *In vitro,* mouse ECs were co-cultured with BMDMs from WT, *Cysltr1-/-* and *Cysltr2-/-* mice in transwell system for 6 hours, analyzed by ELISA and qPCR.

Results: In EC-BMDM co-cultures, BMDMs showed increased expression of CysLT1R and an inflammatory profile, with higher levels of IL-6, IL-1?, GM-CSF, and scavenger receptors like OLR-1, compared to isolated cultures. Interestingly, *Cysltr1-/-* BMDMs co-cultured with ECs exhibited significantly reduced levels of inflammatory cytokines and scavenger receptors compared to WT BMDMs. Importantly, PCSK9 + HFD *Cysltr1-/-* mice exhibited reduced plaque formation, despite higher lipid profiles compared to PCSK9 + HFD WT mice. Further, we found reduced macrophage infiltration and smooth muscle cell migration in plaque areas of *Cysltr1-/-* mice compared to WT mice.

Conclusion: Our study underscores the vital role of CysLT receptors in regulating EC-M? interactions and driving atherosclerosis progression.

Keywords: Cysteinyl Leukotrienes, Atherosclerosis ,Inflammation, Macrophage, Endothelial Cells

