The Role of Cysteinyl Leukotrienes and Their Receptors in EC-Macrophage Interaction and Therapeutic Implications for Atherosclerosis

Somayeh Darzi1*, Lakshminarayan Reddy Teegala1, Emma Elizabeth Sabu Kattuman1, Sailaja Paruchuri2

1College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
2Department of Physiology and Pharmacology, The University of Toledo, Toledo, OH 43614

*Corresponding author: somayeh.darzi@rockets.utoledo.edu

Keywords: Cardiovascular Disease, Atherosclerosis, Cysteinyl Leukotrienes, Endothelial cells, Macrophage

Published: 22 May 2024

Background: Cardiovascular disease (CVD) remains a global health threat with atherosclerosis at the forefront. Atherosclerosis involves low density lipoprotein oxidation, monocyte infiltration through endothelial cells (EC), smooth muscle cell (SMC) proliferation leading to plaque formation and chronic inflammation. During inflammation, cysteinyl leukotrienes (cys-LTs; LTC4, LTD4, LTE4) are released from the membrane via the 5-lipoxygenase pathway and exert their effects via cysteinyl leukotriene receptors (CysLTR) 1 and 2. Since these receptors transduce inflammatory signals and regulate EC and macrophage dysfunction, we hypothesized that they play vital role in macrophage-EC interactions in a co-culture and contribute to atherosclerosis.

Methods: Mouse dermal ECs were co-cultured with bone marrow-derived macrophages (BMDM) in the presence or absence of CysLT1R and CysLT2R antagonists MK571 and BayCysLT2 respectively for 6-hours. Culture supernatant and cells were collected for ELISA and qPCR analysis, respectively. EC contraction was determined by F-actin staining.

Results: We observed a significant increase in pro-inflammatory cytokine Interleukin (IL)-6 in the EC-BMDM co-culture. Further, BMDM in co-culture upregulated IL-6, IL-1β, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Oxidized Low-Density Lipoprotein Receptor-1 (OLR-1) transcripts with a simultaneous reduction in the Vascular Endothelial Growth Factor (VEGF) transcript. ECs in co-culture exhibited an increase in IL-6, and upregulation of adhesion molecules like Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) transcripts and a contractile response revealed by gap formation. Importantly, IL-6 was significantly inhibited by both MK571 and BayCysLT2 suggesting that CysLTR signaling mediate EC-macrophage interactions.

https://dx.doi.org/10.46570/utjms.vol12-2024-1231  ©2024 UTJMS
**Conclusion**: Our results suggest that blocking CysLTR may offer a promising therapy to prevent plaque initiation during atherosclerosis.