Macrophage Lipid Metabolism in the Absence Of Cholesterol Esterification

Harjeet S. Sandhu, Tony Hu, Elena Abramova, Andrew Gow
Rutgers, The State University of New Jersey

Acute Lung Injury (ALI) is characterized by lung inflammation. Acyl-CoA:Cholesterol acyltransferase (ACAT1) is an enzyme that esterifies free cholesterol into cholesterol esters and is critical in lipid handling. ACAT1 inhibitors, like K-604, reduce lung injury. To study their role in macrophages a myeloid specific ACAT1 knock out mouse (Acat1-M/-M) has been generated. We hypothesize that loss of ACAT1 in lung macrophages reduces intracellular cholesterol ester accumulation, leading to upregulation of cholesterol efflux transporters such as ABCA1 and ABCG1, thereby promoting lipid efflux and lowering inflammation. To test this WT and Acat1-M/-M mice were intratracheally instilled bleomycin to induce lung injury or PBS as control. On day 7, at the peak of inflammation, mice were necropsied and bronchoalveolar lavage (BAL) cells and lung tissue collected. Western blot of BAL cells was used to determine ABCG1 protein expression and immunohistochemistry (IHC) to visualize ABCA1 expression. Western blot analysis showed a baseline increased ABCG1 in BAL macrophages from Acat1-M/-M mice compared to the WT, but WT expression increased to match Acat1-M/-M after bleomycin treatment. ABCA1 showed no difference between treatments through IHC, indicating possible less reliance on ABCA1 for cholesterol efflux in Acat1-M/-M. Future work will examine cholesterol uptake mechanisms, like CD36, and cholesterol signaling pathways, such as LXR, to fully understand macrophage cholesterol handling. Supported by NIH R25ES020721, CEED ES005022, and the American Society for Pharmacology and Experimental Therapeutics.