**Introduction:** MRP1 is highly expressed in the human’s lungs and impacts drug treatment and COPD. However, its expression, localization, and activity in distal lung epithelium remain unclear. This study aimed to investigate these aspects in primary human alveolar epithelial cells and the NCI-H441 cell line and explore the effects of CSE and inhaled drugs on MRP1.

**Methods:** Isolate AT2 cells from non - tumor lung tissue. RNA isolation(To provide samples for subsequent q-PCR analysis of mRNA expression levels of ABCC1), q-PCR (Find that the mRNA expression level of ABCC1 gene did not change significantly during the differentiation of AT2 cells to AT1-like phenotype), immunoblot, cell surface protein biotinylation (To confirmed that MRP1 was mainly located in the basolateral membrane of polarized AT1-like cells and NCI-H441 cells), immunohistochemistry, confocal laser scanning microscopy, bidirectional transport, and efflux experiments were performed. Cells were exposed to CSE and various inhaled drugs, and the abundance and activity of MRP1 were analyzed.

**Results:** MRP1 protein abundance increased during the differentiation from AT2 to AT1-like cells, while ABCC1 gene levels remained stable. MRP1 was mainly localized in the basolateral membranes of both cell types. CSE and some inhaled drugs (budesonide, beclomethasone dipropionate, salbutamol sulfate) decreased MRP1 activity. Interestingly, CSE increased MRP1 abundance, but other drugs not. (5μM budesonide decreased by 19.6%; 10μM budesonide decreased by 24.7%; 50μM beclomethasone dipropionate decreased by 55.1%; 100μM salbutamol sulfate decreased by 22.7%)

**Conclusion:** MRP1 is functionally expressed at high levels in the basolateral membranes of human alveolar AT1-like cells. The NCI-H441 cell line can be used as an in vitro model for studying MRP1 in the distal lung epithelium. Tobacco smoke and inhaled drugs can modulate MRP1 activity and abundance, suggesting MRP1 could be a novel therapeutic target for COPD.