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CLCA1/TMEM16 axis in chronic lung disease

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Our previous work identified the calcium-activated chloride channel TMEM16A, as a critical factor for the pathophysiology of pulmonary arterial hypertension. Recently, CLCA1, an endogenous activating factor, has been postulated as a regulator of TMEM16A. CLCA1 stabilizes TMEM16A and prevents its internalization leading to prolonged expression and perhaps function at the cell surface. However, this activation has been shown so far only in an artificial system in vitro. Thus, the current project aims to characterize the CLCA1/TMEM16A axis and its function in chronic lung diseases. Our investigations were carried out both in-vitro and in-vivo. In -vitro studies were performed on the epithelial cell line, A549, where CLCA1 was checked for a physiological role in two different settings. First by overexpressing CLCA1 in A549 cells and second by adding conditional CLCA1 medium to the A549 cells. Results show that CLCA1 causes cell proliferation when CLCA1 is overexpressed. For the first time, we show, that CLCA1 does not require to undergo cleavage inside the cell to get secreted outside the cell. For in-vivo studies, the Fra-2 chronic lung-diseased mouse model was used, where the active level of CLCA1 was first established through western blot. Quantifying the results revealed that the active CLCA1 levels are higher in Fra-2 compared to the WT mouse. Furthermore, TMEM16A is also present at comparable levels in both Fra-2 and WT mice. In conclusion, the CLCA1/TMEM16A axis was successfully established in our Fra-2 chronic disease model. Our new finding that CLCA1 itself causes cell proliferation warrants further investigation.