

TRPA1 channels as novel molecular targets for anti-inflammatory therapies in CF lung

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Background. *Pseudomonas aeruginosa* colonization, prominent inflammation with massive expression of the neutrophil chemokine IL-8 and luminal infiltrates of neutrophils are hallmarks of chronic lung disease in Cystic Fibrosis (CF) patients. The nociceptive Transient Receptor Potential Ankyrin 1 (TRPA1) calcium channels have been recently found involved in non-neurogenic inflammation.

Hypothesis and objectives. TRPA1 channels could be involved in the pro-inflammatory signaling pathways activated in CF airway epithelial cells infected by *P. aeruginosa*. The principal objective is to verify whether TRPA1 channels could be relevant molecular targets for innovative anti-inflammatory therapies in CF patients.

Methods. CF lung sections have been analyzed to verify and localize TRPA1 expression. Several airway epithelial cell lines and primary culture of bronchial epithelial cells derived from patients affected by CF and from healthy subjects have been tested for TRPA1 expression (at mRNA and protein levels) and function (by TRPA1 agonists and inhibitors).

Results. TRPA1 channels are expressed in the CF pseudostratified columnar epithelium facing the bronchial lumina exposed to bacteria, where IL-8 is co-expressed. Inhibition of TRPA1 expression results in a relevant reduction of release of several cytokines, including IL-8 and the pro-inflammatory cytokines IL-1 β and TNF- α in CF primary bronchial epithelial cells exposed to *P. aeruginosa* and to the supernatant of mucopurulent material derived from the chronically infected airways of CF patients.

Spin-off for research & clinical purposes. TRPA1 channels are a relevant part of the pro-inflammatory signaling regulating CF lung

inflammation. The results provide the rationale to test the pharmacological inhibitors of TRPA1 channels in order to intervene in synergy with CFTR correctors and potentiators in the cure of the lung pathology of CF patients.

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