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Summary

STORE-INDEPENDENT ORAI1 SIGNALING DEFINES BASAL CFTR FUNCTION IN SECRETORY EPITHELIA

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A novel SPCA2–STIM1–Orai1 nanodomain drives store-independent calcium influx that maintains basal CFTR activity in secretory epithelial cells through local cAMP production by calcium-calmodulin-sensitive adenylyl cyclases.

KEY POINTS

- Orai1 mediates constitutive, store-independent calcium influx sustained by SPCA2 that occurs independently of ER calcium depletion but requires STIM1, forming discrete apical membrane nanodomains that colocalize with SPCA2, STIM1, PKA, and CFTR.
- Inhibiting Orai1 reduced basal chloride and bicarbonate secretion, disrupted mitochondrial ATP production, and suppressed pancreatic ductal fluid secretion in vitro and in vivo.
- The stimulatory effect of calcium influx on CFTR was mediated via calcium-calmodulin-sensitive adenylyl cyclases AC1, 3, and 8, which co-clustered with Orai1 and CFTR, with their knockdown phenocopying Orai1 inhibition and no additive effect when both pathways were blocked.
- This regulatory module is conserved across secretory epithelia including mouse pancreatic, hepatic, and airway organoids and human pancreatic organoids, representing a key mechanism for maintaining basal fluid secretion and epithelial homeostasis independent of neurohormonal stimulation.

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