A mathematical model of the phosphoinositide pathway in human pulmonary epithelial cells.

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Phosphoinositides are important signaling lipids in the cell membranes. We propose a computational model that accounts for all known species of phosphoinositide's in the plasma membrane of mammalian epithelial cells. It focuses, in particular, on the control of ion channels and the role of the epithelial sodium channel ENaC, which is critically involved in diseases like cystic fibrosis. The model faithfully replicates the steady state of the phosphoinositide pathway system, as well as several dynamic phenomena that had been observed and documented in the literature. Furthermore, local and global sensitivity analysis demonstrates that the model is robust to moderate alterations in any of the parameters. The model was validated against data from siRNA screens and allow us to test various novel hypotheses. With respect to ENaC, which is regulated by PI(4,5)P2, the model suggests a control strategy where the activity of the enzyme PIP5KI is decreased. This reduction in activity is most efficacious in affecting PI(4,5)P2 levels and, consequently, the functionality of ENaC.

References