Inhibition of basal p38 or JNK activity enhances epithelial barrier function through differential modulation of claudin expression

CARROZZINO, Fabio, et al.

Abstract

Tight junctions (TJs) form a barrier to the paracellular diffusion of ions and solutes across epithelia. Although transmembrane proteins of the claudin family have emerged as critical determinants of TJ permeability, little is known about the signaling pathways that control their expression. The aim of this study was to assess the role of three mitogen-activated protein kinases (MAPKs), i.e., extracellular signal-regulated kinase-1/2 (ERK1/2), c-Jun NH(2)-terminal kinases (JNKs), and p38 kinases, in the regulation of epithelial barrier function and claudin expression in mammary epithelial cells. Addition of either PD169316 (a p38 inhibitor) or SP600125 (a JNK inhibitor) induced formation of domes (a phenomenon dependent on TJ barrier function) and enhanced transepithelial electrical resistance, whereas U0126 (an inhibitor of the ERK1/2 activators MEK1/MEK2) had no significant effect. Similar results were obtained using mechanistically unrelated p38 or JNK inhibitors. PD169316 increased the expression of claudin-4 and -8, whereas SP600125 increased claudin-4 and -9 and downregulated claudin-8. Silencing of p38alpha by [...]
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