

# Calcium oscillations in epithelial cells; origin and role for cell contacts and survival

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Na,K-ATPase belongs to the rapidly expanding group of multifunctional proteins. In addition to its well known function as an ion pump, it also serves as a signal transducer activated by ouabain, a Na,K-ATPase specific ligand. Our group studies the ouabain activated calcium signaling pathway in kidney epithelial cells or COS-7 cells, an epithelial cell line derived from monkey kidneys. Exposure of these cells to sub-saturating ouabain concentrations triggers, after a delay time of 5-10 min, low frequency calcium oscillations that spread from cell to cell. The response is mediated by phosphorylation-dependent activation of STIM and direct interaction between the NKA catalytic subunit and the InsP3 receptor.

The ouabain mediated calcium signal activates a large -scale signaling network. In a recently performed phosphoproteomic study in COS-7 cells, treated with a subsaturating concentration of ouabain for 10 and 20 min, we have identified 2580 regulated phosphorylation events on 1242 proteins. Numerous proteins regulating tight and gap junctions were found to be ouabain phosphorylated, suggesting a specific role for ouabain in epithelial cells. Calcium and calmodulin dependent protein kinases, which are known to be particularly sensitive to oscillatory calcium signals, were also enriched among the among the ouabain regulated phosphoproteins. CamK2 $\gamma$ , which inactivates the proapoptotic protein BAD, belongs to the ouabain regulated proteins. Protection from apoptosis is one of the important down-stream effects of ouabain signaling. This protective effect is lost in cells where CamK2 $\gamma$  is down-regulated.

Taken together, our results suggest that ouabain mediated calcium oscillations play an essential role for the function and survival of epithelial cells