

## **A role for secretory pathway calcium ATPase 2 (SPCA2) in calcium transport, breast cancer and mammary gland development**

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The tight control and regulation of intracellular calcium levels is essential for maintaining intracellular homeostasis and this process relies on calcium transporters including P-type calcium-ATPases. The secretory pathway calcium-ATPases (SPCAs), of which two isoforms have currently been identified, are a group of calcium transporters that are involved in the transport of both calcium and manganese ions across the Golgi membrane. In these studies, we investigated the hypothesis that SPCAs, particularly the less widely expressed SPCA2, are important in normal mammary gland physiology and breast cancer pathophysiology. These studies show a pronounced increase in the mRNA levels of SPCA2 in a bank of breast cancer cell lines compared to normal breast cell lines (200-1000 fold,  $p < 0.05$ ). We also observed elevated SPCA2 mRNA levels in 80% of clinical breast cancer samples studied compared with matched control tissue (2-8 fold,  $p < 0.05$ ). Given that the role of the Golgi apparatus in calcium secretion during lactation is unclear, we examined SPCA2 expression in mammary gland isolated from virgin, pregnant, lactating and involuting mice. We show, for the first time, a dramatic up-regulation of SPCA2 mRNA (~35 fold,  $p < 0.05$ ) during lactation. Our results suggest that SPCA2 is involved not only in the supply of calcium ions to the Golgi lumen for the likely regulation of the secretory pathway, but may have a role in enriching calcium in secretory vesicles destined for the alveolar lumen and thus the milk during lactation. These studies therefore indicate a potential role for SPCA2 in the normal functioning of the mammary gland and also implicate this ion transporter in the pathophysiology of breast cancer.