Identifying novel roles in cell communication for disease-related proteins

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A major research interest of my group is in identifying previously unidentified roles in cell communication of proteins associated with neurodegeneration and human neurodegenerative disorders. We have recently identified the role of a chloride channel in regulating vesicle loading and release (Maritzen *et al.*, 2008) and novel roles of Down syndrome-related proteins in regulating exocytosis (Keating *et al.*, 2008; Yu *et al.*, 2008). One of these proteins, known as Rcan1 (or Dscr1), is overexpressed in the brains of Down syndrome (DS) and Alzheimer's disease (AD) individuals and is an endogenous inhibitor of the phosphatase calcineurin. Using mice which knock-out (KO) and transgenically overexpress (Tg) Rcan1 we find that Rcan1 regulates both the rate of exocytosis and vesicle fusion pore kinetics. The number of secretory events in chromaffin cells, a commonly used model of neuronal exocytosis, is decreased by 36% in mice transgenically overexpressing (Tg) Rcan1 ($p<0.05$, $n=23$) and 50% in mice with no Rcan1 (KO) expression ($p<0.01$, $n=21$). Rcan1 also positively influences the speed of vesicle pore opening and closing, resulting in lower levels of release from individual vesicles and more "kiss-and-run" type fusion in Rcan1 Tg cells. The reverse is seen in KO cells. These effects on fusion pore kinetics are due to chronic calcineurin inhibition by Rcan1. We have also investigated effects of Rcan1 on insulin-secreting beta cells in which calcineurin activity is critical (Heit *et al.*, 2006). We find that pancreatic islet size, fasting blood glucose, glucose tolerance and the islet expression of genes important in β-cell survival, proliferation and insulin production are reduced in Rcan1 Tg mice. Rcan1 may therefore be an important new player in both neuronal and endocrine cell communication.

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