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Cav β subunit N- and C-terminal variable domains: roles in N-type (Cav2.2) channel localisation

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Cav β subunits (Cavβs) are multifunctional regulatory proteins which promote trafficking, surface expression and biophysical modulation of Cavs. Whilst the function of the conserved SH3-GK core of βs is largely known, the roles of the hypervariable N- and C-termini that flank the core are not so well understood. Given that Cavβs may function as molecular scaffolds, we have examined the roles of the N- and C- terminal domains of Cavβ subunits in membrane targeting and sub-cellular localisation of Cav channels.

Functional CFP-tagged Cavβ1b, β2a, β3 and β4, were expressed in COS-7 cells either alone, or, with GFP-tagged Cav2.2. When expressed alone, β1b was distributed throughout the cell, β2a and β3 were localised primarily at the plasma membrane (PM), and β4 was found predominantly within the nucleus. Whilst all βs promoted trafficking of GFP-Cav2.2 to the PM, the level of expression differed; β1b > β2a > β3 > β4. We next tested mutant CFP-Cavβ1bs lacking either the N- and/or C-termini. Deletion of the C-terminus caused a striking increase in both cytoplasmic and PM expression of β1b alone, whereas, removal of either the N- or C-terminus reduced membrane targeting of GFP-Cav2.2.

Thus, we highlight roles for both the N- and C-termini of Cavβs in fine-tuning the spatial expression of Cav2.2 (and perhaps all pore-forming α1 subunits), and thence Ca2+ signalling within cells. Our findings are also consistent with recent evidence that Cavβs promote channel-independent protein-protein interactions. Experiments are in progress to define the roles of the N- and C-termini in such interactions.