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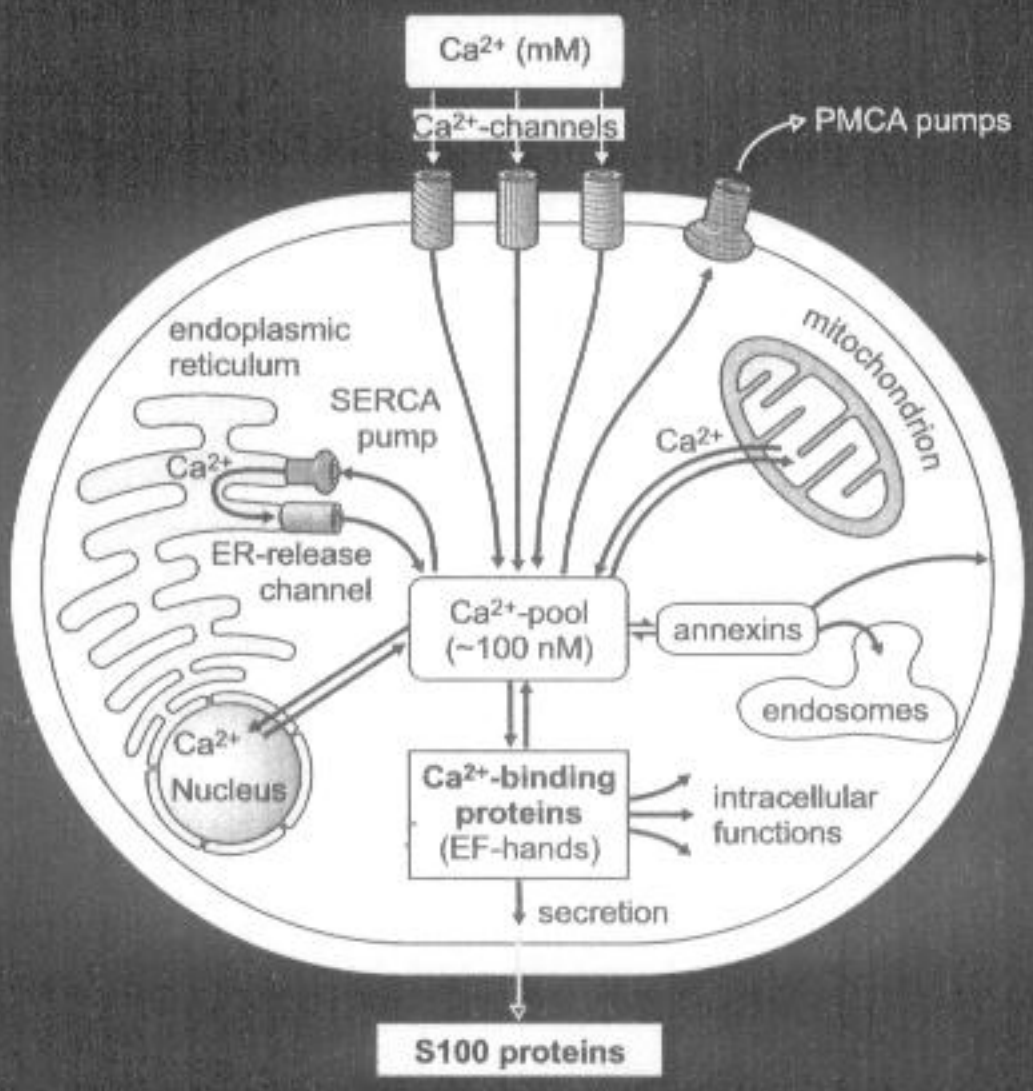

Programme, Abstracts, List of Participants

NEW EVOLUTIONARY MODELS EXTEND THE STRUCTURE-FUNCTION PARADIGM FOR ANNEXINS

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We have studied the relationship between structure and function of annexins by computational sequence analysis of proteins and gene regulatory regions from over 2000 homologs. An updated phylogenetic tree describes the pattern and timing of gene duplications and the extent of evolutionary change in over 100 distinct subfamilies. Features of domain architecture are presented beside the evolutionary tree branches for all subfamilies to distinguish normal divergence from independent, convergent evolution of characteristics common to annexins in all eukaryotic kingdoms. Conservation analysis by hidden Markov models and divergence analysis were used to create unique molecular profiles for each protein subfamily and these were incorporated into 3D molecular models. The results permitted a visual assessment of the functionally important regions of each annexin protein and the molecular basis for divergent functions between subfamilies. Further detailed analysis revealed specific patterns of variation in surface exposed residues likely to influence membrane-binding kinetics and enable specific receptor interactions. These included a preponderance of bulky or hydrophobic residues (Trp, Phe, Tyr, Cys) in the exposed interhelical loops normally associated with carbonyl groups (Gly, Thr) and acidic residues (Glu, Asp) that form the canonical annexin calcium-binding domain. Many other subfamilies displayed a conserved pattern of basic residues, usually in the form of "K/R/H-G-D" motifs reminiscent of the ligand typical for transmembrane integrins. We interpret these data by proposing that the presence of either hydrophobic or basic residues in strategic, external sites normally occupied by calcium-coordinating residues reflects a spectrum of diverse mechanisms responsible for cell membrane interaction. This provides an original molecular basis for interpreting much experimental data that has long demonstrated differing calcium sensitivities, membrane phospholipid specificities, on-off kinetics and over all membrane affinity of different annexins. Key models of newly discovered annexins are presented to highlight these findings, including the first bacterial annexin, octad annexins unrelated to annexin A6, the expanded protist annexin family, the complete plant annexin family replete with defective calcium binding sites substituted by KGD motifs, and a multitude of unique subfamilies from invertebrates. The history of vertebrate annexins will be charted to trace their invertebrate origins and their rapid expansion in primitive fishes, the selective loss or amplification of individual subfamilies in specific lineages, and the emergence of human polymorphisms potentially associated with phenotypic differences.

Reference:
RO Morgan, S Martin-Almedina, JM Iglesias, MI Gonzalez-Florez, MP Fernandez. Evolutionary perspective on annexin calcium-binding proteins. Biochim Biophys Acta 1742: 133-140 (2004).

Keywords: Annexin, computational biology, evolution, functional determinants, membrane binding, receptor docking, structural motifs.