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Multi-author Review

Annexins

Annexins: what are they good for?

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Abstract. Annexins comprise a unique family of calcium- and phospholipid-binding proteins. At least one of the twenty members thus far described from this family can be found expressed in nearly every eukaryotic cell type. As common as these proteins may be, no one clear function for all has been established. Historically, individual members of this family have been given various names describing their ability to associate with a host of intra- and extracellular proteins and with cellular lipid membranes. The collection of reviews in this issue of CMLS represents an effort to offer a coordinated view of the research activities in the field and to extract structural and functional commonalities.
Key words. Annexin; lipocortin; calpactin; endonexin; anchorin; chromobindin; synexin.

Sentences such as those in the abstract are typical of introductions for research articles dealing with any member of the annexin family. These ambiguous sentences are in startling contrast to the otherwise precise language of experimental scientists and reflect a certain helplessness toward proteins that are as capable of altering functions as chameleons do their colours. It is typical of annexin researchers to detect these proteins via untargeted approaches. For example, annexin I (lipocortin I) has been detected by researchers exploring the regulation of phospholipase A2 in inflammation. Annexin II (calpactin I, lipocortin II) was found during the investigation of the cellular calcium metabolism and secretory pathways. Annexin V (anchorin CII, lipocortin V, endonexin II) appeared in affinity chromatography isolation of receptors for collagen and in investigations of secretory pathways. A plant annexin was found as a regulatory element for callose synthase (Delmer and Potikha, p. 546). What do all these findings have in common?

First, calcium-binding sites and the 'calcium pore' are the most conserved elements in the protein structure (Liemann and Huber, p. 516). It is therefore reasonable to assume calcium ions to be part of the core functional aspect of annexins. In fact, the primary sequence of the 27 annexin genes described thus far (Morgan and Fernández, p. 508) restricts the three-dimensional structures to one very basic pattern with almost no variations.

Second, all findings involve, by direct or indirect interference, cell membranes: the substrates for phospholipase A2 are membrane lipids, calcium metabolism involves calcium fluxes across membrane borders, secretory pathways imply lipid vesicle transport, receptors for matrix proteins must reside attached to the outside plasma membrane, and callose is synthesized at the plasmalemma of plant cells.

Third, annexins are elements of many (all?) eukaryotic organisms, single-celled organisms as well as plants and animals. Therefore, mechanisms such as regulation and binding of extracellular matrix molecules (von der Mark and Mollenhauer, p. 539) and regulation of inflammatory processes (Reutelingsperger and van Heerde, p. 527) must be secondary, acquired functions, based upon a primordial function that is evolutionarily older than complex multicellular organisms.

The involvement in vesicle transport has been proposed as the basic function at least for those annexins found to be associated with vesicular transport in secretory active cells (Donnelly and Moss, p. 533). However, not all cells are secretory. If vesicular transport is the primordial function, this feature possibly includes membrane shuttles to intracellular targets. Linked to this concept are the findings on the phosphorylation of some, but not all, annexins in specific metabolic states of cells (Rothhut, p. 522).

Currently, it is very difficult to identify a baseline function for these features since they are expressed in very different cells and organisms and in very different metabolic patterns. Major shifts in subcellular locations experienced by some annexins are evident: from the cytosol to the nucleus, and from intracellular to cell surface locations (even though annexins have no signal peptide sequence and do not pass the Golgi apparatus). However, the name 'annexin', given very early in the history of this protein family, may indeed describe best what the task of these macromolecules is: to annex, to link structural domains together, to facilitate static (matrix receptors) and dynamic (vesicle transport) macromolecular interactions. In one way, annexins seem to share tasks with heat shock proteins (stress proteins, chaperonins). This group (not a family in the strict sense) of proteins was first detected as functional elements of cellular stress responses. Heat shock proteins

have been recognized as a major element of protein folding, maturation, and transport across the cell and cell membranes [1]. Unlike stress proteins, the annexins are expressed constitutively at constant levels and so far little evidence exists for major shifts in expression levels, even in extreme pathophysiological situations (Bastian, p. 554).

It could be argued that the receptor function for extracellular proteins such as collagen and tenascin is the most recently evolutionarily acquired task of annexins. 'Mechanical' and 'transport' capabilities could have been adapted and transformed to hold on continuously to a (literally) 'trans-ported' element (the matrix molecule), calcium-binding and pore sites being used as a means to regulate cellular responses to what is transmitted through the extracellular matrix.

From all these speculations, hypotheses and theories, it is obvious that annexin research is still in its infancy, and calls for the establishment of innovative and exciting research approaches. This is documented in detail in the following eight reviews on annexin genes, structures and functions.

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[1] Feige U., Morimoto R. I. and Yahara I. (eds) (1996) Stress inducible cellular responses. Birkhäuser Verlag, Basel

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