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Themed Section: Annexins VII Programme

EDITORIAL

'Annexins' themed section

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LINKED ARTICLES
This article is part of a themed section on Annexins VII Programme. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-7

The 'annexins' are an evolutionarily ancient family of monomeric proteins which are widely distributed throughout eukaryotic phyla – specifically the animal, plant and fungal kingdoms – but which are largely absent from prokaryotes and yeasts. A characteristic feature of the family is the presence of an 'annexin core domain' which generally comprises four (occasionally more) repeating subunits of approximately 70 amino acids (the 'annexin' repeat). These subunits usually contain characteristic 'type 2' calcium binding sites although in some members of the family, these have been replaced with other motifs.

More than 150 annexins have been identified over 50 species. Twelve proteins have been identified in humans; these are conventionally referred to as annexin (Anx) A1-13 (the Anx-A12 gene is unassigned). The descriptor 'A' denotes their vertebrate origin as opposed to insect, fungal, plant or protist annexins, which are denoted by 'B', 'C', 'D' or 'E' respectively. Most human annexins are thought to be derived from a single ancestral gene (Anx-A13).

In addition to the characteristic core domain, individual vertebrate annexins have a unique N-terminal domain of variable length. This harbours motifs that can recognize and bind to other intracellular protein partners, such as those of the S100 family, and often contains residues that can be modified by post-translational processing, including phosphorylation. The N-terminus is a rapidly-evolving component of these molecules and is probably responsible for the diversity of functions found within the family.

Structurally, in the right intracellular *milieu*, free annexins fold into a concave α-helical disk. Calcium binding sites on the convex side facilitate the attachment of this conformer to plasma membranes or other phospholipid containing structures. The N-terminal domain lies buried in the concave surface, but may 'flip' out in the presence of calcium making it available for binding to other partners.

Why are the annexins of interest to pharmacologists?

Whilst we are only now beginning to understand their biology, it is clear that these proteins are involved in a great number of intracellular processes such as membrane trafficking and organization as well as, surprisingly, functioning as extracellular local hormones as well. The observation (for example) that extracellular Anx-A1 has striking anti-inflammatory properties, and that the pharmacophore resides within a sequence in the N-terminal domain, was certainly not an intuitive finding. It seems, once again, that having developed a useful motif, evolutionary pressure has adapted it again and again to fulfill other jobs. There is a growing list of pathologies – 'annexinopathies' – associated with defects in annexin structure or function.

A further discovery of interest to the pharmacological community was the demonstration that several drugs related to the benzodiazepine or phenothiazine structure can bind to the core domain of these molecules modifying their behavior. Whether this is relevant to the mechanism of action of any of these drugs remains to be seen.

Progress in the annexin field is reviewed by periodic meetings of the annexin community. The 7th International Conference on Annexins was the most recent in this series. It was held on the Charterhouse Square Campus of St Barts and The London School of Medicine, Queen Mary University of London in September 2013. The event was organised and hosted by the William Harvey Research Institute and supported in part by a grant from the British Pharmacological Society. Some of the papers presented at this conference are collected together here in this 'virtual' themed issue and speak to the many roles for annexins.

In the first paper in this issue, Jones and his and colleagues highlight the role of annexins as prominent membrane proteins in the trematode integument and discuss the idea that these could be used to develop an immunotherapy for *Schistsomiasis* (Leow *et al*. 2015). Turning to mammalian systems, Rentero's group investigate the role of Anx-A6 – an

unusual annexin with 8 as opposed to the more usual 4 'annexin repeats' – as a membrane scaffolding protein and the implications of this for regulation of signal transduction (Alvarez-Guaita *et al*. 2015). Anx-A2 is one of those annexins with confirmed extracellular as well as intracellular actions (it can act as a cell surface receptor for tissue plasminogen activator) and in the final paper, Dekker's laboratory has used a 'toolbox' of peptides to study the interaction of Anx-A2 with its principal binding partner (S100A10) and to determine how this modifies and regulates its properties (Liu *et al*. 2015).

We hope that the papers published in this themed section will serve to stimulate interest in this protein family, which we commend as a fertile area for future pharmacological investigation.

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Further reading

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