A Is For . . .

Annexin

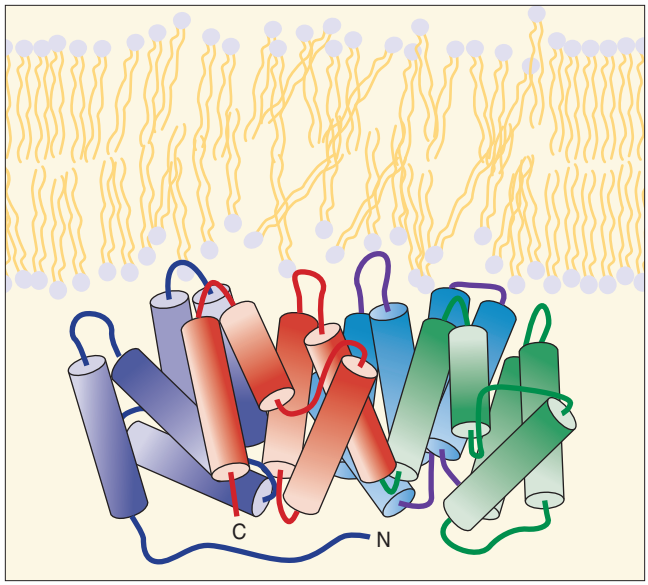
annexin *One of a family of proteins capable of binding in a calcium-dependent manner to negatively charged phospholipids; thought to participate in membrane organization and regulation of calcium flux.*

Among types of calcium-binding proteins, some are considered to be more active than others in calcium signaling, because their properties change in response to calcium binding. Annexins are in that group. Their physiologic functions are not known but are likely to vary for each annexin. Thirteen annexins have been identified so far in vertebrates and more than 160 altogether.

When first found beginning in the 1970s, annexins were given diverse names reflecting their biochemical properties: synexin, chromobindins, calcimedins, lipocortins, and calpactins. Later analysis showed some properties to be shared, along with structure and sequence, so the unrelated names were superseded in 1990.

Each annexin has two principal domains. The carboxy-terminal "core" contains the calcium- and membrane-binding sites on the convex side of a slightly curved disk. The amino-terminal "head," on the concave side of the disk, has a more variable structure that presumably determines the function of each individual annexin.

For some annexins, there is evidence for function in vesicle trafficking or membrane organization, but for others, the most intriguing possibility is also the most recently described.



Annexins consist of a tightly packed, α-helical core that forms a Ca^{2+}-regulated membrane-binding region. Annexins bound peripherally have been proposed to increase membrane permeability, promoting ion flow. Increased calcium levels cause the annexin to bind the membrane more tightly, thus stabilizing it. (Adapted from Gerbe and Moss: *Physiol Rev* 82:331-371, 2002.)

Crystal structures of the conserved carboxy-terminal annexin "core" show a hydrophilic pore, and most annexins have been shown to have calcium channel activity in artificial lipid bilayers (though this property has not been demonstrated so far in living cells). The activity is selective for calcium and displays electrophysiologic properties that correspond to those of uncharacterized calcium channels in nonexcitable cells, so the idea attracts considerable attention.

Two conceptual obstacles exist. First, annexins are generally thought to bind to membranes peripherally, not integrally. Only a single report to date suggests a reversible change in annexin conformation that could produce a membrane-spanning protein. But experimentally, this unfolding and insertion into an artificial membrane occurred only at pH <6, a level probably never reached in a living cell.

Second, increases in local calcium levels are known to bind annexins to membranes more tightly, with the effect of stabilizing the membrane, whereas calcium channel activity requires membrane destabilization. Indeed, the observation is that as the calcium concentration rises, annexin calcium channel activity decreases.

Perhaps, rather than forming ion channels in membranes themselves, annexins are a type of calcium sensor that regulates other channels. In either case, annexins would be both effectors and regulators of calcium flux.

All cell types express a range of annexins, but no single annexin is present in all cells. Annexins also occur outside cells, with receptors for them on cell surfaces and in the extracellular matrix. In fact, extracellular annexin activities are better understood than intracellular ones, though a mechanism for annexin secretion has yet to be described.

Annexin A2, one of the human varieties, appears to be a surface-bound receptor for a number of molecules, including plasminogen and tissue plasminogen activator (tPA). The presence of annexin A2 on the surface of vascular endothelial cells would favor thrombolysis, whereas its absence or reduced activity could predispose to cardiovascular disease.

On annexin A2, the tPA-binding site consists of six amino acids on the amino-terminal tail. One of the six residues is an accessible cysteine, which can be replaced by homocysteine that thus prevents tPA binding. This might be the link between elevated homocysteine levels and risk of atherogenesis, though it must be pointed out that there are other cell surface receptors for tPA and that annexins bound to other proteins have fibrinolytic effects.

RECENT REVIEW

Volker Gerbe and Stephen E. Moss: Annexins: from ftructure to function. *Physiological Reviews* 82:331-371, April 2002.