Expression and functions of annexins in the kidney

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Markoff, Arseni, and Volker Gerke. Expression and functions of annexins in the kidney. Am J Physiol Renal Physiol 289:F949—F956, 2005; doi:10.1152/ajprenal.00089.2005.—This review article summarizes current knowledge about the locations and possible functions of annexin family members in the kidney. Beginning with an introduction on common structural and biochemical features as well as general functional characteristics of annexins, the paper focuses on individual members with documented and/or proposed physiological relevance for renal development, structure, and functions. Three main aspects of annexin function in kidney epithelia emerge from the available experimental data. First, annexins are required for membrane organization and membrane transport events required for the establishment/maintenance of epithelial polarity. Second, there is accumulating evidence of an association of annexins with ion channels, as membrane-guiding auxiliary proteins or modulators of channel activity. Last but not least, some annexins seem to work as extracellular autocrine modulators of receptor function under difference physiological conditions.

annexin protein; annexin physiology; renal localization; calcium

ANNEXINS ARE A MULTIGENE FAMILY OF Ca2+ binding proteins characterized by their ability to interact with negatively charged membrane surfaces in a Ca2+-dependent manner. They are widely expressed among the animal and plant kingdoms with the vertebrate, invertebrate, fungi, plant, and protist annexins falling into five groups termed annexin A, B, C, D, and E, respectively (49). In humans, 12 annexin proteins (annexin A1–A11, annexin A13) have been identified, which often show a tissue- and cell type-specific expression pattern. Structurally, an annexin can be divided into two distinct parts, a highly conserved protein core comprising the COOH-terminal portion of the molecule and a variable NH2-terminal region. Annexin cores are compact structures shaped like a slightly curved disc, which harbor binding sites for the common annexin ligands, Ca2+ ions and phospholipids of cellular membranes. They are dominated by α-helices, which span the disc and are connected via short loops or turns at the two principal sides of the disc, the more convex and the more concave one (Fig. 1). Ca2+ ions are bound at the more convex side, where they serve a bridging function in linking the core unit to phospholipid moieties of membrane phospholipids. This arrangement defines the annexin-type or type II Ca2+ binding site in which a bound Ca2+ ion coordinates simultaneously to oxygens of the protein backbone and the lipid bilayer in membrane-bound annexins (for a review of annexin core structures, see Refs. 26, 40, and 74). Although annexin cores are compact units, they can be subdivided into four homology segments, the annexin repeats, which are easily discernible upon an alignment of annexin core sequences. The repeats are ~70 residues long and share both inter- and intramolecular sequence identities. In the folded core domain, each repeat comprises five α-helices, termed A–E, with residues in the loop between helix A and B and at the end of helix D being involved in Ca2+ binding. Thus annexin cores can be regarded as structurally well-conserved modules enabling annexin proteins to dock peripherally onto negatively charged membrane surfaces (for reviews, see Refs. 16, 60, and 68).

The NH2-terminal domains are unique in sequence, length, and structural fold and thus specific for a given member of the annexin family. Although high-resolution structures are only available for a few full-length annexins, it can be extrapolated that the NH2-terminal domains are located at the concave side of the curved disc (Fig. 1). Such an arrangement enables the NH2-terminal domains to engage in additional, more specific interactions, whereas an annexin is bound to a membrane surface via the conserved core domain. A number of such specific interactions through the NH2-terminal domain have been identified. These include interactions with Ca2+ binding proteins of the EF hand superfamily mediated through the NH2-terminal domains of annexins A1, A2, and A7 (for reviews, see Refs. 15 and 16). In addition to providing protein interaction sites, the NH2-terminal domains of annexins are also targets for various signal transducing kinases, which include src-related tyrosine kinases, receptor tyrosine kinases like the EGF receptor, and protein kinase C. These phosphorylations have been shown to affect phospholipid binding and/or vesicle aggregation by annexins in vitro, but their functional relevance in vivo remains to be established (for a review, see Refs. 16, 60, 67, and 76).

Annexins have been implicated in a wide range of physiological activities. Many of these activities are related to the central and conserved annexin property, i.e., the binding to cellular membranes containing negatively charged phospholipids (Fig. 2). Through work in cell-free model systems and, more recently, through the establishment of dominant-negative annexin mutants and annexin knockdown and knockout models, members of the family have been implicated in the trafficking of membranes and membrane proteins, the regulation of ion channels within biological membranes, and the organization of membrane structures. Annexin functions not at all or indirectly related to their Ca2+-dependent phospholipid bind-
ing have also emerged. These include extracellular activities, in particular by annexins A1, A2, and A5. Although their release from cells, which must follow an atypical mechanism, is not fully understood, anti-inflammatory and anticoagulatory actions of these annexins have been reported, for example, in mouse knockout models (18, 19, 41, 53, 54, 57).

This review focuses on annexins in the kidney. It presents an overview of annexin expression in the different cell types of the kidney and discusses potential functions of the major annexins found in kidney or kidney-derived cells.

ANNEXIN EXPRESSION IN THE KIDNEY

Annexins are often viewed as “ubiquitously” expressed proteins. This is true in the sense that there is probably no cell type in an organism that would not express a set of annexins,
an annexin “build” or fingerprint specific for that cell type. However, there is no member of the annexin protein family that would be expressed in all cell types. This implies diversified and rather specific cellular functions for the annexins, associated with their strictly regulated topical expression. A group of annexins, annexins A1, A2, A4, and A5, are expressed in digestive system and ductal organs (11, 30, 52). These annexins are well represented in the kidney, together with the long isoform of annexin A13, annexin A13b, identified in the dog (13). RIKEN database expression array data (http://read.gsc.riken.go.jp/) also confirm the expression of annexins A1, A2, A4, and A5 in the gastrointestinal tract and ductal organs of the adult mouse, with strongest expression levels in the kidney for annexin A4. During embryonic development, all of these annexins except annexin A13 (no expression analyses performed) peak at day 13 postconception, which coincides with the onset of organogenesis.

Annexins A4 and A5 are members of an earlier cladistic group, whereas annexins A1 and A2 have emerged later as a second group in the evolution of the family. Annexin A13, on the other hand, has been identified as the progenitor of all vertebrate annexins (27). Cladistic groupings in the annexin family correlate with functional cohesions. With regard to intracellular activities, annexins A1 and A2 are mainly involved in exo- and endocytotic pathways, annexin A13b has acquired a highly differentiated exocytotic transport function, whereas annexins A4 and A5 are more closely linked to ion flow regulation (Table 1) (for a review, see Ref. 16).

**Annexin A1**

Annexin A1 was described two decades ago as a major substrate for tyrosine phosphorylation by the epidermal growth factor receptor (EGFR) but meanwhile has also been implicated in a number of processes not linked to EGFR activation. These include extracellular functions in the control of leukocyte extravasation, activation, and apoptosis (for a review, see Refs. 53, 54, and 61). A crystal structure of full-length annexin A1 is available at high resolution (66). The protein has an NH2-terminal domain of 40 residues, the first 10–14 of which represent the binding site for a protein ligand of the S100 family, S100A11 (42, 69). Within cells, annexin A1 is found associated with early endosomes, and this association is dependent on its extended NH2-terminal domain, in particular residues 1–26 (70). These findings demonstrate the regulatory importance of the NH2-terminal domain and provide evidence for an involvement of annexin A1 in endocytotic processes, possibly linked to EGFR-mediated phosphorylation of Tyr 20 in the NH2-terminal domain (14).

Immunohistochemical analysis of normal rat kidney shows that annexin A1 is enriched in epithelia of Bowman’s capsule, the macula densa, and medullary/papillary collecting ducts (Fig. 3), suggesting that expression of the protein could be related to specialized renal functions (47). Interestingly, on ischemic recovery, both the distribution and amount of renal annexin A1 are altered (47). The thick ascending limb stains heavily for annexin A1, and expression of the protein increases at least threefold in the recovering kidney. In this pathophysiological response, however, no correlation between exogenous EGF stimulation and increased annexin A1 levels has been observed.

A series of studies tie glucorticoid actions in the neuroendocrine system to a possible involvement of annexin A1 as a second messenger of hormone release (for a review, see Ref. 8). Juxtacrine/autocrine loops have been proposed as models for the action of annexin A1 during glucocorticoid-induced

### Table 1. Kidney localization references and proposed renal functions of annexins covered

<table>
<thead>
<tr>
<th>Annexin</th>
<th>Expression in Kidney Ref. No(s).</th>
<th>Proposed Functions</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>47, 78</td>
<td>Membrane organization in late endosomes; anti-inflammatory; formyl peptide receptor ligand; 2nd messenger of hormone release</td>
</tr>
<tr>
<td>A2</td>
<td>75, 78</td>
<td>Membrane organization in endocytosis and exocytosis; membrane transport</td>
</tr>
<tr>
<td>A4</td>
<td>24, 34, 39, 71</td>
<td>Regulation of calcium-activated epithelial chloride channels; membrane organization; kidney development</td>
</tr>
<tr>
<td>A5</td>
<td>45</td>
<td>Regulation of receptor activity/internalization; membrane organization</td>
</tr>
<tr>
<td>A13b</td>
<td>13, 35</td>
<td>Regulation of apical membrane transport in renal epithelial cells</td>
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cellular responses. One of the cell culture models studied has involved a human mesangial cell line (CHMC). Here, treatment with annexin A1 inhibits cell growth in a dose-dependent manner, a response similar to that elicited by hydrocortisone (33). A direct effect of annexin A1 antibodies on the reversal of hydrocortisone-induced inhibition of CHMC proliferation was observed. Although the annexin A1 promoter contains possible glucocorticoid response elements, studies on its sensitivity to dexamethasone, a glucocorticoid analog, demonstrate that gene expression is rather insensitive to such treatment (10, 73). Thus annexin A1 most likely is not a primary glucocorticoid response gene but rather could act as a second messenger in glucocorticoid-induced cellular responses, which might be important for kidney development and recovery from physiological stress.

**Annexin A2**

Annexin A2 has also been identified as a phospholipid degradation substrate for tyrosine kinases, in particular the tyrosine kinase encoded by the src oncogene (12, 56). Similar to annexin A1, annexin A2 binds with its NH2-terminal 14 residues to an S100 protein, S100A10, which is related to the S100A11 ligand of annexin A1 (17, 28). In the case of annexin A2, a heterotetrameric complex is formed, which contains a S100A10 dimer linking two annexin A2 chains, which can bridge adjacent membrane surfaces through binding of the annexin A2 cores to opposite membranes (37, 38, 63). This property of annexin A2 is most likely responsible for an intracellular activity related to the organization of certain membrane domains in various cell types. Membrane microdomains (rafts) are implicated in membrane transport processes and also represent platforms for signaling events (for a review, see Refs. 7 and 72). Rafts are lateral membrane lipid assemblies rich in sphingolipids and cholesterol, which form a liquid-ordered phase in a more disordered glycerolipid environment. They are resistant to treatment with anionic detergents in the cold, and they float to low density in sucrose gradients. Proteins described as raft associated are typically anchored in the membrane raft through a fatty acid, isoprene, or lipid moiety (e.g., glycosylphosphatidylinositol or GPI). There is accumulating evidence that some annexins can peripherally associate with the cytoplasmic side of rafts, thereby possibly regulating their assembly and dynamics (for a review, see Ref. 16).

The annexin A2/S100A10 complex is found in the Triton X-100-insoluble fraction of Madin-Darby canine kidney (MDCK) cells (21). Following raft enrichment, the complex can be extracted from the insoluble fraction with detergents known to solubilize GPI-anchored proteins. Moreover, on density gradient fractionation of Triton X-100-insoluble membranes, the majority of the annexin A2/S100A10 complex copurifies with a low-density fraction on sucrose gradients, and it is the most abundant protein component of this fraction (21, 51). This indicates that the association of annexin A2/S100A10 with the low-density material occurs via lipid binding and not through interaction with other proteins. The raft-associated lipid responsible for annexin A2 binding has not been identified unequivocally. However, a direct binding to cholesterol has been suggested (1, 46) and, more recently, a direct interaction with PI(4,5)P₂, a specific lipid component of some rafts, has been observed (22, 62). Interestingly, PI(4,5)P₂ and annexin A2 are found enriched at sites where certain membrane domains (or rafts) are in close contact to an underlying actin-rich cytoskeleton (2, 48, 80). This supports the notion that the annexin A2/S100A10 complex could serve as an interface between certain membrane rafts and the actin cytoskeleton (for a review, see Ref. 23).

Several studies relate annexin A2 to the regulation of membrane domain and cortical actin dynamics during the establishment of cell-cell contacts in polarized monolayers of kidney epithelial cells. Hansen et al. (20) show a direct interaction of annexin A2 with Rac 1-containing complexes, which are involved in membrane dynamics of developing cell-cell contacts in epithelial cells. Also employing MDCK cells, here in Ca²⁺ switch experiments, Yamada et al. (79) provide evidence that a recruitment of annexinA2/S100A10 to cholesterol-containing membrane domains is required for the formation of E-cadherin-based adherens junctions. Finally, Benaud et al. (3) report the direct association of the annexin A2/S100A10 complex with a large protein, AHNAK, which relocates from cytosol to the cytoplasmic face of the plasma membrane on formation of cell-cell contacts and development of cell polarity in MDCK cells. AHNAK (which means “giant” in Hebrew) is a 700-kDa protein also implicated in the maintenance of the structural and functional organization of the subsarcolemmal cytoarchitecture (25). The observed redistribution of AHNAK on formation of cell-cell contacts and cell polarity development in MDCK cells is Ca²⁺ dependent and occurs simultaneously with a reorganization of the cortical actin cytoskeleton. The annexin A2/S100A10-AHNAK interaction involves the COOH-terminal 1,000 amino acids of AHNAK and is mediated via the S100A10 subunit of the heterotetramer. Interestingly, AHNAK and the annexin A2/S100A10 complex are recruited to the sites of early cell-cell contacts, where they colocalize in a cholesterol-dependent manner and AHNAK copurifies with annexin A2/S100A10 in the lipid raft fraction. This AHNAK association is inhibited by downregulation of both annexin 2 and S100A10 using small interfering (si) RNAs. Furthermore, siRNA-mediated downregulation of AHNAK prevents cortical actin cytoskeleton reorganization required to support cell height. The interaction of the annexin A2/S100A10 complex with AHNAK thus seems to play an important role in the regulation of the cortical actin cytoskeleton and membrane cytoarchitecture.

Autosomal dominant polycystic kidney disease (ADPKD) is a disorder that, among other dysfunctions, is also marked by a compromised cytoarchitecture and aberrant ion currents in cyst-lining epithelial cells (for a review, see Ref. 5). The annexin A1 and annexin A2 proteins are localized apically in ADPKD epithelia (Fig. 3) (78). The observed polarized localization of both annexins, together with other proteins displaying channel and integral membrane functions, argues for their involvement in the structuring/stabilization of membrane domains in kidney epithelial cells and perhaps also for a participation in directed ion transport events, which could be disturbed in ADPKD epithelia.

Support for the latter idea, i.e., an involvement of annexin A2 in apical ion transport in polarized epithelia, comes from studies revealing a direct association of the annexin A2/S100A10 complex with epithelial TRPV5 and TRPV6 Ca²⁺ channels (75). The heterotetramer associates specifically with a conserved sequence, VATT, located in the COOH-terminal
tial of TRPV5 and TRPV6, and the association is mediated via the S100A10 chain of the complex. TRPV5 is expressed in renal tubules, where it colocalizes with the annexin A2/S100A10 complex. siRNA-mediated downregulation of annexin 2 inhibits TRPV5- and TRPV6-mediated currents in transfected human embryonic kidney (HEK293) cells. Moreover, experiments with TRPV5 and TRPV6 channel proteins containing mutant S100A10 binding sites show a redistribution of the mutants to the subplasma membrane area, which functionally interferes with plasma membrane channel activity. Thus the annexin A2/S100A10 complex seems to play a crucial role in routing TRPV5 and TRPV6 channels to the apical plasma membrane of polarized epithelial cells.

Annexin A4

Annexin A4 is found in many epithelia, but it is the annexin with highest expression levels in kidney. In a primary culture of rabbit proximal kidney tubular epithelial cells, the protein is localized in the basolateral membrane (43). In contrast, another report shows an apical localization of the protein in bovine kidney epithelial cells of proximal tubules and a cytosolic distribution in the papillary ducts and papilla epithelium (Fig. 3) (34). The difference in annexin A4 localization in primary cultures and nascent kidney proximal tubular epithelial cells might be due to different degrees of polarization in the two types of cell systems.

Analysis of a mouse model of annexin A4 function, where a gene trap has been inserted in the first exon of the gene, reveals multiple transcripts (39). All three transcripts, termed “a,” “b,” and “c,” code for the same protein but are differentially represented in various tissues. The differences in mRNA structure lie in the 5′-untranslated regions (UTRs) and could reflect different transcription regulation strategies, necessary for expression in adequate tissues or specialized cell types (39). The annexin A4a transcript is the most abundant of the three. It is expressed comparatively low in the heart, liver, and lung, intermediate in the kidney and stomach, and high in the small and large intestines. The annexin A4b transcript is restricted to high expression in the digestive tract. Annexin A4c is expressed at low levels in the kidney, liver, and digestive tract. The exon-trap gene inactivation experiment resulted in the generation of a mouse deficient in annexin A4a expression, thus a restricted loss-of-function model. Immunohistochemical comparison of annexin A4-stained tissue sections from a wild-type and annexin A4a-deficient (Anx A4a−/−) mouse shows striking morphological differences in the kidney. Whereas Anx A4 is localized in the renal inner medulla, in the collecting ducts (CD), and the transitional epithelium lining the renal pelvis of wild-type mouse kidneys, the protein is not expressed in the Anx A4a−/− renal medulla. Annexin A4 expression in the Anx A4a−/− mouse is confined to cells interspersed in specific tubules of the renal cortex and in ductus deferens epithelium. This expression stems from the “c” transcript of the gene, which is found at very high cellular concentrations in the particular positive cells. The documented differential expression of annexin A4 suggests that the gene is regulated at both the transcriptional and translational levels. Moreover, the morphological alterations in the kidneys of Anx A4a−/− animals suggest an important role for this protein in kidney development and/or function.

In line with a potential role of annexin A4 in kidney development is a recent study analyzing the formation of pronephric tubules in *Xenopus laevis* (71). In *X. laevis*, transcripts of annexin A4 are present in developing pronephric tubules, and the protein is localized to the luminal surfaces of these tubules. Uptregulation of zygotic transcription is noted at the time of pronephric tubule specification and persists throughout pronephric development. Downregulation of annexin A4 expression with antisense morpholino oligonucleotides results in a shortened, enlarged tubule phenotype, which can be rescued through coinjection of annexin A4 mRNA. Thus annexin A4 in *X. laevis* is required for development of correct pronephric tubules.

What could be the molecular basis for annexin A4 function in kidney development? Although this question has not been addressed to a greater extent, it is interesting to note that annexin A4 can regulate the activity of calcium-activated epithelial chloride channels (9, 29). This regulation seems to depend on an annexin A4-mediated inhibition of the interaction between calmodulin-dependent kinase II and the ion channel. Annexin A4 has also been shown to colocalize apically with aquaporin-2 (AQP2) in renal collecting duct epithelia (24). In AQP2-containing endosomes exposed to Ca^{2+} and annexin A4, water flux rates are unchanged, indicating that annexin A4 cannot directly regulate AQP2. However, annexin A4 increases membrane rigidity and passively reduces water and proton permeability of vesicular membranes. Thus annexin A4-mediated ion and/or water fluxes could affect certain aspects of proper kidney development.

Annexin A5

Annexin A5 exhibits most sequence similarity with annexin A4 but has a different expression pattern and different biochemical properties. In contrast to annexins A1, A2, and A4, it requires rather high calcium concentrations (in the 10-μM range) for phospholipid binding (reviewed in Ref. 60). This could indicate that some annexin A5 associations with phospholipids only occur at high, extracellular concentrations of calcium, although, locally, intracellular Ca^{2+} concentrations could probably also reach levels in the 10-μM range following certain cell stimulations. Regardless of the site of action, i.e., the cytoplasmic or exoplasmic leaflets of cell membranes, the mechanistic basis of annexin A5 activity is mostly linked to its ability to form two-dimensional crystals on planar lipid bilayers. This has been demonstrated by electron and atomic force microscopic studies in situ (6, 55, 64, 65) and could be the basis of a protective annexin A5 shield on syncytiotrophoblasts, which can be disrupted by antiphospholipid antibodies (58).

It has been recently demonstrated that such a crystalline protein network on cell membranes opens a new portal for entry into the cell (32). This network, specific for annexin A5, elicits budding, endocytotic vesicle formation, and cytoskeleton-dependent trafficking of the endocytotic vesicle. The novel, annexin A5-mediated internalization is independent of membrane ruffling and actin polymerization and can mediate the uptake of tissue factor (TF) in a macrophage cell model (59). Downregulation of TF through extracellular annexin A5 has also been observed in a mouse carotid artery injury model (same study). Such regulation of extracellular TF levels...
through annexin A5-mediated cell entry might be part of a more general mechanism to control cell surface receptors under physiological stress conditions.

We have observed recently a direct and specific association of annexin A5 with the extracellular domain of the major protein affected in ADPKD, polycystin-1 (Markoff A, Qian F, Bogdanova N, Rüffer C, Knop M, Kenis H, Reutelingsperger C, Dworniczak B, Horst J, Germino GG, and Gerke V, unpublished observations). Polycystin-1-expressing MDCK cells do not seem to internalize annexin A5 by the above mechanism, and this retention of annexin A5 through polycystin-1 might be a specific response to counteract receptor internalization on the surface of kidney epithelial cells.

Based on its activity to interact specifically with acidic phospholipids, annexin A5 is used widely as a reagent to visualize phosphatidylserine on the surface of apoptotic cells. As a radiolabeled probe, it is thus employed to detect apoptotic changes in tissues of live animals. However, in such scenarios the protein accumulates mainly in the kidney, liver, and gastrointestinal tract, which limits its usefulness for imaging of ongoing apoptosis in the abdominal and thoracic region (4, 31, 36). The exceptionally high kidney uptake of radiolabeled annexin A5, together with a comparatively long half-life of 24 h, could be an indication of specific biological interactions of the protein with renal epithelial cells.

Patients with kidney and other diseases that result in renal malfunctions show elevated urinary concentrations of annexin A5 (44), which could be useful diagnostic markers of acute renal injury. Tissue localization and changes in plasma and urine concentrations of annexin A5 have also been studied in a rat glomerulonephritis model (45). Normal kidneys are positive for annexin A5 in distal tubules, with protein expression being particularly strong in tubules of the inner stripe of the outer medulla. No annexin A5 has been detected in proximal tubules, whereas visceral epithelial cells, Bowman’s capsule of the glomerulus, the vascular endothelium of arterioles and interlobular arteries, and vascular smooth muscle are positive for the protein (Fig. 3). In nephritis, the lumen of distal tubules and the luminal cell membrane are strongly positive for annexin A5, with leakage of the protein being observed from tubular cells. This study also revealed increased urinary levels of annexin A5 after injection of nephritogenic antigen, with urinary concentrations reflecting the severity of damage of renal tissue and the progression of nephritis. Thus changes in annexin A5 in the distal tubule and visceral epithelial cells may be of significance in cell injury of the kidney.

Annexin A13

Annexin A13, the founder gene of vertebrate annexins (27), gives rise to two myristoylated NH2-terminal splice variants (a and b). The short isoform (a) of the human protein has a very restricted, intestine-specific expression (77), whereas the longer isoform (b) has been identified initially in MDCK cells, where it exhibits a unique subcellular localization (13). In polarized MDCK cells, annexin A13b localizes specifically to the trans-Golgi network, exocytotic vesicular carriers, and the apical cell membrane (35). In its native myristoylated form, annexin A13b stimulates apical vesicular transport, whereas overexpression of the unmyristoylated form and annexin A13b antibodies inhibit this route. Thus annexin A13b, which is a lipid raft-associated protein, appears to control the budding at the trans-Golgi network of vesicular carriers that are rich in raft lipids and are destined for the apical plasma membrane. This transport has been shown to employ a microtubule minus end-directed motor (50). The specific, and in some cases regulated, association with raft domains reported for annexin A13 and annexin A2 could reflect a more general function of such annexins in the organization and/or maintenance of membrane dynamics of epithelial cells under physiological conditions (Fig. 3, Table 1).

CONCLUSIONS

The functional relevance of annexins expressed in the kidney appears to be linked to several physiological properties important for epithelial cells (Table 1). First, annexins are required for membrane organization and membrane transport events required for the establishment/maintenance of epithelial polarity. Second, there is accumulating evidence of an association of annexins with ion channels, as membrane-guiding auxiliary proteins or modulators of channel activity. Last but not least, some annexins seem to work as extracellular autocrine modulators of receptor function under different physiological conditions.

ACKNOWLEDGMENTS

We thank John Dedman (University of Cincinnati) for critical perusal of the manuscript.

GRANTS

This work was supported by grants from the German Research Society (DFG), SFB 629 and SFB 293; the University of Muenster Interdisciplinary Centre for Clinical Research (IZKF), Re2-033; and the European Union, EU-MAIM.

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