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Annexins in Translational Research: Hidden Treasures to be Found

Sebastian Schloer[1], Denise Pajonczyk[1], and Ursula Rescher[1]

[1]Institute of Medical Biochemistry, Centre for Molecular Biology of Inflammation, and [2]Interdisciplinary Centre for Clinical Research, University of Muenster, Von-Esmarch-Str. 56, D-48149, Muenster, Germany

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Corresponding author: Ursula Rescher, e-mail: rescher@uni-muenster.de

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Abstract

The vertebrate annexin superfamily (AnxA) consists of 12 calcium (Ca^{2+}) and phospholipid binding proteins which share a high structural homology. In keeping with this hallmark feature, annexins have been implicated in the Ca^{2+}-controlled regulation of membrane events. In this review, we discuss several themes of potential therapeutic value, namely the regulation of the immune response and the control of tissue homeostasis, that repeatedly surface in the annexin action profile. Our aim is to identify and discuss those annexin properties which might be exploited from a translational science and specifically clinical point of view.

Introduction

Annexins stepped into the light in 1978, when a soluble protein was isolated from bovine adrenal glands that caused the aggregation of secretory vesicles in vitro when free Ca^{2+} was present [1]. This protein, initially called “synexin”, turned out to be the first discovered member of a new protein family, the annexins [2]. The Ca^{2+}-dependent binding to phospholipid-containing membranes turned out to be their hallmark, mediated by their signature feature, the annexin repeat. More than 500 different members of the superfamily have now been identified [3]. According to the official nomenclature proposed in 1999, the 12 annexins commonly found in vertebrates constitute the A subclass [4]. Structurally, annexins all share the characteristic and highly conserved “core” domain made up of usually four annexin repeats each of which typically contains a Ca^{2+}- binding motif and mediates the specific binding to negatively charged phospholipids. In 1990, the first crystal structure (of AnxA5) confirmed the predictions [5]. The tightly packed and slightly convex annexin core domain is linked to an N-terminal part (sometimes also called “head” or “tail” domain) that is unique for a given annexin. N-terminal tails are surprisingly diverse in length and sequence, and sometimes contain binding sites for interaction partners, including members of the S100 family of EF-hand-containing Ca^{2+}-binding proteins [6]. In several annexins, the tail is a substrate for kinases, e.g. Src and PKC [7–9]. Phosphorylation is thought to regulate the protein function [5,10] and has been reported to control secretion, at least in the case of AnxA1 and A2, through a yet unknown unconventional pathway of these otherwise cytosolic proteins [11–15]. Not surprisingly, annexins have been implicated in the regulation of a broad range of cellular and physiological processes that are linked

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to cellular membranes, such as vesicle organization, membrane trafficking and scaffolding, endo- and exocytosis, and membrane/cytoskeleton interactions [16–21]. Membrane dynamics is also a recurrent theme in host-pathogen interactions, and annexins might function as host cell-derived auxiliary proteins in shaping the microbe-host interplay [22]. In recent years, a growing number of annexin knock out (KO) mouse models have been constructed [23], and they will certainly prove to be useful tools for investigating annexin functions, both as drugs and therapeutic targets.

Extracellular functions - Detection of Phosphatidylserine, Immuno-evasion and Blood coagulation

During pathophysiological responses, typical changes in the membrane composition and loss of membrane asymmetry are observed. A prominent feature is the translocation of phosphatidylserine (PS), which in viable cells is located in the cytosol-facing leaflet of the plasma membrane, to the outside of apoptotic cells [24]. In the presence of Ca^{2+}, PS is a high-affinity ligand for the annexins [25]. For AnxA5, a K_D value of $5x10^{-10}$ in the presence of Ca^{2+} [26] underscores the high selectivity in its preference for PS over other negatively charged phospholipids, and this specificity is the reason behind the wide use of labelled AnxA5 for the identification of apoptotic cells [27], for example in flow cytometry applications [28,29].

The surface-exposed PS assists in the recognition and efferocytosis of dying cells [30]. This process is immune-calming in its nature [30] and seems to depend on the concomitant externalization of AnxA1 [31], which is part of the apoptotic cell-associated molecular patterns (ACAMPs) [32] that convey the switch towards an anti-inflammatory response. In accordance with the function as an (anxA1-dependent?) “eat-me” signal, the phagocytosis of PS-decorated red blood cells is inhibited when PS is masked [33], for example through PS-binding proteins. Recent findings suggest that exposition of PS on the outer leaflet is not confined to apoptosis but appears to act as an evolutionary conserved global immunosuppressive signal [34], and is also found on the surface of cancer cells [35]. Unfortunately, in this context, PS exposure is not linked to cell elimination but seems to function in immune evasion [34], which, like in apoptotic cells, might depend on cell surface associated AnxA1 [36]. Blocking of PS with AnxA5 might be a strategy to antagonize the immune-suppression and help establish an anti-

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tumor immune reaction. Furthermore, AnxA5 might be used for the development of selective molecular imaging probes for cancer diagnosis and disease management [29,37] and importantly, for targeting drugs to the cancer cells [25,35].

Coagulation

Exposure of PS is also an important step in the regulation of blood clotting [38]. PS on the surface of endothelial cells or membrane vesicles derived from activated platelets greatly enhances the pro-thrombin/thrombin conversion which is a central unit in the coagulation [39]. Annexin A5 is abundantly found on the surface of syncytiotrophoblasts and might protect the placenta from abnormal coagulation [40]. Furthermore, a polymorphism in the AnxA5 gene was found to be associated with recurrent pregnancy loss. Women with the SNP in the AnxA5 gene had a significantly higher risk of fetal loss than non- carriers [41]. The AnxA5 anticoagulant function might depend on its well-established property to self-assemble on PS-containing membranes into an extensive two-dimensional crystal lattice [42] that hinders the assembly of the pro-coagulant complexes. In line with such protective function in the blood clotting regulation, anti-AnxA5 autoantibodies are found in patients suffering from anti-phospholipid syndrome [43], a disease that manifests clinically as recurrent thrombotic events and is associated with fetal loss [44]. The occurrence of AnxA5 autoantibodies [45] is also linked to autoimmune disorders [46] also observed in some patients suffering from multiple sclerosis or systemic lupus erythematosus.

Among the many functions exerted by thrombin is the conversion of fibrinogen to fibrin which, together with platelets, forms a stable haemostatic plug that seals the injured vessel wall. To avoid excessive clot formation, the damaged endothelium slowly secrets components that assist in the conversion of plasminogen entrapped in the clot to enzymatically active plasmin which breaks down the fibrin mesh. AnxA2, possibly as a heterotetramer together with its ligand S100A10, was demonstrated to enhance plasmin generation [47,48]. Consistently, AnxA2 KO mice present defective fibrinolysis and increased thrombotic vascular occlusion and impaired neovascularization [49]. Blast cells of patients with acute promyelocytic leukemia (APL) express AnxA2 to a high amount [50], which might explain the haemorrhagic complications observed in APL patients. In line with the impact of AnxA2 on coagulopathy [50], treatment with the

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retinoic acid receptor ligand, all-trans retinoic acid (ATRA), attenuates AnxA2 expression and improves clinical resolution.

Extracellular functions- annexins as ligands of defined inflammation-related receptors

A conceptually straightforward approach is to therapeutically exploit those annexins which function as endogenous ligands for known receptors. In this regard, the most prominent annexin is certainly AnxA1. Still under its former name lipocortin 1, AnxA1 gained considerable attraction as a key mediator of glucocorticoid actions in inflammation. AnxA1 deficient mice do not respond to glucocorticoid treatment under inflammatory conditions [51]. The full-length protein as well as its famous Ac2-26 N-terminal peptide pharmacophore (which might be proteolytically released from the full length protein [32,52]), act in an anti-inflammatory manner in many experimental conditions, and we refer the reader to the many excellent and comprehensive review articles on that topic [53–56]. A molecular explanation was provided by the discovery that both AnxA1 and the Ac2-26 peptide specifically bind and activate the formyl-peptide receptor (FPR) family [57,58] of heptahelical, G-protein reported AnxA1 anti-inflammatory functions depend on binding to FPRs, as the recognition of an annexin core (derived from annexins other than A1) also contributes to an immune-modulation [59]. In humans, three members of the FPR family are found: FPR1, FPR2, and FPR3, whereas in mice eight FPRs are expressed [60]. The most prominent receptors among the FPR family expressed in the murine model are FPR1 and FPR2 [61]. FPR1 and FPR2 are predominantly expressed on the surface of many immune cells (e.g. neutrophils, macrophages, dendritic cells) but also found in endo- and epithelial cells [62]. A broad range of FPR1 ligands, both agonist and antagonists, have been described [63], and autocrine/paracrine signalling of externalized AnxA1 protein and/or its peptides via the FPRs might explain its well-known immune-modulatory and pro-resolving actions. Upregulation of AnxA1 expression is observed in several inflammatory conditions [64] and thought to function in resolution and tissue protection [65]. Indeed, studies on the use of Ac2-26-containing nanocapsules in the treatment of mucosal injury in the murine model, reported enhanced colonic wound healing, both in the acute and chronic situation [66]. Interestingly, a small peptide derived from the AnxA1 N-terminus attenuated experimental colitis in mice [67]. Chronic inflammation is also observed in obesity [68]. Interestingly, AnxA1 KO mice on a high-fat diet are

more prone to obesity than the control animals [69], and FPR2 activation improved systemic insulin sensitivity [70].

A growing body of evidence points at an anti-inflammatory and neuroprotective function of AnxA1 in the brain and AnxA1-derived molecules might emerge promising tools in the treatment of brain diseases, including stroke and neurodegenerative disorders [71,72]

A caveat to the generalized use of AnxA1 for treatment of excess inflammatory conditions is the observation that LPS, a highly potent pro-inflammatory component derived from the bacterial wall of gram-negative bacteria, triggers the upregulation of AnxA1 expression in a variety of cell types e.g. neutrophils [73]. Indeed, elevated AnxA1 plasma levels are found in 56% of septic patients after hospital admission [74]. While initially beneficial [73], it remains to be investigated whether excess LPS-induced AnxA1 externalization might cause the so-called endotoxin resistance, a dangerous refractive state of the innate immune system characterized by a lowered response towards a second exposure to bacterial lipopolysaccharide [75]. However, the target delivery of AnxA1-derived compounds has tremendous promise to treat a range of inflammatory conditions.

AnxA2 not only impacts fibrinolysis but (in its heterotetrameric form together with S100A10) affects the Toll-like receptor (TLR) signaling. The AnxA2-S100A10 complex activates human and murine macrophages through the TLR4-MyD88 pathway, although the cell's responsiveness requires an additional and yet unknown factor [76–78]. Signaling through the TRAM/TRIF- module of the TLR4 pathway was reported to attenuate Klebsiella-induced lung inflammation in a murine model of acute pneumonia [78]. Monomeric AnxA2 was also shown to bind to and activate TLR2 via its N-terminal domain, thus assisting in the differentiation of antigen-presenting cells [79]. Extracellular AnxA2 was shown to also interact with the proprotein convertase subtilisin/kexin-type 9 (PCSK9), thus interfering with PCSK9-mediated degradation of the hepatic low-density lipoprotein receptor (LDLR) [80–82]

In search of the molecular mechanism underlying the stimulatory effects of AnxA2 on human osteoclast formation [83,84], a novel type I membrane protein was identified as a putative AnxA2 receptor [85]. A recent study linked a single nucleotide polymorphism

(SNP) in the AnxA2 gene (rs7170178) to osteonecrosis in sickle cell patients. The SNP frequency of the AnxA2 gene polymorphism was higher in sickle cell osteonecrosis patients than those without osteonecrosis [86]. Interaction of AnxA2 with the AnxA2 receptor also mediates adhesion and activation of the cells responsible for the initiation and maintenance of multiple myeloma [87] and this signal pathway could be used as a therapeutic target.

Intracellular functions of annexins in inflammatory and wound healing processes

The following sections will cover those intracellular functions of annexins which are of potential relevance in pathophysiological scenarios. In this case, annexins might be used for gene and cell therapy approaches or might serve as targets for cell-penetrating small molecules that interfere with or mimic annexin functions. Additionally, the intracellular delivery of annexin-derived therapeutics (e.g. as cell-penetrating fusion peptides) might be exploited in intracellular protein therapy.

Annexins as biomarkers

Changes in cellular or tissue expression levels have been reported for several annexins and a broad range of diseases (Fig. 1), suggesting a potential use to determine onset and progression of disease and to monitor therapeutic success. The following studies are exemplary only and illustrate the potential use of determining annexin expression profiles for the early detection of common cancers.

Massive dysregulation of annexin expression patterns occur during tumorigenesis e.g. serum levels of AnxA1 are significantly elevated in lung cancer patients. Due to the strong association of AnxA1 to pathological grade and clinical stage, it is a convenient marker for monitoring the course of disease [88]. Furthermore, the AnxA2 expression is significantly associated with tumor size, lymph node metastasis, distant metastasis and clinical stage of laryngeal cancer and therefore a promising candidate for estimating the prognosis of patients with laryngeal carcinoma or gliomas [89].

AnxA10 is already used as a biomarker for hepatocellular carcinoma (HCC) and markedly downregulated during cancer progression [90]. The AnxA10 downregulation,

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together with a characteristic p53 mutation, acts synergistically toward high-grade, high-stage HCC and goes along with poorer prognosis [90].

Regulation of cytosolic phospholipase A2 (cPLA2) enzymatic activity

Very early on, the ability of annexins, and especially AnxA1 and AnxA2, to inhibit cPLA2, thus interfering with arachidonic acid release and eicosanoid formation, has been acknowledged. Mechanistically, the function was explained by competition for the lipid substrates [91–93]. However, cPLA2 might be inhibited in a more direct manner [94]. Given the fundamental role of this enzymatic activity in eicosanoid production, annexins might serve as a starting point to discover new lead structures for further cPLA2 inhibitors.

Cell surface presentation of integral plasma membrane molecules

The AnxA2-S100A10 tetramer has been shown to interact with (and possibly regulate) a number of integral plasma membrane molecules including ion channels and receptors, like the Ca^{2+}-selective Transient Receptor Potential vanilloid type 5 and 6 channels (TRPV5 and TRPV6) [95], the acid-sensing ion channel ASIC [96], the two-pore-domain potassium channel TASK-1 [97], the chloride channel Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) [98] the GPCR CCR10 [99] and the 5-HT1B receptor [100]. Interfering with these S100A10 interactions could be envisioned for the treatment of the corresponding diseases, including depression [100], although a beneficial effect of an upregulation of S100A10 expression, e. g. through 1,25-dihydroxyvitamin D3 [95], yet needs to be demonstrated.

Plasma membrane repair

Very recently, another important annexin function related to cellular processes controlling damage appeared. To maintain a functional plasma membrane (PM), eukaryotic cells are able to repair PM injuries. The resealing is Ca^{2+}-dependent and depends on a complex machinery. It can probably occur through different mechanisms, depending on the kind and extent of injury. Defective PM repair manifests very impressively in skeletal muscle and is linked to degenerative muscle diseases such as myopathies and muscular dystrophies [101]. A growing body of research suggests that several annexin family members facilitate the required membrane fusion events during

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the healing of PM lesions [102–104]. Here, gene therapy, i.e. the transfer of DNA encoding functional annexin proteins into the target cells, might be used to treat conditions caused by defective PM repair mechanisms.

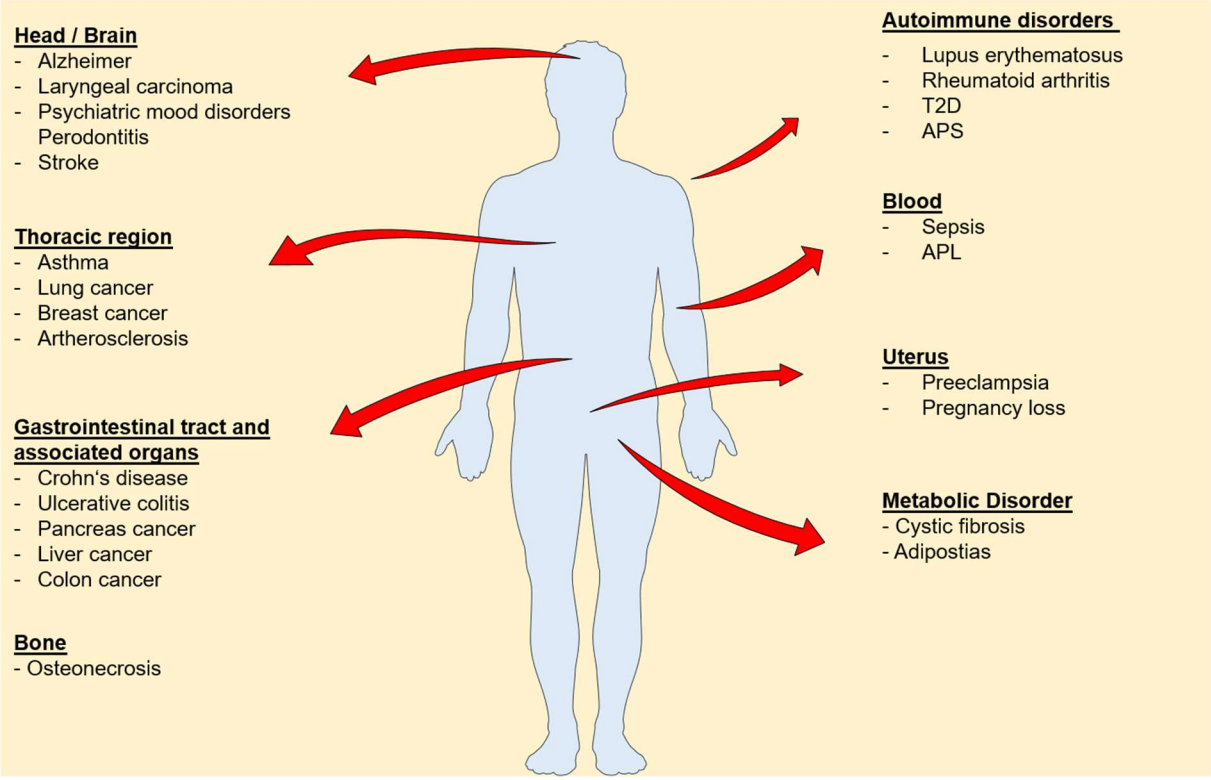

Figure 1. Constituent overview of diseases associated with changes in annexin expression levels. Abbreviation: T2D: Type 2 diabetes mellitus; APS: antiphospholipid syndrome; APL: promyelocytic leukemia.

Conclusion

This review summarizes the potential clinical use of the annexins. While by no means being exhaustive (we apologize to any colleague whose excellent work had to be excluded in the interest of space), we believe that this collection of exemplary articles helps bring together annexin-themed basic science and translational research which will inspire a fresh look and open up a whole new world for these proteins to be conquered.

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Author contributions

All authors have made substantial contributions to the manuscript. Conceptualization, S.S. and U.R. Data Curation, S.S and D.P.; Writing – Original Draft Preparation, S.S.; D.P. Writing – Review & Editing, S.S.; D.P.; U.R. Supervision, U.R.; Project Administration, U.R.; Funding Acquisition, U.R.

Conflicts of Interest

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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