Annexins in cell migration and adhesion

In the late 1970s and early 1980s, while searching for scaffolding and bridging proteins that could bring together membranes or proteins, several groups independently discovered the first annexins. These proteins were initially named after their biochemical properties, including synexin, chromobindins, calcimedins, lipocortins as well as calpactins. However, after detailed characterization of their structural and functional properties, it soon emerged that all these different proteins belonged to a highly-conserved protein family, then named annexins. Over the last 2 decades the increased use of gene knockdown approaches and mouse models lacking individual annexins has made it increasingly evident that annexins have a wide variety of critical cellular functions, including proliferation, differentiation, apoptosis, membrane repair and inflammatory response.

Moreover, in recent years, several annexins have been identified as critical players in cell adhesion, migration and invasion, relevant to several human diseases, and providing opportunities for novel therapeutic approaches. Interestingly, although the annexin family is highly conserved, implicating functional redundancy within this family, the underlying mechanisms how individual annexins affect adhesive and migratory behavior appear to be very different. Highlighting ongoing research that addresses hot topics in annexin research, this special focus issue contains a variety of articles, each centered around an individual member of the annexin family. Several research articles provide novel molecular insights on annexin A1, A2 and A8 in cancer progression and angiogenesis, while 2 review articles summarize current knowledge on adhesive and migratory behavior influenced by AnxA1 and AnxA6 in cardiovascular disease and cancer cell motility, respectively.

De-regulated annexin A1 expression has been observed in metastatic prostate cancers, and Bizzarro and coworkers identify upregulation of AnxA1 during hypoxia, which contributes to an increased metastatic potential and correlates with poor prognosis of prostate cancer patients. Foley et al. address the role of annexin A2 for the progression of pancreatic ductal adenocarcinoma. The majority of these tumors are comprised of stromal cells and extracellular factors secreted from these stromal cells into the microenvironment act through annexin A2 to promote invasion and metastasis. Heitzig and coworkers investigate how annexin A8 regulates endothelial cell sprouting during angiogenesis. Using AnxA8-deficient human umbilical vein endothelial cells, they identify a defective formation of integrin- and VEGFR-containing complexes that correspond with severely disturbed angiogenic sprouting. The Soehnlein group summarizes current knowledge on the therapeutic relevance of annexin A1 and annexin A1-derived peptides in the protection against atherosclerosis, a common cause of cardiovascular disease. Atherosclerosis is in part triggered by an inflammatory response and at later stages characterized by chronic inflammation. Binding of extracellular annexin A1 to formyl-peptide receptors promotes the resolution of inflammation and several studies in animal models have demonstrated that administration of annexin A1 and its peptide Ac2-26 modulate leucocyte recruitment, thereby protecting against atheroprogression. The underlying mechanism also appear beneficial in stroke and myocardial infarction, providing novel opportunities for pro-resolving approaches in the clinic. Finally, Grewal and coworkers provide an overview of the multiple and diverse scaffold functions that enable annexin A6 to impact on cancer cell motility. Extracellular as well as several intracellular activities of AnxA6, ranging from cell signaling, membrane and actin re-arrangements as well as cholesterol homeostasis seem to contribute to modulate cell adhesion and migration. Some of those, such as expression profiles as well as association with exosomes, implicate potential to become a biomarker for the prognosis of certain cancers.

This special focus issue is not aiming for a comprehensive overview of annexin research, but reflects some recent developments in this field. This includes a snapshot of several annexins in different cancers, as well as annexin A1 research in cardiovascular research, the latter underscoring an increasingly developing trend from bench-to-bedside in annexin research. We trust that basic as well as clinically-orientated researchers interested in molecular sciences, would greatly benefit from this issue that provides novel research data from several annexin laboratories as well as summaries and discussions on recent knowledge in this field.
Thomas Grewal graduated in Biology from the University of Cologne (Germany). He obtained his Ph.D. in 1993 in the laboratory of Albrecht Sippel (University of Freiburg, Germany) on macrophage-specific gene regulation. From 1993 – 1997 he then studied the regulation of lipoprotein receptors in atherosclerosis during postdoctoral fellowships, first with Keith Stanley at the Heart Research Institute (Sydney, Australia) and then with Jean Davignon at the Clinical Research Institute in Montreal (Canada). He then joined the team of Ulrike Beisiegel at the University Hospital Eppendorf (Hamburg, Germany) to led a research team studying the role of annexins in hepatic LDL endocytosis and the intracellular processing of triglyceride-rich lipoproteins. In 2003, he took a research position as group head at the Center for Immunology (St Vincent’s Hospital, Sydney) to examine how annexin A6 coordinates membrane transport and cell signaling in cancer and cardiovascular disease. He joined the Faculty of Pharmacy (University of Sydney, Australia) in 2007. Utilizing a multi-disciplinary approach involving biochemistry, molecular cell biology, and state-of-the-art microscopy, he continues to examine how annexin A6 and other annexins coordinate cholesterol and fatty acid transport, and how this affects the localization/activity of signaling complexes and receptors in cell growth and cell mobility.

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