Regulation of CFTR function by annexin A2-S100A10 complex in health and disease

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Abstract. Annexin A2 and S100A10 proteins form a heterotetrameric complex and belong to different families of Ca^{2+}-binding proteins. Annexins are non-EF-hand-type Ca^{2+}-binding proteins that exhibit Ca^{2+}-dependent binding to phospholipids and membranes in various tissues. They have been implicated in many Ca^{2+}-regulated processes, including regulation of membrane organization, trafficking and interact with many targets such as ion channels. S100 proteins comprise a family of small proteins characterised by the presence of two consecutive EF-hand type Ca^{2+}-binding motifs, interact with ion channels and regulate diverse processes and play a role as Ca^{2+} sensors. Several annexin–S100 complexes have been characterized and require calcium. In this regard, S100A10 binding to annexin A2 is an exception in that it is regulated by a post-translational modification of annexin A2 and occurs independently of calcium concentration. This review focuses on the regulatory mechanism behind annexin A2–S100A10 complex formation, its role in regulating chloride transport in health and cystic fibrosis and the potential of this mechanism to integrate calcium and cAMP signalling in airway epithelia. We propose that cAMP/PKA-dependent activation of chloride flux (through CFTR and ORCC) requires the mobilisation of a multi-protein complex involving calcium binding proteins from three different families (annexin 2, S100A10 and Calcineurin A).

Key words: Annexin A2 — S100A10 — cAMP — Calcium — Cystic fibrosis — CFTR

Introduction

Epithelial cells not only provide a protective barrier but play an important role in the normal function of the respiratory system. One such function is the maintenance of the fine balance between ion secretion and re-absorption across the respiratory epithelium, which is a critical determinant of the height of the fluid layer that lines the respiratory tract, the periciliary layer. This layer facilitates the function of cilia present on the apical surface of the cells, which in turn drives the movement of mucous, fluid and trapped bacteria out of the respiratory tract. Thus, the mechanisms that regulate active salt and water transport have important implications for understanding lung fluid balance under both normal and pathologic conditions. For example, the importance of epithelial ion movement is highlighted in the disease cystic fibrosis (CF) - a monogenic disorder resulting from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP/PKA and ATP-regulated chloride channel in epithelia (Riordan et al. 1989). However, how CFTR interacts with other membrane and non-membrane proteins to control trans-epithelial transport of ions and water under normal (and pathologic conditions) remains an open question.

Annexin A2, S100A10 and calcineurin

We have been interested in the annexin gene family and its relationship to ion transport and CFTR function for a number of years (Muimo et al. 1998; Muimo et al. 2000; Borthwick et al. 2007). Initial work, conducted in Anil Mehta's laboratory,

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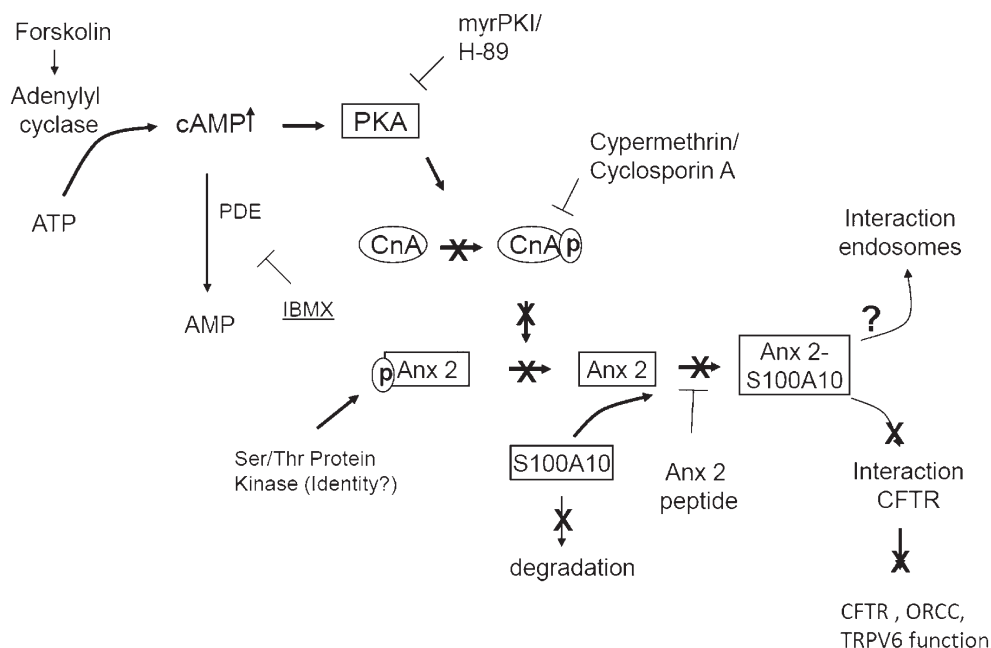E-mail: r.muimo@sheffield.ac.uk

Figure 1. Schematic representation of the pathways involved in modulation of the annexin A2-S100A10/CFTR complex in airway epithelia, showing the likely components involved in modulation of CFTR ion channel activity. Potential cargo proteins and lipids bound to the annexin A2 complex are not shown for clarity. The → sign does not mean that the promoted reaction is necessarily direct. X indicates processes defective in F508del CF cells. Reproduced with permission from Cellular Signalling 20(6), 1073-1083.

indicated that chloride concentration could signal to the apical membrane by regulating phosphorylation of a number of soluble proteins within the apical membrane. We identified one of the soluble proteins as annexin 1, and established that its chloride sensitive phosphorylation occurred on histidine residue(s) (Muimo et al. 2000). Recently, we found that a cAMP/PKA/calcineurin A-dependent multi-protein complex involving annexin A2–S100A10 must be assembled with cell surface membrane CFTR before this channel can open (Borthwick et al. 2007) (see also Fig. 1). Crucially, disruption of the annexin A2-S100A10/CFTR complex in wild type cells significantly attenuates CFTR function and obtunds CFTR-regulated outwardly rectifying chloride channels (ORCC) that generate ORCC-mediated currents.

Annexin A2 is a member of the annexin family of soluble proteins that bind to certain negatively charged phospholipids in cellular membranes in a calcium-dependent manner. The annexin COOH-terminal core is conserved and contains non-EF-hand-type Ca^{2+}-binding sites, their NH_2-terminal tail is unique and enables the protein to interact with distinct cytoplasmic partners. They are involved in diverse cellular processes including inflammation, and ion transport (Perretti and Flower 2004; Gerke et al. 2005) processes that are defective in CF for obscure reasons. Interestingly, previous analysis shows annexins not only share significant sequence homology with that part of

CFTR bearing the most common F508del-CFTR mutation including the (normally invariant) missing phenylalanine residue at position 508 (Chap 1991), but these family members are also associated with endosomes, caveolae, clathrin coated vesicles, and other membrane compartments, engaged in endo-/exo-cytosis (Thiel et al. 1992; Turpin et al. 1998; Gerke and Moss 2002; Zobiack et al. 2003; Gerke et al. 2005). It is worth noting that, in many cell types, full activation of CFTR depends on vesicular transport and subsequent fusion of vesicles containing mature CFTR with the plasma membrane (Bradbury et al. 1994; Bradbury 1999). This Ca^{2+} -dependent vesicle-mediated process is triggered by cAMP/PKA and requires the C-terminus of CFTR (Weber et al. 1999). Annexin A2-S100A10 regulate exocytic apical transport in polarised epithelia (Jacob et al. 2004). For unknown reasons, CFTR mutation induces defective endosome function and CFTR recycling through such compartments (Poschet et al. 2002). Interestingly, annexin A1 expression is down regulated in CF, annexin A5 binds CFTR and is overexpressed in CF epithelia from foetal trachea (Della Gaspera et al. 1995; Bensalem et al. 2005; Trouve et al. 2007). On the other hand, annexin A4 regulates Ca^{2+}-dependent Cl- conductance in epithelia (Kaetzel et al. 1994). It may also be relevant that annexin A2 is a ligand for *Pseudomonas aeruginosa* (Kirschnek et al. 2005), a leading cause of premature death in CF patients,

given that our data suggest annexin A2 is abnormally located in F508del-CFTR CF cells (Borthwick et al. 2008b).

S100A10 (previously known as p11, calpactin I light chain) belongs to the S100 protein family of small (10–14 kDa) Ca^{2+}-binding proteins that regulate various intracellular and extracellular processes and which exist as homo-/heterodimeric functional units in various tissues (Rescher and Gerke 2008). Amongst the S100 family, S100A10 is unique in that it is unable to bind Ca^{2+} because it lacks three amino acid residues in the N-terminal EF-hand motif and the crucial amino acids are substituted in the C-terminal motif (Rescher and Gerke 2008). The first fourteen N-terminal residues of annexin A2 constitute the S100A10-binding site (Kube et al. 1992). Several studies using knockout animals have suggested important biological roles for S100A10. Using conditional mouse knock out suffering a specific S100A10 deletion in nociceptive sensory neurons, Foulkes et al. (2006) have demonstrated a role in nociception, resulting from decreased sodium current. Svenningsson et al. (2006) generated a general S100A10 mouse knock out to analyse the physiological relevance of the S100A10–5-HT1B receptor interaction. They found that that S100A10–/– mice is viable but exhibits a depression-like phenotype with reduced responses to 5-HT1B agonists; this suggests that S100A10 is not required for normal development, but the lack of this complex causes a depressive disorder.

Calcineurin (Cn) is a serine/threonine protein phosphatase regulated by $[Ca^{2+}]i$ and calmodulin (CaM) (Crabtree 1999) and couples Ca^{2+}-signalling to various processes including inflammation, lymphocyte activation, gene expression, ischemic injury and apoptosis (Tong et al. 1995; Crabtree 2001; Vega et al. 2003; Borthwick et al. 2007). It is a heterodimer consisting of a 61-kDa catalytic subunit (CnA) and a calcium-binding 19-kDa regulatory subunit (CnB) (Crabtree 1999). Three isoforms of the catalytic subunit (*CnAα, CnAβ,* and *CnAγ*) and 2 isoforms of the regulatory subunit (*CnB1* and *CnB2*) have been identified (Crabtree 1999). A rise in cytosolic Ca^{2+} concentration induces a conformational change in CaM and CnB leading to CnA activation. Compared to lymphocyte, cardiomyocytes and brain cells, the role of Cn in epithelia remains poorly characterised. Our recent data shows that in membrane of airway and gut epithelia, PKA induces serine phosphorylation of CnA and a CnA-dependent complex between annexin A2-S100A10 and CFTR or the calcium influx channel, TRPV6 (Borthwick et al. 2007; Borthwick et al. 2008a) and thus, provides new evidence for 1) CnA regulation of CFTR and TRPV6 channels and 2) a interaction between cAMP and Ca^{2+} signalling in epithelia. However, it is not known whether the PKA-dependent activation of CnA is restricted to membrane, which CnA isoform is involved and whether CnB, CaM and Ca^{2+} also play a role in the PKA-dependent activation of CnA.

Annexin A2-S100A10 complex and CFTR function

Whereas other annexins require Ca^{2+} to bind their S100 ligands, formation of the annexin A2-S100A10 heterotetrameric complex occurs independently of Ca^{2+} concentration. Instead of Ca^{2+}, the annexin A2-S100A10 complex is modulated by post-translational modifications including phosphorylation and N-terminal acetylation of annexin A2 (Johnsson et al. 1986; Chasserot-Golaz et al. 1996; Jost and Gerke 1996) but the precise regulatory mechanisms remained unclear and as a result the interaction was considered constitutive. Recent work from our laboratory has established that formation of annexin A2-S100A10 complex is regulated by cAMP/PKA and protein phosphatase (calcineurin A) and leads to a functionally important interaction with CFTR in airway and gut epithelial cells (Borthwick et al. 2007). Pharmacological agents that inhibit CnA and an acetylated peptide corresponding to the S100A10 binding domain on annexin A2, disrupt complex formation in wild type cells and significantly attenuate CFTR function. *In vitro,* PKC phosphorylates Ser-11 within the S100A10 binding domain (amino-acids 1-14) of annexin A2, and phosphorylation at this site most likely leads to a direct spatial interference with S100A10 binding (Johnsson et al. 1986; Jost and Gerke 1996). Additionally, PKC phosphorylates annexin A2 on Ser-25 but phosphorylation on this site does not affect S100A10 binding (Johnsson et al. 1986).

The annexin A2-S100A10 complex is suitably matched to link membranes and/or vesicles to cytoskeletal proteins to regulate membrane organization, mediate membrane-membrane associations and control plasma membrane receptors and ion channels. Annexin 2 preferentially binds to anionic phospholipids, such as phosphatidylinositol 4,5-bisphosphate, which is enriched in lipid rafts in the plasma membrane, while S100A10 binds and provides a bridge to link the complex to ion channels and cytoskeletal proteins, such as actin. In this regard, this complex controls the recruitment and/or function of Na^+, K^+, Ca^{2+}, and Cl^- channels (including wild type CFTR) and 5-HT1B receptors (Girard et al. 2002; Okuse et al. 2002; van de Graaf et al. 2003; Svenningsson et al. 2006; Borthwick et al. 2007; Borthwick et al. 2008a). In the epithelial membrane of the airway and gut, PKA induces formation of the CnA-dependent complex not only between annexin A2-S100A10 and CFTR but also between annexin A2-S100A10 and the calcium influx channel, TRPV6 (Borthwick et al. 2007; Borthwick et al. 2008a). S100A10 binds the TRPV5/6 Ca^{2+} channels and the background K^+ channel (TASK 1) via C-terminal VATTV and SSV motifs, respectively (Girard et al. 2002; van de Graaf et al. 2003). Thus, CFTR may also possess a similar binding motif for annexin A2-S100A10 complex. However, S100A10 also binds the tetrodotoxin-insensitive, voltage-gated Na^+ channel (Nav1.8), via the N-terminus which lacks the two

motifs described above (Okuse et al. 2002). In the annexin A2 –S100A10/CFTR complex, S100A10 acts as the bridging protein (Borthwick et al. 2007) but sequence analysis shows that CFTR lacks the above S100A10 binding motifs. Thus, the CFTR binding site for S100A10 may be novel and distinct from previously described motifs.

Annexin A2 association fails towards S100A10 and F508del-CFTR.

CF is characterised by impaired salt and water transport in several tissues including the respiratory and gut epithelia (Riordan et al. 1989). In such epithelia, the cAMP/PKA regulated and ATP-dependent CFTR chloride channel fails to control the transport of chloride, bicarbonate and hence water. However, how CFTR controls transepithelial transport and how CFTR interacts with other membrane and soluble proteins to carry out this process remain open questions. Interestingly, only a poor correlation exists between the CF genotype and lung phenotype suggesting that additional cellular factors may influence the pulmonary manifestations of the disease. In addition to defects in epithelial ion and water transport, CF is associated with multiple cellular defects including inflammation, abnormal trafficking, exocytosis and endocytosis (Yankaskas 1999; Hodson 2007).

The F508del-CFTR mutation (the most common CF mutation) causes improper folding and processing of CFTR. Delivery of F508del-CFTR to the plasma membrane is impaired and may be responsible for the lack of cAMP/PKA-dependent Cl^- conductance (Kopito 1999). Controversially, recent evidence demonstrates the presence of some of this mutant form of CFTR at the apical membrane (Kalin et al. 1999; Penque et al. 2000; Varga et al. 2004), which nevertheless remains dysfunctional. Comparative studies of purified F508del-CFTR and wt-CFTR reconstituted in planar lipid bilayers have demonstrated that Cl^- channel activity of F508del-CFTR is similar to that of wild-type CFTR (Li et al. 1993), which suggests that other regulatory elements act on CFTR within the cell. Crucially, it is increasingly evident that CFTR interacting proteins (CIP's) play an important role in regulating CFTR function (Guggino and Stanton 2006). However, most of the CIP's identified to date are inhibitory to CFTR function. In order to identify proteins that might play a role in CFTR activation, we analysed protein-protein interactions involving CFTR under conditions whereby CFTR function is activated. Our model invokes the idea that at baseline, cell surface CFTR is held inactive (in complex with proteins inhibitory to CFTR function – e.g. syntaxin 1A, syntaxin 8; AMPKα (Cormet-Boyaka et al. 2002; Hallows et al. 2003; Bilan et al. 2004), but after protein kinase A is activated, additional component plasticity occurs which is permissive for channel opening.

Disruption of the annexin A2-S100A10 interaction has implications for membrane organization and channel modulation. The significant attenuation of CFTR function following disruption of the annexin A2-S100A10/CFTR complex in wild type cells (Borthwick et al. 2007) by agents that disrupt complex (PKA/CnA inhibitors and acetylated annexin A2 N-terminal peptide), predicted defective annexin A2-S100A10/CFTR complex formation in CF cells. Correspondingly, we found that although some F508del-CFTR could be detected on the plasma membrane of CFBE41o- cells (Borthwick et al. 2008b), formation of either the annexin A2-S100A10 or the annexin A2-S100A10/CFTR complex fails in CFBE41o- cells (Borthwick et al. 2008b) (see also Fig. 1). Thus, loss of annexin A2-S100A10/CFTR complex formation may contribute to defective cAMP-induced Cl^- currents and suggests CFTR mutation affects these multi-protein interactions. Defective complex also suggests a feedback loop, whereby normal CFTR plays an important role in the function of the proteins that regulate its own activity.

S100A10 normally undergoes degradation in the absence of its partner, annexin A2, in many cell types (Rescher and Gerke 2008). The mechanisms and degradation pathway is as yet unknown. A crucial difference exists between CF and non-CF airway epithelial cells (Borthwick et al. 2008b) in that unlike non-CF cells, avidin pull down from CFBE41o- cells (homozygous F508del-CFTR expressing) (biotin surface labeled ± cAMP stimulation), co-precipitates biotin-labeled F508del-CFTR and only a small amount of S100A10, but without its normally obligate annexin A2 partner. Yet by western blot, both annexin A2 and S100A10 are detectable in the very same input fractions from CFBE41o- cells. The absence of obligate partnership between annexin A2–S100A10 in CFBE41o- cells was confirmed by immunoprecipitation of either CFTR, annexin A2 or S100A10 (Borthwick et al. 2008b) and is surprising given that S100A10 normally degrades when annexin A2 is down regulated in many cell types (Rescher and Gerke 2008). This implies that S100A10 is abnormally resistant to degradation in some way in CF cells (perhaps due to a defective degradation pathway) or binds to some other protein to promote its stability.

Conclusions

Ca^{2+}- and cAMP-dependent pathways integrate to regulate the interaction between annexin A2-S100A10 and CFTR by controlling the phosphorylation and dephosphorylation of annexin 2. Whereas the phosphorylation of annexin 2 is Ca^{2+}-dependent and interferes with S100A10 binding, dephosphorylation is cAMP -dependent and is permissive to the interaction leading to regulation of chloride flux. Given that annexin A2-S100A10 controls the recruitment and function of several other channel proteins (including Na^+,

K^+, Ca^{2+} and Cl^- channels), and CFTR regulates several other channels and proteins, this complex appears vital for epithelial ion transport and function. Future experiments are expected to characterize the interaction further, identify additional annexin A2-S100A10/CFTR interaction partners and their role in epithelial ion transport and function.

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