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

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Annexin A2 and S100A10 proteins form a heterotetrameric complex and belong to different families of Ca²⁺-binding proteins. Annexins are non-EF-hand-type Ca²⁺binding proteins that exhibit Ca²⁺-dependent binding to phospholipids and membranes in various tissues. They have been implicated in many Ca²⁺-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 Ca²⁺-binding motifs, interact with ion channels and regulate diverse processes and play a role as Ca2+ 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).