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Review

Functional interaction of the cystic fibrosis transmembrane conductance regulator with members of the SLC26 family of anion transporters (SLC26A8 and SLC26A9): Physiological and pathophysiological relevance☆

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ABSTRACT

The solute carrier 26 (SLC26) proteins are transmembrane proteins located at the plasma membrane of the cells and transporting a variety of monovalent and divalent anions, including chloride, bicarbonate, sulfate and oxalate. In humans, 11 members have been identified (SLC26A1 to SLC26A11) and although part of them display a very restricted tissue expression pattern, altogether they are widely expressed in the epithelial cells of the body where they contribute to the composition and the pH regulation of the secreted fluids. Importantly, mutations in *SLC26A2*, *A3*, *A4*, and *A5* have been associated with distinct human genetic recessive disorders (*i.e.* diastrophic dysplasia, congenital chloride diarrhea, Pendred syndrome and deafness, respectively), demonstrating their essential and non-redundant functions in many tissues. During the last decade, physical and functional interactions of SLC26 members with the cystic fibrosis transmembrane conductance regulator (CFTR) have been highly documented, leading to the model of a crosstalk based on the binding of the SLC26 STAS domain to the CFTR regulatory domain. In this review, we will focus on the functional interaction of SLC26A8 and SLC26A9 with the CFTR channel. In particular we will highlight the newly published studies indicating that mutations in SLC26A8 and SLC26A9 proteins are associated with a deregulation of the CFTR anion transport activity in the pathophysiological context of the sperm and the pulmonary cells. These studies confirm the physiological relevance of SLC26 and CFTR cross-regulation, opening new gates for the treatment of cystic fibrosis.

This article is part of a Directed Issue entitled: Cystic Fibrosis: From o-mics to cell biology, physiology, and therapeutic advances.

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Abbreviations: cAMP, cyclic adenosine monophosphate; CF, cystic fibrosis; CFBE41o-, cystic fibrosis bronchial epithelial cell line; CFTR, cystic fibrosis transmembrane conductance regulator; CHO-K1, Chinese hamster ovary-K1; DHPLC, denaturing high performance liquid chromatography; ENac, epithelial Na channel; HBE, human bronchial epithelial; HEK, human embryonic kidney; IRBIT, IP_3 receptor binding protein released with IP_3; PKA, protein kinase A; sAC, soluble adenylate cyclase; SLC26, solute-linked carrier 26; STAS, sulfate transporter and anti-sigma factor antagonist.

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1. Introduction

1.1. The SLC26 family of anion transporters

The solute carrier 26 (SLC26) proteins are multifunctional transmembrane proteins mediating the transport of various monovalent and divalent anions including Cl^- (chloride), HCO_3^- (bicarbonate), SO_4^{2-} (sulfate), iodide (I^-) and $C_2O_4^{2-}$ (oxalate), mainly across the plasma membrane of epithelial cells and contributing to the composition and the pH of secreted fluids in the body. SLC26 belong to the highly conserved superfamily of amino acid-polyamine-organocation (APC) transporters and SLC26-related proteins have been found in various organisms among which, bacteria, yeast, algae and plants (SulP/Sultr proteins). In mammals, 11 members have been identified and designated as SLC26A1 to SLC26A11, SLC26A10 most probably corresponding to a pseudogene (Table 1).

SLC26 proteins share a common structure including (i) a highly conserved transmembrane region involved in the anion transport activity, which comprises 10–14 hydrophobic spans and (ii) a less conserved cytoplasmic region which comprises the STAS domain (sulfate transporter and anti-sigma factor antagonist), involved in protein–protein interaction and regulation. In addition, several members carry a PDZ binding domain at their carboxy-terminal extremity (for reviews see Ohana et al., 2009; Alper and Sharma, 2013). In the last three years, significant progress in the field of SLC26s structure has been completed as X-ray crystallography and NMR studies achieved the modeling of the STAS domain for two bacterial and one mammalian members of the SLC26/SulP family (*Escherichia coli* YchM, *Mycobacterium tuberculosis* Rv1739c SO_4^{2-} transporter, *Yersinia enterocolitica* SLC26A2, rat SLC26A5/Prestin) (Babu et al., 2010; Pasqualetto et al., 2010; Compton et al., 2011; Sharma et al., 2011). However, no structure of the transmembrane region has been reported so far. One additional structural feature of the SLC26s that has emerged during the last years is their capacity to form homo-dimers and -oligomers, most probably *via* their transmembrane regions; this property was in particular documented for SLC26A5/Prestin in mammals (Detro-Dassen et al., 2008; Compton et al., 2011).

SLC26 members mediate the transport of various anions and the mechanisms associated are variable between the different members. Surprisingly, they can be multiple for a single transporter. The current classification of the SLC26 family, based on their mode of transport, comprises three main groups: the SO_4^{2-} transporters [SLC26A1 and A2], the Cl^-/HCO_3^- exchangers [SLC26A3, A4 and A6] and the ion channels [SLC26A7 and A9] (for reviews see Ohana et al., 2009; Alper and Sharma, 2013). So far SLC26A5 anion transport activity has not been reported in mammals but only in chicken, zebra fish and insects (Schaechinger and Oliver, 2007; Hirata et al., 2012); however SLC26A5 activity as a motor protein was shown to be anion-dependent (Rybalchenko and Santos-Sacchi, 2008). Regarding SLC26A8 and SLC26A11, they have been poorly characterized and their mode of transport is ill defined. In total, although useful, the above current classification is complex because of the lack of correlation with sequence similarities and most importantly the capacity for some members to behave as both channels and anion exchangers depending on the substrates available and probably their cellular and sub-cellular localization, as illustrated for SLC26A3 and A6.

SLC26 family members are undoubtedly essential to various physiological functions and differentiation processes; in human, pathogenic "loss of function" mutations in *SLC26s* have been associated with four hereditary genetic diseases: diastrophic dysplasia (SLC26A2), congenital chloride diarrhea (SLC26A3), Pendred syndrome (SLC26A4) and deafness (SLC26A5) (Everett and Green, 1999; Dawson and Markovich, 2005), which are all transmitted following an autosomal recessive mode of inheritance. These phenotypes are in line with the restricted tissue expression profiles observed for most of the *SLC26* genes. To date knock out and knock in mouse models have been generated for all SLC26 members except SLC26A11. These models did reproduce most of the clinical features of the SLC26 human-related diseases when applicable (Liberman et al., 2002; Forlino et al., 2005; Schweinfest et al., 2006; Dallos et al., 2008; Dror et al., 2010; Lu et al., 2011). Interestingly, inactivation of the genes not related so far to a human disease also generated a specific phenotype in the tissues where the concerned SLC26s were to be expressed (*i.e.* kidney, liver, stomach, testis, etc.) (Jiang et al., 2006; Touré et al., 2007; Xu et al., 2008, 2009; Dawson et al., 2010), suggesting that in humans, mutations in other *SLC26* genes could be pathogenic.

1.2. Interaction of the SLC26 family members with CFTR

SLC26 proteins are expressed throughout the entire body and most interestingly they were shown to be co-expressed with the cystic fibrosis transmembrane conductance regulator (CFTR) in various epithelia. The existence of physical and functional interactions between the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel and several members of the SLC26 family of anion transporters is now well established. Pioneer work described a mutual regulation between CFTR and two members of the SLC26 family: SLC26A3 and SLC26A6 (Ko et al., 2002, 2004; Chernova et al., 2003). In the proposed model, physical interaction between CFTR and SLC26s first involves the binding of their PDZ domains with a common scaffold protein bringing them to close proximity and allowing subsequent direct interaction of the STAS domain of the SLC26s with the R domain of CFTR (Fig. 1). Interestingly, this interaction was shown to be enhanced by PKA-mediated phosphorylation of the R domain (Ko et al., 2002, 2004; Shcheynikov et al., 2006). Following this discovery, physical and/or functional interaction of CFTR were further documented for SLC26A3, A6

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