J Bioenerg Biomembr (2007) 39:373–378
DOI 10.1007/s10863-007-9100-3

Sodium pump localization in epithelia

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Published online: 31 October 2007

Abstract In epithelial cells, the sodium pump, in coordination with several other ion transporting proteins and channels, acts to regulate directional water and ion flux across the epithelial barrier. This function is dependant on the polarized localization of the sodium pump to a single plasma membrane domain. In most epithelial cell types the sodium pump is found in an exclusively basolateral position. Despite the clear importance of maintaining a polarized distribution of the sodium pump, surprisingly littleis known about the specific mechanisms responsible for the targeting and trafficking of the sodium pump to the basolateral surface. We briefly discuss our current understanding of factors which may act to regulate the cellular distribution of the sodium pump, including the potential role of the sodium pump β-subunit. Several previous, studies have suggested that the expression of the β2 isoform (instead of β1) may cause the apical localization of the sodium pump. This appeared to be confirmed by Wilson et al. *Am J Pathol*, 156: 253–268, 2000 who found that MDCK cells stably transfected with the β2 subunit express the sodium pump at the apical surface. However, careful examination by Laughery et al.,*Am J Physiol*, 292: F1718–F1725, 2007, showed that the apical targeting of the pump was caused by the presence of butyrate in the cell growth media and was not due to the presence of the β2 isoform. These findings are discussed below, along with potential explanations as to how butyrate may influence the polarity of the sodium pump in epithelial cells.

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Keywords Sodium pump · Epithelia · Ion transport · Membrane · Cell polarity · Trafficking · Butyrate · MDCK

The sodium pump

The Na^+,K^+-ATPase or sodium pump is the major active transport protein found in the plasma membrane of virtually all animal cells (Kaplan 2002). The sodium pump utilizes the energy from one molecule of ATP to actively transport three Na^+ions out of the cell and two K^+ions into the cell, thereby maintaining high Na^+ and K^+ gradients across the plasma membrane. This action makes the sodium pump the major determinant of cytoplasmic Na^+ concentration (Therien and Blostein 2000). The resulting Na^+ gradient across the plasma membrane is utilized for the secondary transport of many substances into or out of the cell including protons, calcium, glucose and amino acids. However, the role the sodium pump plays in fluid and electrolyte homeostasis is arguably it's most important.

The functional sodium pump consists of two protein subunits, a catalytic α-subunit and a glycoprotein β-subunit. These two subunits are thought to assemble in a 1:1 ratio creating an αβ heterodimer. The catalytic α-subunit contains ten membrane-spanning regions (Lutsenko and Kaplan 1995; Hu and Kaplan 2000), it contains binding sites for ATP, Na^+, K^+ and ouabain as well as the catalytic phosphorylation site (Lingrel and Kuntzweiler 1994). The β-subunit spans the plasma membrane only once and is thought to be important for proper maturation, delivery and insertion of the αβ heterodimer into the plasma membrane and appears to influence the catalytic activity of the enzyme (Jaisser et al. 1994; Geering 2005).

The sodium pump is found in relatively high levels in many epithelia where it works in concert with a host of

other ion transporters and channels to regulate directional water and ion flux across the epithelial barrier. Depending on the arrangement of these transporters and channels on the apical and basolateral plasma membrane surfaces, the epithelia can act to either absorb or secrete solutes. This polarized location of transporters is a fundamental property of epithelial cells. In nearly all epithelial cell types the sodium pump is found in an exclusively basolateral location. The rare exceptions to this rule are the choroid plexus (Quinton et al. 1973; Ernst et al. 1986; Marrs et al. 1993) and retinal pigment epithelium (RPE) (Okami et al. 1990; Gundersen et al. 1991) where the sodium pump is found on the apical surface. Despite the importance of the specific polarized distribution of the sodium pump in epithelia for directional water and ion flux, the mechanisms which correctly target and traffic the sodium pump to the appropriate plasma membrane domain are still unresolved.

Membrane protein trafficking

The route taken by integral membrane proteins from their synthesis in the ER to their final destination in the cell varies depending on the cell type as well as from protein to protein. The mechanisms that direct this trafficking are diverse and complex, and involve various trafficking mechanisms, including targeting sequences/motifs, patterns of *N* and *O*-linked glycosylation as well as the inherent affinity of certain proteins for different lipid environments, such as lipid rafts. In many cells, an indirect pathway is taken, where proteins are initially delivered non-specifically to each membrane surface, and once there, certain proteins are specifically re-internalized and either degraded or targeted to the other surface. This is the case in hepatocytes where most plasma membrane proteins are initially sent to the basolateral surface, and apically destined proteins are subsequently endocytosed and transported to the apical domain by the process of transcytosis (Bartles et al. 1987). In many epithelial cells, plasma membrane proteins are sorted in the trans-golgi network and targeted directly to either the apical or basolateral membrane surfaces. These processes are the topic of several recent reviews (Muth and Caplan 2003; Nelson 2003; Rodriguez-Boulan et al. 2005).

Trafficking of the sodium pump to the basolateral membrane

Previous studies have yielded some information regarding the mechanisms by which the sodium pump is delivered to its proper plasma membrane domain. Several studies have shown that the assembly of α and β subunits into the αβ heterodimer is essential for the release of the sodium pump from the ER, (Geering et al. 1989; McDonough et al. 1990; Gottardi and Caplan 1993b, Laughery et al. 2003) where the process of *N*-linked glycosylation is initiated. The sodium pump is then delivered to the golgi, where β-subunit *N*-glycosylation processing is completed. Following exit from the golgi, the sodium pump trafficks to the basolateral plasma membrane (in most cells). However, the route taken from the golgi to the basolateral membrane has been the topic of much study and controversy. Using pulse labeling and immunoprecipitation of *N*-azidobenzoyl ouabain (Forbush et al. 1978) bound to the sodium pump, Caplan et al. (1986) determined that newly synthesized sodium pump only appears at the basolateral surface of MDCK cells. This suggested that the sodium pump is intracellularly sorted and trafficked directly to the basolateral membrane. However, when this question was later examined by Hammerton et al. (1991) using radioactive pulse labeling and cell surface biotinylation techniques, the sodium pump was found to be delivered in approximately equal amounts to both the apical and basolateral membrane of MDCK cells. The sodium pump which appeared at the apical surface was found to have a very short half-life (less than 1 hour), while sodium pump expressed at the basolateral surface was much more stable. This indicated that the sodium pump is not sorted and targeted to a specific membrane domain, but is trafficked indiscriminately to both plasma membrane surfaces, with apical pumps being quickly removed from the surface. These contradictory results, in the same cell type, were the topic of much controversy. The seemingly irreconcilable observations were later explained by Mays et al. (1995) who determined that the initial studies utilized two different sub-clones of the same parent MDCK cell line, and these two clones handled the sodium pump differently. The MDCK cell line used by Hammerton et al. (1991), which initially traffics the sodium pump to both apical and basolateral membrane surfaces, was found to not properly polarize its plasma membrane lipids, as glycosphingolipids were found in both the apical and basolateral membranes, as opposed to their normal, exclusively apical distribution. This aberrant glycosphingolipid distribution appears to allow the sodium pump to be transported to the apical surface. This argument was strengthened by observations that treatment of MDCK cells (that normally distribute glycosphingolipids) with fumonisin, a drug which inhibits sphingolipid synthesis, leads to the random trafficking of the sodium pump to both apical and basolateral membrane domains (Mays et al. 1995). The generality of the role of the lipid distribution in sodium pump delivery does not appear to have been subsequently systematically examined.

Under normal conditions, MDCK cells appear to sort and traffic the sodium pump via an uncharacterized mechanism

directly to the basolateral membrane. This view was strengthened in a series of studies which examined trafficking of chimeras constructed from the basolateral Na^+,K^+-ATPase and the closely related, yet apically localized (in gastric cells), H^+,K^+-ATPase. From these studies, a dominant sorting sequence was initially determined to reside within 519 amino acids of the NH_2 terminus which caused the basolateral targeting of the Na^+,K^+-ATPase, and the apical targeting of the H^+,K^+-ATPase (Gottardi and Caplan 1993a; Gottardi and Caplan 1993b). In a subsequent study, the basolateral targeting mechanism of the sodium pump was compromised when the predicted 4th transmembrane domain of the α-subunit was replaced by the homologous sequence from the H^+,K^+-ATPase. This mutation caused the sodium pump to traffic to the apical surface (Dunbar et al. 2000). That this segment plays a major role in sodium pump basolateral targeting has not been further established.

The stability and longer half-life of the sodium pump in the basolateral membrane, observed by Hammerton et al. (1991), may be explained by sodium pump association with the cytoskeleton. Ankyrin and fodrin are major components of the cell cytoskeleton and are known to associate with integral membrane proteins forming a membrane-cytoskeletal complex, which may be important for maintaining the spatial organization of proteins within the plasma membrane (Marchesi 1985; Nelson and Hammerton 1989). Several studies have shown that the sodium pump associates with ankyrin and fodrin (Nelson and Veshnock 1986, 1987a, b; Morrow et al. 1989; Nelson and Hammerton 1989), and have identified specific binding regions on the sodium pump α-subunit for ankyrin (Nelson and Veshnock 1987b; Devarajan et al. 1994; Thevananther et al. 1998). This connection is further strengthened by the fact that ankyrin and fodrin are localized predominantly (perhaps exclusively) to the basolateral membrane of MDCK cells (Nelson and Veshnock 1986). Although the association between the sodium pump and the cytoskeleton may not be responsible for targeting the protein to the basolateral membrane, it is thought that once delivered, this association likely stabilizes the pump in this location. The systematic examination of cytoskeleton-pump interactions in polarized epithelial cells should shed light on the importance of these phenomena. Several sequences within the α subunit have been identified as ankyrin binding sites (see Morrow et al. 1989; Sweadner and Donnet 2001) and a direct examination of their involvement seems worthwhile.

Trafficking of the sodium pump to the apical membrane

The mechanisms that cause apical trafficking of the sodium pump in the choroid plexus and RPE are also not well understood. Interestingly, the association between the α-subunit and the cytoskeleton is also evident in those cell types, which exhibit an apical sodium pump. In both the choroid plexus (Marrs et al. 1993; Marrs et al. 1995) and RPE (Gundersen et al. 1991; Ruiz et al. 1995), the ankyrin/fodrin cytoskeleton is also localized beneath the apical membrane and associates directly with the sodium pump. Some reports also suggest the sodium pump is localized to the apical surface (discussed below) in renal epithelial cysts developed in polycystic kidney disease, along with components of the cytoskeleton including actin, fodrin and ankyrin (Wilson et al. 1991).

Another mechanism that has been widely discussed is the possibility that the particular isoform of the β-subunit expressed influences the final localization of the sodium pump. In cell types with a basolaterally localized pump, the α1 and β1 isoforms are most widely expressed and make up the sodium pump heterodimer (e.g. in the intestine and kidney). However, in those cell types with an apically localized sodium pump, the β2 isoform has been observed. This is the case in the both the choroid plexus which expresses both the β1 and β2 isoform (Watts et al. 1991; Zlokovic et al. 1993) and the RPE, which has been reported to express the β2 isoform (Ruiz et al. 1996). However it has been subsequently observed that β2 protein is not expressed in RPE cells (Wetzel et al. 1999; Kaplan, Clifford & Bystriansky, unpublished). The possibility that the expressed isoform of the β-subunit somehow influences sodium pump trafficking is strengthened by observations in developing nephron and in patients with polycystic kidney disease (PKD). In normal adult kidney nephron, the sodium pump heterodimer is composed of α1 (Gloor et al. 1990; Farman et al. 1991; Tumlin et al. 1994) and β1 (Clapp et al. 1994) isoforms, and is exclusively expressed in the basolateral membrane (Kyte 1976a, b). However, in the developing nephron, the sodium pump is also seen at the apical surface (Avner et al. 1992; Burrow et al. 1999) and is made up of α1 and β2 isoforms (Burrow et al. 1999). Although there is there is little if any β1 protein expressed in the developing nephron, mRNA for β1 and β2 is expressed in approximately equal amounts (Burrow et al. 1999). In PKD the sodium pump has been detected at the apical surface of cyst cells and correlated with the expression of the β2 isoform (Wilson et al. 1991, 2000). However this is controversial as many studies either failed to confirm the apical localization of the sodium pump or show evidence that it is expressed only in the basolateral membrane (Kawa et al. 1994; Grantham et al. 1995; Brill et al. 1996; Takahashi et al. 1997) in PKD.

These observations led to the suggestion that expression of the β2 isoform may cause the apical trafficking of the sodium pump in renal cells. The β1 and β2 isoforms

share a 36.5% amino acid sequence identity (human) and differ greatly in their pattern of glycosylation as the β1 isoform contains three sites for *N*-glycosylation while the β2 isoform contains nine (Vagin et al. 2005). This is interesting as glycosylation has been identified as a potential mechanism for apical trafficking of some proteins (Yeaman et al. 1997; Gut et al. 1998; Benting et al. 1999). In HGT-1 cells, the serial addition of up to five additional glycosylation sites to β1 was found to result in a step-wise increase in the apical localization of the pump (Vagin et al. 2005). Vagin et al. (2005) also found that expression of YFP-tagged β2 in MDCK cells did not alter trafficking as the sodium pump remained expressed exclusively a the basolateral surface. This is in contrast to an earlier study which found that MDCK cells stably transfected with the β2 subunit express the β2 protein at the apical surface. This led to their suggestion that the inappropriate expression of this subunit in kidney cells caused apical localization of the sodium pump and hence cyst formation (Wilson et al. 2000). The discrepancy between these studies was resolved by the work of Laughery et al. (2007), who showed that the apical expression of the sodium pump seen in MDCK cells by Wilson et al. (2000) was in fact due to the addition of butyrate to the cell growth media. The basis of this novel effect of butyrate remains to be determined.

Selective basolateral localization of overexpressed Na^+, K^+-ATPase β1- and β2-subunits is disrupted by butyrate treatment of MDCK cells

The novel effects of butyrate were revealed in the work of Laughery et al. (2007). These findings are summarized as follows. A cell line was developed that provides tetracycline-regulated expression of sodium pump β-subunit constructs in MDCK cells. Two such cell lines were used, which are able to express either β1flag or β2myc proteins in addition to the endogenous β1 subunit. The cellular localization of endogenous α and β1 subunits and induced β2myc proteins in β2myc MDCK cells was determined by either confocal imaging, cell fractionation or by cell surface biotinylation.

When butyrate is added to the cell growth media a significant increase in the expressed levels of tetracycline-induced β2myc protein is seen, compared to tetracycline-exposed cells grown in media without butyrate. The presence of butyrate in the cell growth media also causes the appearance of β2myc protein at the apical surface of the cells (in addition to the basolateral surface). While tetracycline-induced β2myc is seen at the apical surface when butyrate is present, endogenous β1 and α remain almost exclusively basolateral. This suggests that the β2myc protein that is trafficked to the plasma membrane may not be associated with the α-subunit. Immunoprecipitation of associated plasma membrane proteins with an α-subunit antibody revealed that endogenous β1 subunits interact with α while no evidence is seen for a β2myc-α-subunit interaction. This suggests that α1 has a higher affinity for the endogenous β1. To determine if the influence of butyrate on β2myc expression is isoform-specific a tetracycline-regulated β1flag MDCK cell line was used. Cell-surface biotinylation showed that without butyrate exposure, tetracycline-induced β1flag cells express endogenous α1 and β1-subunits, as well as the expressed β1flag protein exclusively at the basolateral membrane. However, as was the case with the β2myc cells, butyrate exposure causes the mispolarization of a large proportion of the tetracycline-induced β1flag protein to the apical surface. E-cadherin was properly localized to only the basolateral membrane regardless of whether or not butyrate was included in the growth media. This confirms that the appearance of α and β1 at the apical surface was not due to a general loss in cell polarity. Thus, it seems clear that there is no β subunit isoform-specific apical delivery of the sodium pump in MDCK cells, and apparently butyrate causes a change in sodium pump sorting.

The basis of the effects of butyrate

The mistargeting of sodium pump subunits is somehow caused by the presence of butyrate in the cell growth media. Butyrate is a small fatty acid that has been found to have a variety of cellular effects and has been used to boost heterologous protein expression. Butyrate can inhibit histone deacetylase activity, which can modify protein expression, and lead to cell cycle arrest and induce apoptosis (Kruh 1982; Leschelle et al. 2000). Additionally, butyrate may act as a chemical chaperone as it is know to have facilitating effects on protein folding (Chaudhuri and Paul 2006). By acting as a chemical chaperone, butyrate may influence the folding kinetics of sodium pump subunits or of an important protein involved in the trafficking pathway which influences the polarity of delivery. Butyrate has also been shown to increase apical membrane CFTR in MDCK cells, via an unknown mechanism (Moyer et al. 1999). The observation that butyrate exposure leads to the enhanced expression of β1flag and β2myc in tetracycline-induced MDCK cells may be explained by reports that butyrate increases expression off the CMV promoter (Wacker et al. 1997; Moyer et al. 1999), that is employed in the tetracycline-regulated MDCK cells. However, it is unlikely that the aberrant apical delivery of these subunits is simply the result of expressing an excess of protein, which overloads a cellular targeting mechanism since a large increase in β-subunit expression following tetracycline

exposure (in the absence of butyrate) does not result in the apical delivery of the sodium pump. In addition, when butyrate is used, no disruption of the specific delivery of e-cadherin, another basolateral protein is seen, suggesting that the normal targeting mechanism has not been compromised.

Conclusions

It is striking that the polarized delivery of the sodium pump, which is at the center of both renal and gastrointestinal function, remains almost entirely a mystery. A greater understanding of the development of epithelial cell polarity (and its maintenance, which is not the same) has begun to emerge. However, for any specific mammalian membrane protein the structural features and mechanisms that lead to its polarized location remain obscure and the extent to which the answer is cell- and protein-specific provide enormous challenges to a rationalization of any general principles. In the case of the sodium pump, very little is known.

Acknowledgements This work was supported by National Institute of Health Grants GM-39500 and HL-30315. We would like to thank R.J. Clifford for her critical comments on the manuscript

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