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Review

Transport protein sorting in polarized epithelial cells

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Abstract: In order to carry out their physiological functions, the cells of transporting epithelial tissues must be able to polarize their cell surface domains. Different collections of membrane transport proteins must be distributed to distinct domains of the plasma membrane, and cells must be coupled to one-another through junctional complexes that help organize polarized domains and regulate the permeability of the paracellular pathway. This exquisite organization requires that epithelial cells possess a sorting apparatus that can target newly synthesized transport proteins to the appropriate surface domains. Furthermore, the transport proteins themselves must possess information embedded within their structures that specifies their sites of ultimate functional residence. The nature of this information, and of the protein-protein interactions involved in its interpretation, is beginning to be elucidated. The initial formation of the polarized state involves signaling cascades that epithelial cells use to orient themselves to sites of cell-cell and cell-matrix contact. Recent evidence suggests that one component of these cascades is a kinase that also serves as a cellular energy sensor.

Key words: polarized epithelia; transport proteins; tight junctions; sorting signals

极化上皮细胞中转运蛋白的分选

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摘 要：上皮组织细胞必须极化其表面区域以执行其转运生理功能。不同膜转运蛋白定位于细胞膜的不同区域，而细胞与细胞之间则须通过紧密连接复合体紧密连接成极化区域，并调节旁细胞途径的通透性。精密的机体要求上皮细胞具备一个筛选装置，用于将新合成的转运蛋白定位于合适的表面区域；转运蛋白本身也必须内含规定其功能位置的分选信号。目前上皮细胞蛋白分选和蛋白质之间相互作用已被逐渐阐明。上皮细胞通过细胞信号转导途径形成极化初始状态，将自己定位于特定位置，调节细胞与细胞之间、细胞与基质之间的相互作用。最近研究发现其信号转导通路的一个成员是一种 AMP 激活的蛋白激酶(AMP-stimulated protein kinase, AMPK)，它也是细胞能量感受器。

关键词：极化上皮细胞；转运蛋白；紧密连接；分选信号
中图分类号：Q257

1 Introduction

Few cell types more elegantly embody the dictum that “form follows function” than do those of polarized epithelia. Epithelial cells constitute the boundaries that separate an organism’s extracellular fluid compartment from the external environment in which that organism exists. As such, epithelial cells must be capable of acting as the continuous physical barrier that prevents a sudden and catastrophic merger between the constituents of those two spaces. This barrier function, however, though biologically critical and mechanistically fascinating, is only the simplest of the biological tasks that polarized epithelial cells are called upon to perform. In fact, it is the ability of polarized epithelial cells to mediate the vectorial transport of fluid and solutes that essentially determines the composition of the organism’s internal environment.

The cell surface membranes of polarized epithelial cells

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are divided into morphologically and compositionally distinct domains that are separated by intercellular tight junctions[1]. While the basolateral plasma membrane domain is in contact with the extracellular fluid compartment, the apical domain generally confronts a lumen that is often ultimately contiguous with the outside world. These two cell surface domains manifest almost completely different inventories of membrane proteins. For the purposes of this discussion, it is the polarized distribution of ion transport proteins among these portions of the epithelial plasma membrane that provides the physiological justification for epithelial polarity[2]. It is the combination of a basolateral Na^+,K^+-ATPase and an apical Na^+, glucose co-transporter, for example, that allows the intestine to exploit the energy inherent in the sodium gradient created by the sodium pump to efficiently absorb glucose against a steep concentration gradient[3]. If ion transport proteins were not asymmetrically distributed between the surface domains of transporting epithelial cells then it would not be possible to generate and maintain the gradients of ions and non-electrolyte solutes that are required for homeostasis.

In order to achieve their polarized distributions, the newly synthesized ion transport proteins expressed by epithelial cells must be sorted to the appropriate domains of the cell surface and retained there following their deliveries. This sorting function requires that each transport protein must contain within its structure information sufficient to specify the protein's site of ultimate functional residence to the epithelial cell's sorting machinery. Furthermore, in order for this information to be interpreted and acted upon, each transport protein must interact with the trafficking proteins that constitute the cellular sorting machinery. It is becoming increasingly clear that these interactions with elements of the cellular sorting and trafficking machinery often play tremendously important roles in acutely regulating the activities of epithelial transport systems[2]. In addition, perturbations in these interactions, or in the trafficking steps that they mediate, account for the pathology associated with a number of human diseases. A small illustration of these large and important principles is provided through the following discussion of some work on relevant systems that our laboratory has pursued over the past few years.

2 The Na^+,K^+-ATPase and gastric H^+,K^+-ATPase: close cousins that go their separate ways

Among the many proteins that are differentially distributed between epithelial plasmalemmal domains are the Na^+,K^+- and gastric H^+,K^+-ATPases[4]. The Na^+,K^+-ATPase, or sodium pump, uses the energy of one molecule of ATP to drive 3 sodium ions out of the cell and 2 potassium ions into the cell against substantial concentration gradients. The activity of this enzyme energizes such diverse functions as the maintenance of the membrane potential and the renal and intestinal handling of solutes[5,6]. The gastric H^+,K^+-ATPase is expressed in the parietal cells of the stomach, where it exploits a very similar enzymatic mechanism to catalyze the electroneutral exchange of intracellular protons for extracellular potassium ions, thus generating the enormous proton gradients associated with gastric acid secretion[7].

The Na^+,K^+-ATPase and the H^+,K^+-ATPase share a great deal of structural homology. They are both composed of an α subunit that is predicted to span the membrane 10 times and a β subunit that spans the membrane once in a type II orientation. During the biosynthesis of these pumps, the β subunits assemble with the α subunits during each enzyme's residence in the endoplasmic reticulum. This association is required for the holoenzyme complex to reach the plasma membrane[8-10]. The α subunits of the Na^+,K^+-ATPase and H^+,K^+-ATPase share ~65% sequence identity, while the amino acid sequences of the β subunits are approximately 35% identical[11-15]. Despite this close relationship, however, they differ in several important attributes. One of these differences is dramatically reflected in the subcellular distribution of these ion pumps. The Na^+,K^+-ATPase is concentrated at the basolateral membranes of most epithelial cell types[16], whereas the H^+,K^+-ATPase accumulates at the apical surface and in subapical storage vesicles in the acid-secreting parietal cells of the stomach[17,18]. The two ion pumps also manifest distinct ion affinities, transport stoichiometries and inhibitor sensitivities[7].

Studies from our laboratory established that the gastric H^+,K^+-ATPase α and β subunits, when transfected into the proximal tubule-like pig kidney cell line LLC-PK1, assemble and are ultimately found exclusively at the apical membrane. The endogenous Na^+,K^+-ATPase, on the other hand, is restricted to the basolateral plasma membrane in H^+,K^+-ATPase transfected cells[19,20]. By generating chimeric constructs between the two related pumps, we have been able to examine the regions of the pump sequences required for their correct localizations in polarized epithelial cells[19-21] (Fig. 1). Through an analysis of the sorting behaviors of a number of such chimeric pumps expressed by transfection in LLC-PK1 cells, we have identified a H^+,K^+-ATPase signal motif that is sufficient to redirect the normally basolateral Na^+,K^+-ATPase to the apical surface

in transfected epithelial cells. This motif resides entirely within the fourth of the H^+, K^+-ATPase α subunit's ten predicted transmembrane domains[21]. While it is sufficient to specify sorting, however, the generation of further chimeras has suggested that this transmembrane motif does not act alone. In fact, the discontinuous sequence domains that flank the fourth transmembrane domain can cooperate to recapitulate the fourth transmembrane domain's apical sorting signal. Thus, the apical sorting determinant appears to be the product of a conversation between the fourth transmembrane domain and the motifs that abut it. We also find that a similar conformational interaction dramatically influences the cation selectivities of these pump chimeras[22-24].

The gastric H^+,K^+-ATPase-driven secretion of acid into the lumen of the stomach is regulated very tightly. In the resting state, the majority of H^+,K^+-ATPase is restricted to the tubulovesicular elements (TVEs), a system of membranes that resides beneath the plasma membrane. Upon stimulation of the parietal cell by secretagogues there is a transient rise in the intracellular levels of cAMP, IP_3, diacylglycerol, and Ca^{2+}. Some combination of these second messengers induces the TVEs to fuse with the apical plasma membrane, thus allowing the H^+,K^+-ATPase to secrete protons directly into the lumen of the gastric gland[25-27].

To date, it does not appear that the H^+,K^+-ATPase itself undergoes any covalent modifications during the activation of acid secretion. Instead, the membrane fusion events

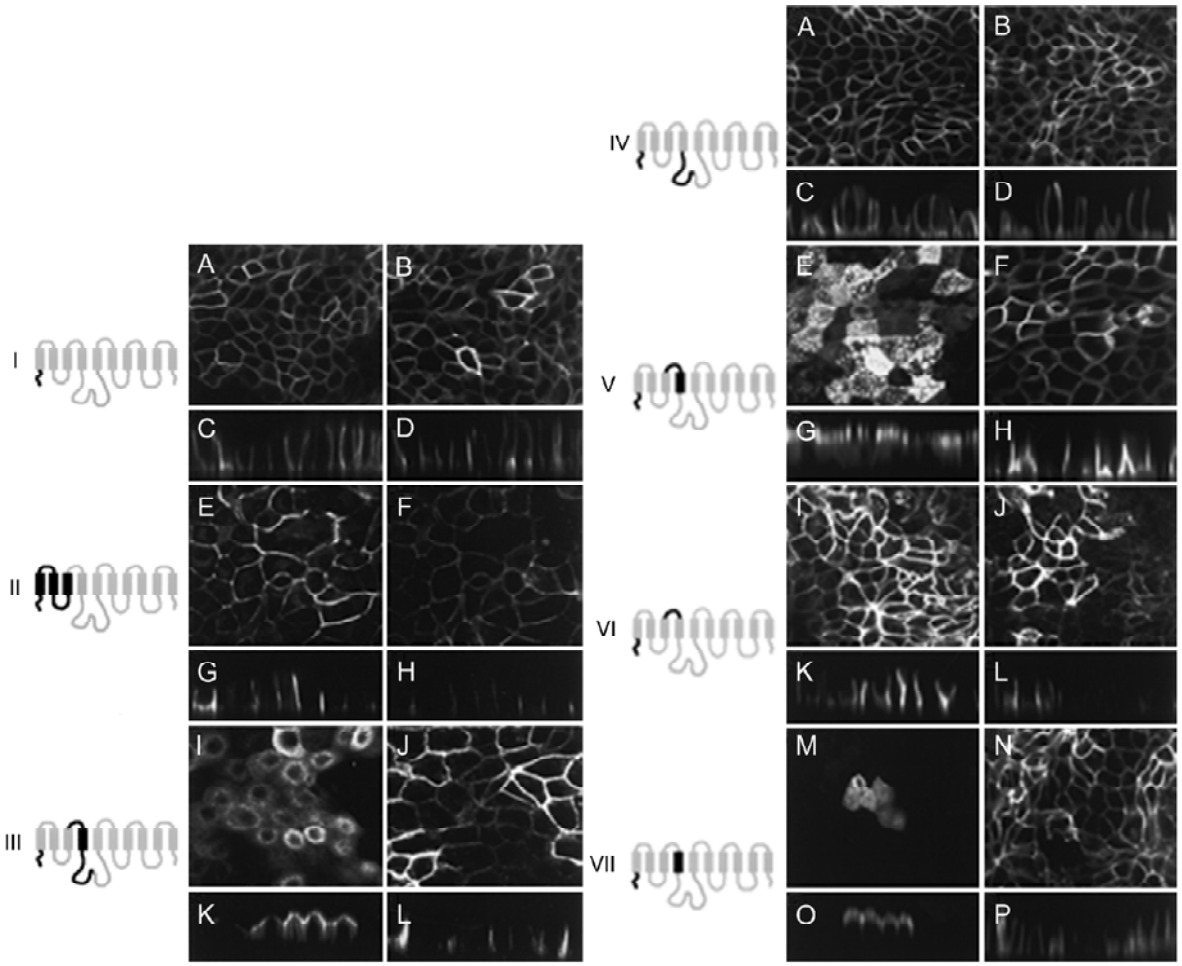

Fig. 1. Distributions of chimeric ion pumps (I-VII) in polarized cells. Chimeras were prepared between the α subunits of the Na^+,K^+-ATPase (gray) and the gastric H^+,K^+-ATPase (black). The schematic diagram adjacent to the Roman numeral indicates each chimera's design and topology. The chimeras were expressed by transfection in polarized LLC-PK1 cells and chimera localization was determined by confocal immunofluorescence microscopy. Chimera localizations are depicted in panels A, C, E, G, I, K, M and O, while endogenous Na^+,K^+-ATPase localization is depicted in panels B, D, F, H, J, L, N and P. Both en face (A, B, E, F, I, J, M, N) and XZ cross section (C, D, G, H, K, L, O, P) views are presented. As revealed by the behavior of chimera VII, sequences in the fourth transmembrane domain of the α subunit are sufficient to specify pump sorting. This figure is adapted from reference 21.

regulate the ability of the pump to actively secrete protons. Upon the withdrawal of stimulation, the enzyme, along with large portions of the plasma membrane, is re-internalized to create the TVEs. The β subunit of the gastric H^+,K^+-ATPase contains a tyrosine-based endocytosis motif which is necessary for the re-internalization of the holoenzyme[28]. We have found that transgenic mice expressing H^+,K^+-ATPase β subunit in which the critical tyrosine residue is mutated to an alanine fail to re-internalize the enzyme, leading to hyper-secretion of acid and chronic gastritis. We have found that the tetraspan protein CD63 interacts with the gastric H^+,K^+-ATPase β subunit and, through this interaction, exerts dramatic effects on the trafficking behavior of the pump subunit polypeptide[29]. CD63 is associated primarily with the membranes delimiting late endosomes, lysosomes and secretory vesicles[30]. We find that it is also present in TVEs, and that it interacts with the H^+,K^+-ATPase in gastric parietal cells *in situ*. Co-expression of CD63 and the H^+,K^+-ATPase in COS7 cells results in the redistribution of the β subunit from the cell surface to an intracellular compartment, demonstrating that this interaction influences the sorting and surface stability of the pump polypeptide[29]. Thus, a protein motif as well as a protein interaction, both of which were identified based upon their cell biological relevance to protein trafficking, may also account, at least in part, for the regulation of gastric acid secretion, a fundamental physiological process.

3 AMPK: regulator of cellular energy status and epithelial junctions

In order for the sorting mechanisms discussed in the preceding section to be effective in producing the appropriate distributions of ion transport proteins among the two polarized domains of the epithelial plasma membrane, these domains must first be established and segregated from one another. An enormous body of research has been focused on exploring the mechanisms through which epithelial cells first establish their characteristic polarity. It is clear that cell-cell contacts mediated by the calcium-dependent adhesion proteins of the intercellular adhesion junctions are required to initiate complete polarization[31]. Furthermore, formation of the tight, or occluding, junctions that limit paracellular permeability also helps establish polarity by preventing the diffusion of membrane proteins between the two plasma membrane domains[32]. Recent work suggests that the formation of these junctions is tied to processes that regulate cellular energy metabolism.

Epithelial cells involved in fluid and electrolyte transport are major consumers of biological energy. Most transporting epithelial cells are richly endowed with mitochondria that provide the pumps with the copious quantities of ATP that they consume in order to generate the ion gradients that power transepithelial fluid and solute movement. Not surprisingly, therefore, even brief interruptions in the substrates required for ATP generation can lead to profound damage to epithelial cells, manifest in the loss of epithelial polarity and the redistribution of transport proteins[33].

Muscle cells are similarly prodigious users of biological energy. Recent research has shown that myocytes keep a close watch on cellular energy levels and, when these levels fall, the myocytes activate pathways that reduce non-essential energy consumption and activate alternative mechanisms for energy generation. A single enzyme known as AMP-stimulated protein kinase (AMPK) appears to measure cellular energy levels and to initiate the appropriate responses in the event of their decline[34,35]. When ATP levels fall, AMP levels rise. AMPK is composed of three subunits (α, β and γ), one of which (γ) binds AMP and undergoes a conformational change in response to this binding event. This conformational change in turn allows the α subunit to become a substrate for phosphorylation by an upstream kinase that is necessary and sufficient to activate the kinase α subunit's intrinsic kinase activity. Once activated, the AMPK goes on to phosphorylate and regulate the activities of a wide variety of proteins to readjust the balance between energy production and consumption.

The best characterized of the upstream "AMP-kinase kinases" is LKB1, a kinase first identified as the product of the Peutz-Jaeger syndrome tumor suppressor gene[36,37]. Mutations in the gene encoding LKB1 lead to the formation of numerous hamartomatous neoplasms. It is especially interesting in this context that transfection of the human colonic epithelial cell line CaCo-2 with cDNAs encoding co-factor polypeptides that constitutively activate LKB1 endows the transfected cells with the capacity to develop a polarized phenotype in the absence of cell-cell or cell-matrix contact[38]. It would appear, therefore, that LKB1 can act as a critical control point in the epithelial polarization pathway. Presumably, LKB1 normally functions downstream of signals received through cell-cell and cell-matrix contacts to initiate the constellation of biochemical and structural rearrangements required to produce polarity. In keeping with this interpretation, disruption of LKB1 activity suppresses the capacity of epithelial cells to polarize[39].

Since AMPK is one of the substrates of LKB1, and since energy deprivation events that activate AMPK can exert profound effects on epithelial polarity[40,41], we wondered

whether AMPK is an important effector in the LKB1 polarization signaling pathway. We and others find that pharmacological activation of AMPK speeds the formation of tight junctions in polarizing MDCK cells[42,43]. Tight junctional organization was measured by monitoring the deposition of the tight junction-associated protein ZO-1. In keeping with these observations, expression of a dominant-negative AMPK construct in MDCK cells profoundly slows the acquisition of mature, structurally intact junctional strands. It remains to be determined how AMPK influences junction assembly. Future studies will focus on identifying the substrates of AMP kinase activity that participate in recruiting ZO-1 to the sites of forming occluding junctions. It is interesting to note that although junctions form more slowly in the absence of AMPK activity, the junctions that form under these circumstances appear to be morphologically normal. It will be important to determine, therefore, what other signaling mechanisms can replace AMPK to support junction formation in cells that lack functional AMPK expression. Finally, it is worth noting that in *Drosophila*, disruption of the gene encoding AMPK impairs the maintenance of polarized plasma membrane domains in epithelial tissues subjected to energy stress[44]. Similarly, energy deprivation is sufficient to initiate *Drosophila* epithelial polarization[44]. These data suggest that in the *Drosophila* system AMPK plays a role not only in tight junction formation but also in the formation and maintenance of polarized plasma membrane domains. We have not observed a similar dependence of AMPK activity of membrane domain differentiation in MDCK cells. It will be interesting to assess what other mechanism present in MDCK cells compensate for the loss of AMPK and allow polarization to proceed.

4 Conclusion

A large number of laboratories have made great strides in identifying the molecular natures of the signals that specify the sorting behaviors of ion transport proteins in polarized epithelial cells. Perhaps more importantly, these efforts are beginning to yield insights into the nature of the protein-protein interactions and subcellular signaling pathways that interpret these signals and act upon the information that they convey. The processes that initiate and maintain epithelial polarization involve a variety of signaling cascades, at least one of which also plays a fundamental role in sensing cellular energy levels. These observations suggest that the capacity of epithelial cells to polarize is intimately connected to the mechanisms that regulate their metabolism. Future work will no doubt refine our understanding of these interconnecting signals and signaling pathways, and will provide important insights into a variety of human diseases.

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