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REVIEW

The Role of Ion Transporters in the Pathophysiology of Infectious Diarrhea

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SUMMARY

Intestinal ion transporters ensure fluid and electrolyte homeostasis. Several are modulated during enteric infections, potentially contributing to diarrhea. This review surveys changes in the abundance and/or regulation of transporters that occur in these conditions, pointing to possible novel targets for therapy.

Every year, enteric infections and associated diarrhea kill millions of people. The situation is compounded by increases in the number of enteric pathogens that are acquiring resistance to antibiotics, as well as (hitherto) a relative paucity of information on host molecular targets that may contribute to diarrhea. Many forms of diarrheal disease depend on the dysregulation of intestinal ion transporters, and an associated imbalance between secretory and absorptive functions of the intestinal epithelium. A number of major transporters have been implicated in the pathogenesis of diarrheal diseases and thus an understanding of their expression, localization, and regulation after infection with various bacteria, viruses, and protozoa likely will prove critical in designing new therapies. This article surveys our understanding of transporters that are modulated by specific pathogens and the mechanism(s) involved, thereby illuminating targets that might be exploited for new therapeutic approaches. ***(Cell Mol Gastroenterol Hepatol 2018;■:■–■; https://doi.org/10.1016/j.jcmgh.2018.02.009)***

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Q5 Q6 Q7 The intestinal epithelium is responsible for absorbing nutrients, such as sugars and peptides, as well as electrolytes and water.[1] Most water absorption occurs in the small intestine, with residual water absorption occurring in the colon. Absorptive processes are predominant in villi whereas secretory processes are predominant in the crypts. To facilitate solute and water absorption, the intestines rely on transporters that permit the movement of solutes through the cell membrane. Water then follows passively via both paracellular and transcellular routes. The transporters that mediate solute uptake or secretion are expressed differentially throughout the intestines, and have a wide range of substrates. Under normal conditions, the various transporters work together to provide an optimum balance between absorption and secretion, with absorption predominating to reclaim the 8–9 L of fluid that are used daily during digestion and absorption of meals in human beings. However, during pathologic states, such as infections with diarrheal pathogens, this balance is disrupted, with either increased secretion, loss of absorption, or both.[1] Although the gut has a substantial reserve capacity for absorption, ultimately this imbalance can cause diarrhea.

Diarrhea is an almost ubiquitous sign of enteric infection, leading to the question of what benefit it provides for the microbe or the host. For the microbe, diarrhea presumably facilitates the colonization of additional hosts, particularly in settings in which sanitation is compromised. For the host, the diarrheal response, although potentially harmful in terms of dehydration, also may represent a primitive host defense mechanism, reducing microbial colonization and perhaps restricting cellular entry by invasive species.[2] Because of its risks, diarrhea often calls for treatment in serious cases and/or particularly vulnerable hosts. However, most currently available antidiarrheal agents may have side effects, target motility rather than transport processes themselves, and often are relatively ineffective, particularly in the setting of life-threatening infectious diarrhea. There is therefore a need for new therapies, for which it is important to understand the underlying mechanism(s) of diarrhea.

Overview of Epithelial Transport Function

The transport of ions across the plasma membrane is crucial for cellular homeostasis. There are 3 major mediators of ion transport: (1) transporters (both cotransporters and exchangers), (2) ion channels, and (3) pumps.

Abbreviations used in this paper: **ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; cAMP, adenosine 3′,5′-cyclic monophosphate; CDI, *Clostridium difficile* infection; CFTR, cystic fibrosis transmembrane conductance regulator; CLCA1, chloride channel accessory 1; CT, cholera toxin; CXCR2, C-X-C motif chemokine receptor 2; DRA, down-regulated in adenoma; ENaC, epithelial sodium channel; EPEC, enteropathogenic *Escherichia coli*; EspG, _____; ETEC, enterotoxigenic *Escherichia coli*; GPR39, _____; KCC, potassium-chloride cotransporter; LPA, lysophosphatidic acid; LT, heat-labile toxin; NHE, sodium/hydrogen exchanger; NHERF2, sodium/hydrogen exchanger regulatory factor 2; NKCC, sodium-potassium-2 chloride cotransporter; ORT, oral rehydration therapy; PKC, protein kinase C; SGLT1, sodium-glucose cotransporter 1; SLC, solute carrier; ST, heat-stabile toxin; Tcd, *Clostridium difficile* toxin; TNF, tumor necrosis factor; ZnR, zinc sensing receptor.**

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Transporters are transmembrane proteins that mediate the transport of ions and sometimes other solutes, such as glucose or amino acids. Some also may transport drugs or metabolites. Cotransporters bind to their substrates on one side of the membrane, causing a conformational change that releases the substrates on the other side of the membrane. Exchangers transfer a solute into the cell in exchange for one that is secreted out of the cell. In either case, the activity of transporters is driven by the prevailing combined electrochemical gradients for the solutes in question.

Ion channels are pore-forming transmembrane proteins that open as "gates" in response to a variety of cellular signals, allowing high-capacity solute passage. The direction of ion movement depends on the electrochemical gradient for that solute across the membrane.

Pumps expend cellular energy, in the form of adenosine triphosphate (ATP) hydrolysis, and allow for "uphill" transport of 1 or more of their substrates. An example is the Na^+,K^+ adenosine triphosphatase (ATPase), which exports 3 sodium ions for every 2 potassium ions taken up into the cell, maintaining a low intracellular sodium concentration and sustaining the negative membrane potential.

Intestinal epithelial cells control the secretion and absorption of electrolytes through various arrangements of the ion transporters described earlier, which function together to maintain fluid balance; this fluid balance is impaired during diarrhea.[1] Impairments in transporter function can occur during infections and in inflammatory diseases, or may be caused by genetic mutations.

Major Transporters Implicated in Infectious Diarrhea

Although the intestines express a large array of distinct transport proteins, only a subset have been examined for their possible contributions to infectious diarrhea (Table 1). Thus, we focus on those transporters here (Figures 1 and 2). They include the following.

1. Sodium/hydrogen exchangers (NHEs): NHE3 (solute carrier [SLC]9A3) (and to a lesser extent, NHE2 [SLC9A2]) are responsible for electroneutral NaCl absorption in the small intestine and colon, by functioning in partnership with a chloride/bicarbonate exchanger.[3]

2. Sodium/glucose cotransporter (SGLT1, SLC5A1): this transporter is responsible for the absorption of both glucose and sodium ions postprandially.[4]

3. Down-regulated in adenoma (DRA [SLC26A3]): this transporter is a Cl^-/HCO_3^- exchanger, and is responsible for Cl^- absorption (and also transports SO_4^{2-}). DRA functions in concert with NHEs in the electroneutral absorption of NaCl.[5]

4. Epithelial sodium channel (ENaC): this channel mediates electrogenic Na^+ absorption and is localized to the distal colon.[6]

5. Ca^{2+}-activated chloride channels[7]: these channels mediate the efflux of chloride ions and are activated by increases in intracellular Ca^{2+} concentration. Their precise molecular identity in the gut still is controversial, although 1 candidate is chloride channel accessory 1 (CLCA1).[8] Other studies have implicated transmembrane protein 16A[9,10] (anoctamin 1), although the precise relative roles, if any, for both channels is still under investigation.

6. Sodium/potassium/chloride cotransporter 1 (NKCC1 [SLC12A2]): this transporter mediates the uptake of Na^+, K^+, and $2Cl^-$ ions across the basolateral membrane, and thereby supplies chloride for secretion.[11]

7. Cystic fibrosis transmembrane conductance regulator (CFTR): this is an adenosine 3′,5′-cyclic monophosphate (cAMP)- and guanosine 3′,5′-cyclic monophosphate–regulated chloride channel present primarily at the apical surfaces of epithelial cells, and mediates chloride efflux as part of the chloride secretory mechanism.[1] It also can transport bicarbonate.

8. Na^+,K^+ ATPase: This establishes and maintains a low intracellular Na^+ concentration that is a driving force for several different transport mechanisms, both secretory and absorptive.[12]

Regulation of Transport

The transporters discussed earlier can be regulated in 3 main ways to effect changes in overall levels of epithelial transport.[1] First, changes in transcription/translation of a given transporter will result in changes in its abundance, and associated changes in the capacity of the epithelium for transport function. Second, transport activity may be controlled by trafficking of a given transporter into or out of the plasma membrane. Finally, transporter activity may be acutely regulated by post-translational modifications, such as phosphorylation by various kinases, or may be modulated directly by intracellular second messengers such as free cytosolic calcium. Each of these mechanisms has been implicated in dysregulated transport in the setting of infection.

Epithelial Dysfunction in Diarrhea: Relative Roles of Secretion and Absorption

Intestinal epithelial cells play the key role in diarrheal pathogenesis. The epithelium is the first line of defense and host-microbe interactions are crucial in the development of infectious diarrhea. In addition to its transport functions, moreover, the epithelium also forms a barrier that may protect the host from the intrusion of microbial pathogens or toxins. Intestinal barrier dysfunction also may play a significant role in diarrheal disease (so-called "leak-flux" diarrhea).[13–15] However, in this review, we have focused mostly on the role of ion transporters in infectious diarrhea.