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Review

The role of molecular remodeling in differential regulation of tight junction permeability

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ABSTRACT

Tight junctions create a paracellular barrier that is essential for survival of complex organisms. In many cases tight junctions define separate, generally sterile, tissue compartments. In the skin and gut, tight junctions must also seal the paracellular space to prevent microbiota from accessing the internal milieu. This is a relatively simple task in the integument, where an absolute barrier is effective. However, intestinal epithelial tight junctions are charged with the far more complex task of supporting paracellular transport of water, ions, and nutrients while providing a barrier to microbial translocation. The delicate nature of this balance, which is disrupted in disease, makes the intestine a unique organ in which to explore the complexities of tight junction permeability and barrier regulation. Here we review recent progress in understanding the molecular determinants of barrier function and events responsible for regulation, and dysregulation, of tight junction permeability.

Contents

1. Introduction to tight junction physiology 203
2. Intestinal epithelial tight junction barriers are selectively permeable and can be modulated by diverse stimuli 204
   2.1. Distinct pathways of paracellular flux 205
   2.2. Immune regulation of tight junction permeability 206
   2.3. Pore pathway effectors 206
   2.4. Leak pathway regulation 207
3. Tight junction function is regulated by continuous remodeling of protein–protein interactions 207
   3.1. Analysis of tight junction remodeling provides insights into mechanisms of pore pathway regulation and potential for therapeutic modulation 208
   3.2. TNF-induced barrier regulation requires altered tight junction protein interactions and dynamic behavior 209
4. Future directions 209
   Acknowledgements 210
   References 210

1. Introduction to tight junction physiology

Epithelial and endothelial tight junctions can be simply characterized on the basis of their permeability. For example tight junctions within epithelia of the skin and urinary bladder are relatively impermeable, with electrical resistances exceeding 5000 Ω cm^2. In contrast, resistance of small intestinal, colonic, and proximal renal tubular tight junctions is typically below 100 Ω cm^2. These differences reflect tissue function, as a robust epidermal barrier is essential to survival and the urinary bladder must prevent dissipation of ion gradients and urine concentration or dilution achieved within the renal tubules.

In contrast to skin and bladder, transporting epithelia take advantage of selectively permeable tight junctions to drive passive, paracellular absorption and secretion. Because tight junctions are incapable of active transport of the sort accomplished by transcellular transporters, it is critical that the latter generate favorable gradients that drive passive, trans-tight junction transport in the

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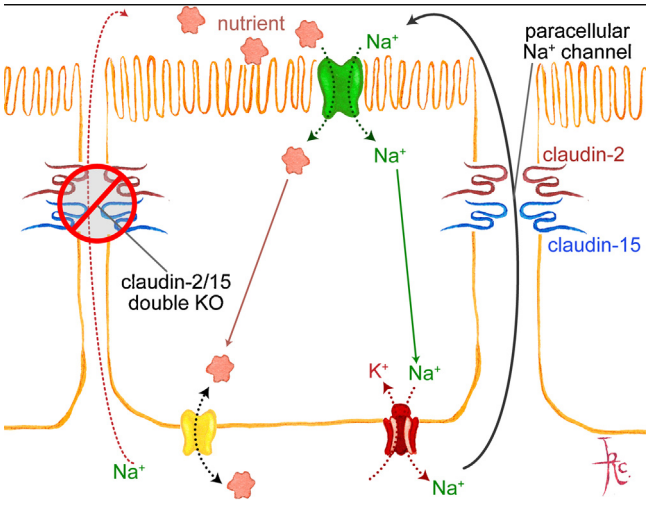

Fig. 1. Paracellular flux is required for Na^+ recycling. Claudin-2 and -15 form paracellular channels that facilitate Na^+ flux. When claudin-2 and claudin-15 are absent, the tight junction is relatively impermeant to Na^+. Thus, transcellular Na^+ absorption, e.g. by apical Na^+-nutrient cotransport and the basolateral Na^+/K^+-ATPase, depletes luminal Na^+. The residual luminal Na^+ is insufficient to support further Na^+-nutrient cotransport.

appropriate direction. For example, claudin-16-mediated paracellular Ca^{2+} and Mg^{2+} reabsorption in the renal tubule depends on the lumen-positive potential generated by transepithelial transporters [1].

Paracellular permeability is also essential for recycling of ions, such as Na^+, that drive absorption [2]. This is highlighted by the fact that mice lacking claudins 2 and 15, both of which can form paracellular Na^+ channels, die of malnutrition as a result of decreased paracellular cation flux and limited recycling of Na^+ absorbed by transcellular pathways back to the lumen. The resulting reduced luminal Na^+ is insufficient to serve as the driving force for transcellular Na^+-dependent nutrient absorption (Fig. 1) [2]. Thus, in transporting epithelia, the tight junction allows passive paracellular flux that contributes significantly to overall transepithelial absorption and secretion.

2. Intestinal epithelial tight junction barriers are selectively permeable and can be modulated by diverse stimuli

Leaky epithelia, such as those found in the small intestine and colon, are not simply less effective barriers than tight epithelia. Instead, different leaky epithelia have increased permeability to specific types of solutes and water. For example, paracellular permeability within the small intestinal crypt epithelium is greater than that of villous epithelium [3]. This allows the crypt to be a primarily secretory compartment, which helps limit microbial colonization within the crypt space.

The most well-defined example of tight junction regulation in response to physiological stimuli is that following activation of SGLT1-mediated Na^+-nutrient cotransport [4,5]. In this process, brush border Na^+-nutrient cotransport activates NHE3-mediated Na^+–H^+ exchange [6] and myosin light chain kinase (MLCK)-dependent actomyosin contraction [5]. These events augment the transcellular Na^+ gradient and increase tight junction permeability [5], respectively, to enhance paracellular water absorption. This physiology is, in part, responsible for the great success of oral rehydration solutions containing glucose and carbohydrates. Notably, the increase in tight junction permeability is limited to small molecules, e.g. mannitol, with radii $\leq$3.6 Å; larger molecules such as inulin, with a radius of 11.5 Å, are excluded [5,7]. This allows small nutrients, such as glucose, to be carried along with water and results in paracellular amplification of transcellular glucose transport when luminal glucose concentrations are high [8]. At the same time, the size-selectivity of permeability regulation limits paracellular flux of proteins and microbial products between the lamina propria and gut lumen (Fig. 2A).

Processes similar to those that enhance paracellular water and nutrient absorption following initiation of Na^+-glucose cotransport also contribute to cytokine-mediated diarrheal disease. For example tumor necrosis factor-α (TNF) and the TNF core family member LIGHT both enhance tight junction permeability by a myosin light chain kinase-dependent process similar to that associated with Na^+-glucose cotransport [9–12]. However, while TNF induces net water secretion into the gut lumen, LIGHT modestly augments paracellular water absorption [12]. These disparate effects do not reflect differences in extent or mechanism of tight junction regulation triggered by the two cytokines. Instead, the distinct effects of

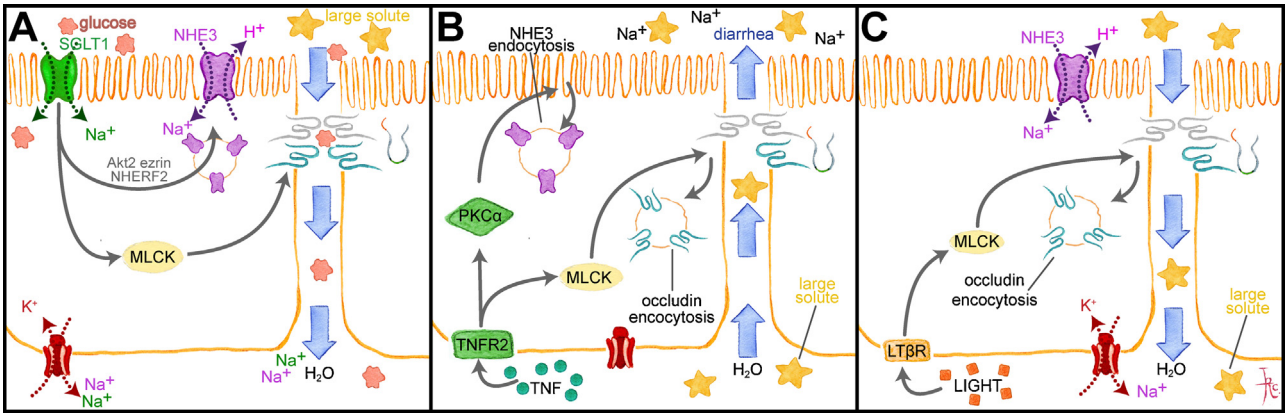

Fig. 2. Physiological and pathophysiological regulation of tight junction permeability and passive water transport s by diverse stimuli. (A) SGLT1-dependent Na^+ and glucose cotransport triggers a signaling cascade in which Akt2 and MLCK are activated. Akt2 and ezrin promote NHE3 trafficking to the apical membrane to increase transcellular Na^+ transport, while MLCK enhances tight junction permeability to small, nutrient-sized molecules, e.g. glucose. Transcellular deposition of Na^+ and glucose in the basolateral space creates an osmotic gradient that draws water and glucose across the more permeable paracellular path. (B) TNF binds to TNFR2 and activates PKCα and MLCK. NHE3 endocytosis is triggered by PKCα, which reduces transcellular Na^+ absorption, thereby reducing the transepithelial Na^+ gradient. MLCK activation causes occludin endocytosis that increases tight junction permeability to large solutes, including proteins. These changes result in passive water and solute flow into the lumen. (C) Like TNF, LIGHT (lymphotoxin-like inducible protein that competes with glycoprotein D for herpes virus entry on T cells) activates MLCK to cause occludin endocytosis and increased tight junction permeability to large solutes. However, LIGHT does not inhibit NHE3, which continues to generate a transepithelial Na^+ gradient that enhances passive water absorption.