Seminars in Cell & Developmental Biology 42 (2015) 22–29

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Claudin switching: Physiological plasticity of the Tight Junction

Christopher T. Capaldo[a], Asma Nusrat[a,b,*]

[a] Epithelial Pathobiology and Mucosal Inflammation Research Unit, Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA 30322, United States
[b] Department of Pathology, University of Michigan, Ann Arbor, MI 48109, United States

ARTICLE INFO

Article history:
Available online 7 May 2015

Keywords:
Tight Junction
Claudin
Inflammation
Homeostasis

ABSTRACT

Tight Junctions (TJs) are multi-molecular complexes in epithelial tissues that regulate paracellular permeability. Within the TJ complex, claudins proteins span the paracellular space to form a seal between adjacent cells. This seal allows regulated passage of ions, fluids, and solutes, contingent upon the complement of claudins expressed. With as many as 27 claudins in the human genome, the TJ seal is complex indeed. This review focuses on changes in claudin expression within the epithelial cells of the gastrointestinal tract, where claudin differentiation results in several physiologically distinct TJs within the lifetime of the cell. We also review mechanistic studies revealing that TJs are highly dynamic, with the potential to undergo molecular remodeling while structurally intact. Therefore, physiologic Tight Junction plasticity involves both the adaptability of claudin expression and gene specific retention in the TJ; a process we term claudin switching.

© 2015 Published by Elsevier Ltd.

Contents

1. Introduction

Epithelial tissues provide boundaries between biological compartments. In addition to a protective barrier, the epithelium allows for the regulated passage of nutrients, ions, and solutes through either transcellular or paracellular pathways. Transcellular pathways require polarized plasma membrane-bound transporters or channels, which translocate ions and molecules across the cell. In contrast, the passage of ions and solutes through the paracellular pathway is regulated by intercellular structures called Tight Junctions (TJ) [1–3]. By electron microscopy, the TJ is visualized as a region of close membrane fusion at the lumen-facing apex of adjacent epithelial cells [4]. Structurally, the TJ is composed of webs of proteinaceous filaments (called strands), which span

* Corresponding author at: University of Michigan, Department of Pathology, 109 Zina Pitcher Place, 4057 BSRB, Ann Arbor, MI 48109-2200, United States. Tel.: +1 734 764 5712.
E-mail address: anusrat@umich.edu (A. Nusrat).

http://dx.doi.org/10.1016/j.semcdb.2015.04.003
1084-9521/© 2015 Published by Elsevier Ltd.

the extracellular space to interact with TJs on adjacent cells. The physiological properties of the TJ seal depend on several factors, namely, the number of strands present, the amount of physical stress on the seal, and the primary protein composition of the strands [1,5,6]. In some model systems the number of strands has been correlated with the physiologic "tightness" of the barrier. For example, the proximal convoluted tubule of mouse kidney consists of one TJ strand and is electrophysiologically "leaky", while the urinary bladder has up to five strands and is relatively impermeable to ions and solutes [4,5]. However, in the model intestinal epithelial cell line, MDCK the relationship of strand number and paracellular permeability does not hold true, and the barrier properties are determined by composition of claudin family of Tight Junction transmembrane proteins [7]. TJ strand maintenance depends on interactions between the strands and a proteinaceous cytoplasmic plaque [8]. TJ plaque protein constituents are numerous, form complex interactions, and serve as scaffolds that connect the TJ strands to intercellular signaling proteins and the actin cytoskeleton [9]. The actin cytoskeleton forms a belt around the apical circumference of the cell adjoining the Apical Junctional Complex that encompasses the TJ and adherens junctions. Tension within this perijunctional F actin belt has been reported to control dynamic TJ function and barrier properties [6]. Importantly, TJ "tightness" is determined by the protein composition within strands themselves. TJ transmembrane proteins compose the strands, which include the proteins; Junctional Adhesion Molecules, Coxsackie Adenovirus Receptor, occludin, and, most importantly, the claudin family proteins [10]. Indeed, the complement of claudin proteins determines TJ barrier properties in epithelia.

The claudins constitute a large family of tertaspan transmembrane proteins. Molecularly, two extracellular loop domains mediate interactions between cells, and plaque protein interactions involve short cytoplasmic tails. There are as many as 27 claudin genes in the human genome and growing evidence points to claudins as the linchpin of TJ physiology [11]. They are required components for TJ strand formation, are sufficient to form pores within the strand, regulate strand number and complexity, and transmit actomyosin tension across the TJ [1,12–14]. Conceptually, the claudin-based junctions were once believed to be static, highly cross-linked structures, however, this view has evolved into a more nuanced understanding of TJs as structures that undergo continuous molecular remodeling [14–17]. What is less clear is when and how TJ remodeling occurs. This review will focus on the claudin family of transmembrane proteins and highlight research that supports a physiological role for TJ claudin remodeling, or switching. Evidence is provided by studies in multiple experimental models, as well as physiological and pathological systems in humans. These studies support an emerging model of TJs, including claudins, as dynamic and adaptable to extracellular signals and stimulus, with dramatic consequences for tissue physiology.

1.1. Pore claudins

The paracellular passage proceeds through one of two mechanisms; the so-called "pore" and "leak" pathways [18–20]. The leak pathway allows for large molecule flux in a non-selective manner and is thought to involve low probability TJ strand breakages or transient paracellular gaps between cells [21,22]. The molecular mechanisms of the leak pathway are not clear, but appear to be regulated by levels of the transmembrane protein occludin and tricellulin, the scaffolding protein ZO-1, and the degree of tension of the perijunctional actin cytoskeleton [23–27]. In contrast, the pore pathway is low capacity, and ion charge and size-selective. Claudins function to a greater or lesser degree as paracellular pores [1,28,29] and can generally be grouped into two categories "tight" sealing claudins (1, 3, 5, 11, 14, and 19) and "leaky" pore forming claudins (2, 10, 15, and 17) [29–31]. For example, exogenous claudin 2 expression in vitro is sufficient to increase epithelial monolayer permeability to Na^+ [7,32]. In contrast, claudin 4 is considered "tightening" and overexpression restricts Na^+ flux [13]. Claudin-based pore characteristics are determined by the amino-acid sequence of the extracellular loop domains, which interact with loop domains of claudins within the opposing TJ [1,33–36]. Claudins form both homotypic and heterotypic interactions across the junction, therefore, there is considerable potential for diverse interactions and pore characteristics [37]. This property is exemplified by studies in murine kidney showing that claudin 4 is no longer tightening when expressed with claudin 8, which combines with 4 to form a Cl-pore [38]. Several claudins have been found to behave in this manner (4, 7, 8, and 16), with effects on barrier dependent on the complement of claudins expressed within the cell [30]. Pore pathway capacity is also related to the number of pore forming claudins expressed within the TJ. For example, increased expression of claudin 2 believed to increase the number of pores within the TJ [20]. Therefore, the barrier properties of a given tissue relate to both the character and proportions of the claudins expressed. This feature of TJ physiology was demonstrated in studies pairing claudin isoform expression with barrier function. For example, along the gastrointestinal tract, electrophysiological barrier "tightness" is highest in the duodenum, which expressed higher levels of claudins 1, 3, 5 and 8, when compared to jejunum and ileum, which expresses high levels of 2, 7 and 12 [39]. Taken together, claudins regulate TJ barriers by forming pores, whose character is based on the complement of isoforms expressed.

One final mechanism of the claudin based barrier regulation is the likelihood that some relationship exists between the leak and pore pathways, although this relationship is poorly understood. Select claudin isoforms, when expressed in cells that don't produce endogenous TJs, will assemble strands of differing number and organization [40,41]. In one study, claudin 19 expression led to linear strand arrays, while claudin 14 and 7 reconstituted anastomosing and branched strands [40]. What is less clear is the relationship between claudin expression and strand break occurrence. A potential role for claudins exists, for example, as the leak pathway is known to involve tricellulin, an occuldin-like protein that is restricted to contact points involving three cells. Claudin interactions are required to stabilize tricellulin and related proteins [42,43]. Attempts have been made to model TJ behavior and barrier properties, resulting in speculation that claudin pores fluctuate between open and closed states [18]. However, it has also been posited that TJ barrier properties can best be modeled as having transient strand breaks [44]. Further studies would be required to assess the role claudins in pore and leak pathways, and how these two pathways may intersect. In review, claudin family proteins are central players in the regulation of the paracellular pathway, regulating pore capabilities and strand organization.

1.2. Diverse claudin expression among tissues and during development

Claudin expression and function varies spatially as well as developmentally and efforts are underway to catalog claudin expression in various tissues including; kidney [45], along the gastrointestinal tract [46], skin [47], lung [48], inner ear [49], capillary endothelium [50], and other epithelial systems (reviewed in [51]). Contemporaneous studies have attempted to identify claudin function using transgenic knockout mice (reviewed in [52]). Knockout studies have demonstrated the importance of specific claudins in physiological regulation of junction permeability in various tissues and give clues to human disease. This is illustrated by the identification of claudin 16 as a pore forming claudin, as claudin 16 knockout mice

Download English Version:

https://daneshyari.com/en/article/2202557

Download Persian Version:

https://daneshyari.com/article/2202557

Daneshyari.com