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Brief review

Role of claudins in renal calcium handling☆

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ABSTRACT

Paracellular channels occurring in tight junctions play a major role in transepithelial ionic flows. This pathway includes a high number of proteins, such as claudins. Within renal epithelium, claudins result in an ionic selectivity in tight junctions. Ascending thick limb of loop of Henle (ATLH) is the most important segment for calcium reabsorption in renal tubules. Its cells create a water-proof barrier, actively transport sodium and chlorine through a transcellular pathway, and provide a paracellular pathway for selective calcium reabsorption. Several studies have led to a model of paracellular channel consisting of various claudins, particularly claudin-16 and 19. Claudin-16 mediates cationic paracellular permeability in ATLH, whereas claudin-19 increases cationic selectivity of claudin-16 by blocking anionic permeability. Recent studies have shown that claudin-14 promoting activity is only located in ATLH. When co-expressed with claudin-16, claudin-14 inhibits the permeability of claudin-16 and reduces paracellular permeability to calcium. Calcium reabsorption process in ATLH is closely regulated by calcium sensor receptor (CaSR), which monitors circulating Ca levels and adjusts renal excretion rate accordingly. Two microRNA, miR-9 and miR-374, are directly regulated by CaSR. Thus, miR-9 and miR-374 suppress mRNA translation for claudin-14 and induce claudin-14 decline.

Rol de las claudinas en el manejo renal del calcio

Palabras clave:
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RESUMEN

Los canales paracelulares que se encuentran en las uniones estrechas tienen un papel fundamental en los flujos iónicos transepiteliales. Esta vía está formada por un gran número de proteínas, entre ellas, las claudinas. En el epitelio renal, las claudinas confieren selectividad iónica a la unión estrecha. La rama gruesa ascendente de Henle (RGAH) es el segmento tubular renal más importante en la reabsorción tubular de calcio. Sus células forman una barrera impermeable al agua, transportan activamente sodio y cloro por la

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vía transcelular y proveen una vía paracelular para la reabsorción selectiva de calcio. Varios estudios han llevado a un modelo en el que distintas claudinas forman el canal paracelular, especialmente la claudina 16 y 19. La claudina 16 media la permeabilidad paracelular catiónica en la RGAH mientras que la claudina 19 incrementa la selectividad catiónica de la claudina 16 bloqueando la permeabilidad aniónica. Recientemente se ha encontrado que la actividad promotora de la claudina 14 está localizada exclusivamente en la RAGH. Cuando se coexpresa con la claudina 16, la claudina 14 inhibe la permeabilidad de la claudina 16, reduciendo la permeabilidad paracelular al calcio. El proceso de reabsorción de calcio en la RGAH está estrechamente regulado por el receptor sensor de calcio (CaSR) que monitorea los niveles circulantes de Ca ajustando la tasa de excreción renal de forma acorde. Dos micro-ARN, los mir-9 y mir-374, son regulados directamente por el CaSR. Los miR-9 y miR-374 suprimen la traslación del ARNm de la claudina 14 e inducen su decaimiento.

Introduction

Epithelial transport can occur by the transcellular route, across epithelial cells, or via a paracellular route between epithelial cells. In the last decade, evidence has accumulated supporting the fundamental role of paracellular channels in transepithelial flux of ions. The paracellular channel or route is found in the tight junctions (zonulae occludentes) of the epithelium in vertebrates. Tight junctions are the most apical structure of the intercellular junctional complex. Tight junctions are composed of a large number of different proteins. Of those, membrane proteins probably play a central role in determining paracellular permeability, as their extracellular domains protrude into the paracellular space, with an ideal position to influence paracellular movement of solutes. The cell membrane proteins of the tight junction include occludins, junctional adhesion molecules (JAM), and claudins. Claudins include a large family of at least 26 proteins that were first identified in 1998.[1] It was subsequently found that claudin-16, also known as paracellin-1, was mutated in familiar hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC).[2]

FHHNC appeared to be due to a defect in paracellular reabsorption of calcium and magnesium in the thick ascending limb of the loop of Henle (TAL). This was a first indication that claudin-16, and by extension claudins in general, might play an important role in the paracellular ion permeability of the kidney. In a recent genomic association study, the gene for claudin-14 was identified as being associated with increased risk for development of hypercalciuric nephrolithiasis,[3] making this protein another candidate for involvement in reabsorption of bivalent cations. All this information led us to re-examine the significance of claudins present in the kidney and their regulation of tubular calcium reabsorption.

Claudin structure

Claudins are 21 to 28 kDa proteins with 4 transmembrane domains, 2 extracellular loops, 2 cytoplasmic domains–one amino and one carboxyl terminal–and a short cytoplasmic loop. The first extracellular loop (ECL1) of claudins consists of approximately 50 amino acids with a common motif (GLWCC). It contains positively and negatively charged amino acids. The charges on ECL1 regulate ion selectivity by means of electrostatic effects. The second extracellular loop (ECL2) consists of approximately 25 amino acids with a predicted helix-loop-helix motif that mediates the intracellular interactions of claudins. The C-terminal domain contains the PDZ binding domain that is critical for interaction with the submembrane protein ZO-1 and the correct localisation of the claudin in the tight junction. In the renal epithelium, claudins have been shown to confer ion selectivity to the tight junction, resulting in differences in transepithelial resistance and paracellular permeability. For example, claudin-4, 5, 8, 11, and 14 selectively decrease tight junction permeability to cations, particularly to sodium, potassium, hydrogen, and ammonium, whereas claudin-2, 15, and 16 increase permeability to cations, particularly sodium, potassium, calcium, and magnesium.[4]

Claudin expression in different tubular segments

Most claudins are expressed in the renal tubule. Each segment and cell type expresses multiple isoforms. It is thought that the particular group of claudins expressed in each tubular segment determines the unique permeability properties of those segments.[5] Claudin-2 is highly expressed in the proximal tubule, mainly in the terminal part of the proximal tubule and the initial part of the thin descending loop of Henle; the fundamental role is to form paracellular cation-selective pores with high sodium conductivity. Claudin-10a and claudin-17 are both known to form anion-selective paracellular pores and are potential candidates for mediating paracellular reabsorption of chloride in the distal part of the this tubular segment. Claudins-16 and 19 are expressed in the thin and thick ascending limb of the loop of Henle and are clearly required for the paracellular reabsorption of bivalent cations. Some investigators think that these 2 claudins form the paracellular pore that mediates permeability to calcium and magnesium in the TAL. Others, such as Hou et al., have found