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MODERN CONCEPTS ON THE BIOLOGICAL ROLE AND CLINICAL SIGNIFICANCE OF CLAUDINS

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Abstract. At present, sufficient data and information have been accumulated on changes in claudins levels in various gastroenterological diseases. However, the issue of claudins content in intestinal pathologies remains poorly studied. Currently, post-giardiasis inflammatory bowel disease (IBS) is being actively studied. According to Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) in the Russian Federation, giardiasis ranks second after enterobiosis. Every year, up to 70–75% of children under the age of 17 fall ill with it. In addition, there is evidence that 5 to 10% of children diagnosed with IBS were previously infected *Lamblia intestinalis*. Giardiasis attacks the intestinal barrier and promotes the degradation of tight junction proteins such as Zo-1, claudin-1 and claudin-4. Claudins levels were decreased due to damage to the intestinal barrier. The role of excess claudins in IBD remains controversial. The studies examine the positive and negative effects of claudine-isoform levels on the human body depending on conditions. In addition to diseases, the level of claudins also depends on the content of cytokines.

Key words: *claudin; giardiasis; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD); intestinal barrier.*

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О БИОЛОГИЧЕСКОЙ РОЛИ И КЛИНИЧЕСКОМ ЗНАЧЕНИИ КЛАУДИНОВ

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Резюме. На сегодняшний день накоплено достаточно сведений и информации об изменениях уровня клаудинов при различных гастроэнтерологических заболеваниях. Однако до сих пор остается малоизученным вопрос содержания клаудинов при кишечных патологиях. В настоящее время ведется активное изучение постлямблиозного синдрома раздраженного кишечника (СРК). По данным Роспотребнадзора, в Российской Федерации лямблиоз занимает второе место после энтеробиоза. Ежегодно им заболевают до 70–75% детей в возрасте до 17 лет. Кроме того, имеются данные, что от 5 до 10% детей с выявленным СРК были ранее инфицированы *Lamblia intestinalis*. Лямблиоз поражает кишечный барьер и способствует деградации белков плотных контактов, таких как Zo-1, клаудин-1 и клаудин-4. Уровень клаудинов был понижен в связи с поражением кишечного барьера. Вопрос о роли избыточного содержания клаудинов при ВЗК остается спорным. В исследованиях рассматриваются положительные и негативные влияния уровня изоформы клаудина на организм человека в зависимости от условий. Помимо заболеваний, уровень клаудинов зависит также от содержания цитокинов.

Ключевые слова*: клаудин; лямблиоз; синдром раздраженного кишечника (СРК); воспалительные заболевания кишечника (ВЗК); кишечный барьер.*

INTRODUCTION

The primary constituents of the dense compounds found in the epithelial cells of vertebrates are several integral membrane proteins belonging to the claudine family [1]. Dense compounds, also known as contacts, are complex structures that operate as a paracellular barrier between the apical and basolateral regions of the plasma membrane, regulating specific permeability and preserving cellular polarity.

Claudines consist of four transmembrane α-helices, two extracellular loops with variable amino acid sequences, and short cytoplasmic N- and C-ends. Extracellular loops, notably the first, participate in the creation of ionoselectic channels due to homophilic and heterophilic contacts between claudines on adjacent cell membranes [2]. There are now 27 known kinds of claudines. The full range of functions of these proteins is unknown and continues to be studied. Lal-Nag and M. Morin demonstrated that transdermal water loss caused dehydration in mice harboring Claudin-1. [3, 4]. In mice lacking claudine 11 and 14, the loss of dense connections from the basal cells of the vascular strip resulted in the development of deafness. Due to the loss of nerve conductivity along peripheral myelinated fibers and Schwann cell densities, claudine-19 deficiency resulted in behavioral abnormalities. According to other research, individuals with inflammatory bowel disease (IBS) have lower levels of claudine-1 protein expression, which is correlated with the illness's protracted course [5, 6]. The diversity of claudines thus points to a critical role for them in the control of paracellular transport and the operation of dense connections. The link between claudine structure and function, expression regulation mechanisms, and the pathological consequences of dysregulation of these dense contact proteins (DCP) are the subjects of an increasing amount of research. Determining the DCP level for different diseases is of some importance.

INFLAMMATORY BOWEL DISEASE

One of the most frequent bowel pathologies are inflammatory bowel disease (IBD) — Crohn's disease (CD) and ulcerative colitis (UC). It has been suggested that a change in the level of Claudine plays a role in the pathogenesis of IBD [7]. Indeed, the anomalies of most of the claudin isoforms lead to impaired intestinal barrier functions [8]. A number of studies have been conducted on patients with UC and CD [9]. Changes in the level of claudine under the IBD were detected based on a study of the intestinal epithelium biopsy material. Ulcerative colitis increased the expression of claudine-1, -2 and -18 and lowered the regulation of claudine-3, -4 and -7. CD also showed elevated levels of claudine-1 and claudine-2 and decreased expression of claudine-3 in the intestine epithelium [10].

In their study, Preeti Raju and Nitesh Shashikanth conclude on the pathogenic role of elevated level of claudine-2 in the development of colitis and try to solve this problem by exposure to casein kinase-2 [11]. The authors argue that such a solution requires further research and could be used as a CMV therapy. However, there is a contrary view. C.T. Capaldo and Claudin Barriers have shown resistance to colitis at high levels of claudin [12]. This hypothesis was demonstrated in an experiment with mice that were transgenically modified for increased production of claudine-2. Claudine-2 was later shown to be protective of chemically induced and pathogen-induced colitis. In places with pathologies such as immuno-mediated colitis, high levels of claudine-2 exacerbate the disease, and the removal of this isoform of claudine is beneficial.

Other isoform studies suggest the important role of Claudines in the IBD — participation in cell proliferation and migration at the cellular level. However, claudine-2 increases the flow of antigens to different tissues. This may be due to the effect of claudine-2 expression on cell division. If the damage is due to a pathogen, high levels of claudine-2 can have a positive effect by accelerating regeneration processes. However, in case of chronic damage, the increased isoform content is destructive due to the enhanced action of antigens. Thus, the elevated content of claudine may in different cases indicate beneficial and pathogenic changes [13].

To diagnose inflammatory bowel disease, it is essential to determine the level of claudine. Some studies show a relationship between dense contact lesions and the level of claudine-3 in urine in patients with IBD. In this pathology, the level of claudins in urine is increased dramatically [14, 15].

In addition to inflammatory bowel diseases, the content of claudine also varies with irritable bowel syndrome. According to some reports, the expression of claudine-1 decreases in patients with IBS [16].

IRRITABLE BOWEL SYNDROME

The IBS is a set of functional impairments that include abdominal pain, lessening after the act of defecation, occurring at least three days per

month during the last three months, with a total duration of at least 6 months [17]. It has been proven that the level of claudine-1 in patients with IBS with diarrhea is lowered [18, 19].

Some cytokines play an important role in changes in the level of claudine under the IBS. Tumor necrosis factor alpha (TNFα) and interferon-gamma contribute to the degradation of dense contacts by affecting the claudins. These cytokines are often found in tests of patients with IBS. Thus, cytokines are involved in altering the epithelial barrier by affecting claudine [20, 21]. A study by V. Ivashkin and Y. Poluektov demonstrates changes in cytokines and claudins at IBS [22].

A number of conclusions were drawn from the data. In IBS, a statistically significant increase in the expression of flammable cytokine TNFα and cytokine IL-2 is detected. The anti-inflammatory cytokine IL-10 content in the bioptat was significantly reduced, as was the content of claudine-3, -5 [23, 24]. The authors suggest that the level of claudine is reduced by the degranulation of mast cells due to the release of tryptase. In addition, degranulation causes the release of inflammation mediators and activates lymphocytes, resulting in cytokine imbalance [25].

AFTER GIARDIASIS IRRITABLE BOWEL SYNDROME

Giardiasis is one of the most common diseases in the world. The causative agent is Giardia lamblia, transmitted by fecal-oral via direct or indirect contact of the parasite cysts with water and food [26, 27]. Symptoms of giardiasis may be absent or exhibit acute watery diarrhea, nausea, epigastric pain [28–30].

Infection of Lamblia intestinalis can provoke the development of post-exposure IBS, contributing to the destruction of the intestinal barrier. A number of studies have been carried out on newborn mice with exogenous infection. Hypersensitivity syndrome was found in mice 50 days after infection, due to nausea, crypt hyperplasia and increased immune cell count. The work also found an intercellular bacterial translocation through the epithelial barrier, which can be observed with giardiasis [31]. In addition, the authors concluded that giardiasis causes persistent damage to dense contacts, especially claudin. Bacterial translocation was associated with increased neutrophilic infiltration. Proinflammatory cytokines also played a key role in the process, with an increased number of them. For example, mice showed elevated levels of interferon-α and interferon-γ, TNF, and IL-1 [32]. Thus, bacterial inflammation may persist after the removal of giardia for a long time, which may contribute to the development of post-infectious intestinal disorders [33].

Other studies found a high prevalence of giardiasis infection in patients with IBS in duodenal biopsy and stool research. The authors conclude that infection of Lamblia intestinalis may be one of the possible causes of symptoms in patients with IBS [34, 35]. There are also studies showing inverse relationships. Many patients diagnosed with IBS are susceptible to infection with Lamblia intestinalis [36]. At the same time, the change in the level of clausines in the case of a post giardiasis IBS remains an issue of discussion.

CONCLUSION

Thus, varied claudine contents are shown by these illnesses; yet, claudine can still be harmful and speed up the progression of sickness. The problem was not thoroughly investigated and needed to be given more careful thought. Nonetheless, claudins play a significant diagnostic function in gastrointestinal diseases, and physicians should modify the course of treatment for patients with IBD and IBS based on their claudine levels.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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