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PERMEABILITY OF THE INTESTINAL EPITHELIAL BARRIER: EVALUATION CRITERIA, ROLE IN THE PATHOGENESIS OF CELIAC DISEASE

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ABSTRACT. The main structures responsible for maintaining the integrity of the intestinal barrier are tight junctions. Evidence of their role was obtained using electron microscopy and electrophysiology. A new and promising direct method for assessing the intestinal barrier function is confocal laser endomicroscopy. There is a growing interest in indirect assessment of the integrity of the mucosa using potential biomarkers. The levels of β-zonulin in stool and serum, and claudin levels in the blood are studied in various diseases. The article reflects the literature data on studies examining the possibilities of non-invasive methods for assessing the state of the epithelial barrier in the diagnosis of celiac disease and monitoring compliance with a gluten-free diet by the patient. Despite a large number of studies demonstrating increased intestinal permeability in celiac disease, the question of the place of dysfunction of the epithelial barrier of the small intestine in the pathogenesis of celiac disease remains relevant. The question of whether the barrier dysfunction is primary or a consequence of celiac disease itself has not yet been resolved.

KEYWORDS: *claudin, zonulin, confocal laser endomicroscopy, epithelial barrier, intestinal permeability, celiac disease*

ПРОНИЦАЕМОСТЬ ЭПИТЕЛИАЛЬНОГО БАРЬЕРА КИШКИ: КРИТЕРИИ ОЦЕНКИ, РОЛЬ В ПАТОГЕНЕЗЕ ЦЕЛИАКИИ

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РЕЗЮМЕ. Основными структурами, отвечающими за поддержание целостности кишечного барьера, являются плотные контакты. Доказательства их роли получены с помощью электронной микроскопии и электрофизиологии. Новым и перспективным прямым методом оценки барьерной функции кишечника является конфокальная лазерная эндомикроскопия. Растет интерес к косвенной оценке целостности слизистой оболочки с помощью потенциальных биомаркеров. Изучают уровни зонулина в стуле и в сыворотке крови, уровни клаудинов в крови при различных заболеваниях. В статье отражены литературные данные об исследованиях, посвященных изучению возможности неинвазивных методов оценки состояния эпителиального барьера при диагностике целиакии и контроля за соблюдением безглютеновой диеты пациентом. Несмотря на большое количество исследований, демонстрирующих повышенную проницаемость кишечника при целиакии, актуальным остается вопрос о месте в патогенезе целиакии дисфункции эпителиального барьера тонкой кишки. Вопрос о том, является ли дисфункция барьера первичной или следствием самой целиакии, все еще не решен.

КЛЮЧЕВЫЕ СЛОВА: *клаудин, зонулин, конфокальная лазерная эндомикроскопия, эпителиальный барьер, кишечная проницаемость, целиакия*

The intestinal barrier is a complex system that provides highly selective protection of the internal environment of the body from external influences using both immune and non-immune mechanisms. The main structures maintaining the integrity of this barrier are tight junctions (TJs). Their importance has been confirmed by electron microscopy (EM) and electrophysiological studies. In the apical region of the epithelium there is an intercellular gap (around 90 Å) named *zonula occludens* or tight junctions, followed by the *zonula adherens* (gap of 200 Å), followed by the *macula adherens* or desmosomes (gap of ~240 Å) [1]. Recently, two types of TJ-regulated pores have been identified: high-capacity charge-selective pores that allow small ions and small uncharged molecules to pass through (the "pore" pathway), and large pores with low selectivity (the "leak" pathway) that are permeable to large ions and molecules regardless of charge. At the molecular level, the first pore is regulated by claudins and the latter by the tight junction proteins such as occludin and the *zonula occludens* (ZO) family [1].

Confocal laser endomicroscopy (CLE) is a modern direct method for assessing intestinal barrier function. Using a confocal probe equipped with a 488 nm laser, increasing gaps between epithelial cells (1), leakage of fluorescein into the intestinal lumen (2), and epithelial cell shedding (3) can be directly visualized after intravenous administration of fluorescein [2, 3]. This method has been used to study intestinal permeability in various conditions and has shown increased duodenal permeability upon exposure to food antigens [1, 4, 5].

Due to the labor-intensive nature and limited availability of direct tests for intestinal permeability both *ex vivo* and *in vivo*, there is growing interest in indirect methods for assessing mucosal integrity, including potential biomarkers, such as zonulin.

Zonulin, a 47 kDa human pre-haptoglobin, is similar to cholera toxin (zonula occludens toxin — ZOT). Zonulin is synthesized in the liver and enterocytes. It can be isolated from a membrane complex (claudin-occludin-guanylate kinase-like zonula occludens (ZO) proteins 1, 2, and 3), which forms tight junctions in the apical part of the intestinal epithelium [6–8]. Recently, zonulin has been considered as a family of structurally and functionally related proteins [1]. Secreted into the lumen of the gastrointestinal tract, zonulin stimulates protease-activated receptors (PAR) and epidermal growth factor receptors (EGFr), which induce the "opening" of epithelial junctions, increasing paracellular permeability, and allows molecules with a molecular weight of more than 3.5 kDa to cross the intestinal barrier [9].

In most studies, zonulin is determined in two biological environments: blood and stool [10]. Determination of zonulin in stool may indicate the rate of its production in enterocytes, and in the blood — the transport of this protein from the intestinal lumen to the submucosa, between intestinal epithelial cells [8, 9]. The half-life of zonulin in the blood varies and ranges from 4 minutes to 4 hours, which leads to a significant spread in concentration (from undetectable to very high) [10, 11]. Increased zonulin concentrations have been shown in various conditions, including celiac disease, type 1 diabetes mellitus, inflammatory bowel disease, obesity, schizophrenia, and others [9].

Two decades ago, increased zonulin protein concentration was shown in patients with active celiac disease by the group of Fasano. Gliadin induced release of zonulin by binding to CXCR3 and elevated permeability *ex vivo* in biopsies of healthy volunteers and patients with quiescent celiac disease. However, both the baseline permeability and permeability after the addition of gliadin were higher and the luminal zonulin release was more pronounced and prolonged in patients with celiac disease [1].

A recent study examined serum zonulin levels in children at risk for celiac disease starting 12 months before diagnosis compared to controls without celiac disease, and identified clinical factors that contribute to disease manifestation. Children with celiac disease showed a significant increase in zonulin levels for about 18 months (range 6–78) before diagnosis compared to children without the disease. A correlation was found between the number of antibiotic courses and the increase in zonulin levels in patients with celiac disease. The authors suggest that zonulin may be used as a biomarker for preclinical assessment of celiac disease in children at risk, and multiple antibiotic courses may increase their risk of developing the disease by increasing zonulin levels [12].

Another study determined reference values of fecal zonulin concentrations in children under 16 years of

age. It was statistically significant that zonulin levels in children with clinical manifestation of celiac disease were significantly higher than in healthy children and children who followed a gluten-free diet for 6 months. The authors suggest using zonulin levels as an additional tool for monitoring adherence to a gluten-free diet [13].

When comparing the amino acid composition of zonulin and its Zot active fragment, similarities in amino acids were found. An octapeptide (GGVLVQPG) was synthesized, named FZI/0, AT1001, and recently larazotide acetate corresponding to 8 amino acids of this fragment was also synthesized [1]. Larazotide acetate (LA) is a single-chain peptide that acts as a tight junction regulator to restore intestinal barrier function. The main function of LA is to act as an anti-zonulin receptor inhibitor to reduce zonulin-induced increases in increase in intestinal barrier permeability [14]. The mechanism of action of LA is thought to be associated with the redistribution and rearrangement of tight junction proteins and actin filaments to restore intestinal barrier function. Recent studies have shown that LA inhibits myosin light chain kinase, which likely reduces tension on actin filaments, thereby facilitating tight junction closure [14]. Currently, phase III clinical trials have been completed in which LA was administered orally to adult patients with celiac disease as an adjunct therapeutic to enhance the intestinal barrier function. The results of these studies are encouraging: the biological safety of LA has been confirmed. A greater reduction in intestinal symptoms was also shown in patients receiving LA in combination with a gluten-free diet compared to those following the diet alone. However, statistically significant differences in the lactulose to mannitol ratio compared with placebo group were not observed [15, 16]. Further studies are needed to clarify whether there are other mechanisms of action of LA on intestinal permeability and how it can be applied in clinical practice.

Claudins are integral transmembrane proteins that span the membrane bilayer four times. These proteins form structural and functional regions that include four transmembrane domains, two extracellular loops, one cytoplasmic loop, and N- and C-cytoplasmic domains. In the intestine, abnormalities of claudins 2, 3, 4, 7, 12, and 14 lead to impaired intestinal barrier function [17]. It is believed that changes in claudin levels play an important role in the pathogenesis of various diseases, including celiac disease [18–21].

The question of the nature of the epithelial barrier defect in celiac disease remains open. It may occur secondarily due to the inflammation localized in the lamina propria of the small intestine mucosa in the active form of the disease. The epithelial barrier defect may also be primary, since claudin levels are altered both in patients with quiescent celiac disease on a gluten-free diet and in relatives of patients who do not have this disease [22, 23].

Recently, V. Kumar et al. identified genes associated with celiac disease that define the barrier, providing genetic evidence for the importance of barrier function in the pathogenesis of the disease [8]. It is significant that the barrier function is maintained by a complex interaction of proteins, where the main structural elements are tight junction proteins: occludin, claudins, and scaffolding proteins such as ZO-1 [24]. Although structural changes in barrier function in celiac disease may be related to the composition of enterocyte tight junctions and epithelial transcytosis of gliadin peptides, the number of studies aimed at elucidating the mechanisms of these changes is insignificant [20, 25–28]. One recent study showed that monocytes obtained from patients with celiac disease are able to induce a barrier defect in intestinal epithelial cells [29].

In addition, despite the large number of studies showing increased intestinal permeability in celiac disease, the question of whether the barrier dysfunction is primary or a consequence of celiac disease itself remains relevant.

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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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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.

REFERENCES

1. Vanuytsel T., Tack J., Farre R. The Role of Intestinal Permeability in Gastrointestinal Disorders and Current Methods of Evaluation. Front Nutr. 2021;8:717925. DOI: 10.3389/fnut.2021.717925.
2. Buchner A.M. Confocal laser endomicroscopy in the evaluation of inflammatory Bowel disease. Inflamm Bowel Dis. 2019;25:1302–1312. DOI: 10.1093/ibd/izz021.
3. Chang J., Ip M., Yang M., Wong B., Power T., Lin L. et al. The learning curve, interobserver, and intraobserver agreement of endoscopic confocal laser endomicroscopy in the assessment of mucosal barrier defects. Gastrointest Endosc. 2016;83:785–791. DOI: 10.1016/j.gie.2015.08.045.
4. Chang J., Leong R.W., Wasinger V.C., Ip M., Yang M., Phan T.G. Impaired intestinal permeability contributes to ongoing bowel symptoms in patients with inflammatory bowel disease and mucosal healing. Gastroenterology. 2017;153:723–731. DOI: 10.1053/j.gastro.2017.05.056.
5. Queneherve L., David G., Bourreille A., Hardouin J.B., Rahmi G., Neunlist M. et al. Quantitative assessment of mucosal architecture using computer-based analysis of confocal laser endomicroscopy in inflammatory bowel diseases. Gastrointest Endosc. 2019;89:626–636. DOI: 10.1016/j.gie.2018.08.006.
6. Farre R., Vicario M. Abnormal barrier function in gastrointestinal disorders. Handb Exp Pharmacol. 2017;239:193–217. DOI: 10.1007/164.2016.107.
7. Khavkin A.I., Bogdanova N.M., Novikova V.P., Yudina D.V. Zonulin: physiological and clinical significance in the perinatal period. Voprosy ginekologii, akusherstva i perinatologii. 2020;19(5):132–139. DOI: 10.20953/1726-1678-2020-5-132-139. (In Russian).
8. Łoniewska B., Węgrzyn D., Adamek K., Kaczmarczyk M., Skonieczna-Żydecka K., Adler G. et al. The Influence of Maternal-Foetal Parameters on Concentrations of Zonulin and Calprotectin in the Blood and Stool of Healthy Newborns during the First Seven Days of Life. An Observational Prospective Cohort Study. J Clin Med. 2019;8(4):473. DOI: 10.3390/jcm8040473.
9. Khavkin A.I. Bogdanova N.M., Novikova V.P. Biological role of zonulin and the effectiveness of its use as a biomarker of increased intestinal permeability syndrome. Rossiyskiy vestnik perinatologii i pediatrii. 2021;66(1):31–38. DOI: 10.21508/1027-4065-2021-66-1-31-38. (In Russian).
10. Linsalata M., Riezzo G., D'Attoma B., Clemente C., Orlando A., Russo F. Noninvasive biomarkers of gut barrier function identify two subtypes of patients suffering from diarrhoea predominant-IBS: a case-control study. BMC Gastroenterol. 2018;18(1):167. DOI: 10.1186/s12876-018-0888-6.
11. Wegh C.A.M., de Roos N.M., Hovenier R., Meijerink J., Besseling-van der Vaart I. et al. Intestinal Permeability Measured by Urinary Sucrose Excretion Correlates with Serum Zonulin and Faecal Calprotectin Concentrations in UC Patients in Remission. J Nutr Metab. 2019;2019:2472754. DOI: 10.1155/2019/2472754.
12. DaFonte T.M., Valitutti F., Kenyon V., Locascio J.J., Montuori M., Francavilla R., Passaro T., Crocco M., Norsa L., Piemontese P., Baldassarre M., Fasano A., Leonard M.M. CD-GEMM Study Group. Zonulin as a Biomarker for the Development of Celiac Disease. Pediatrics. 2024;153(1): e2023063050. DOI: 10.1542/peds.2023-063050.
13. Martínez Gallego M.Á., Crespo Sánchez M.G., Serrano Olmedo M.G., Buño Soto A., Álvarez Casasempere S., Nozal P., Martínez-Ojinaga E., Molina Arias M., Losantos-García I., Molero-Luis M. Trends in Faecal Zonulin Concentrations in Paediatric Patients with Celiac Disease at Baseline and on a Gluten-Free Diet: Exploring Correlations with Other Faecal Biomarkers. Nutrients. 2024;16(5):684. DOI: 10.3390/nu16050684.
14. Slifer Z.M., Krishnan B.R., Madan J., Blikslager A.T. Larazotide acetate: a pharmacological peptide approach to tight junction regulation. Am J Physiol Gastrointest Liver Physiol. 2021;320(6):G983–G989. DOI: 10.1152/ajpgi.00386.2020.
15. Paterson B.M., Lammers K.M., Arrieta M.C., Fasano A., Meddings J.B. The safety, tolerance, pharmacokinetic and pharmacodynamic effects of single doses of AT-1001 in coeliac disease subjects: a proof of concept study. Aliment Pharmacol Ther. 2007;26:757–766. DOI: 10.1111/j.1365-2036.2007.03413.x.
16. Kivelä L., Caminero A., Leffler D.A., Pinto-Sanchez M.I., Tye-Din J.A., Lindfors K. Current and emerging therapies for coeliac disease. Nat Rev Gastroenterol Hepatol. 2021;18:181–195. DOI: 10.1038/s41575-020-00378-1.

17. Barrett K.E. Claudin-2 pore causes leak that breaches the dam in intestinal inflammation. J Clin Invest. 2020;130(10):5100–5101. DOI: 10.1172/JCI140528.
18. Garcia-Hernandez V., Quiros M., Nusrat A. Intestinal epithelial claudins: Expression and regulation in homeostasis and inflammation. Ann NY Acad. Sci. 2017;1397:66–79. DOI: 10.1111/nyas.13360.
19. Luettig J., Rosenthal R., Barmeyer C. et al. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. Tissue Barriers. 2015;3(1–2):e977176. DOI: 10.4161/21688370.2014.977176.
20. Schumann M., Gunzel D., Buergel N. et al. Cell polarity-determining proteins Par-3 and PP-1 are involved in epithelial tight junction defects in coeliac disease. Gut 2012;61(2):220–228. DOI: 10.1136/gutjnl-2011-300123.
21. Szakal D.N., Gyorffy H., Arato A. et al. Mucosal expression of claudins 2, 3 and 4 in proximal and distal part of duodenum in children with coeliac disease. Virchows Arch. 2010;456(3):245–250. DOI: 10.1007/s00428-009-0879-7.
22. Schumann M., Siegmund B., Schulzke J.D., Fromm M. Celiac Disease: Role of the Epithelial Barrier. Cell Mol. Gastroenterol. Hepatol. 2017;3:150–162. DOI: 10.1016/j.jcmgh.2016.12.006.
23. van Elburg R.M., Uil J.J., Mulder C.J., Heymans H.S. Intestinal permeability in patients with coeliac disease and relatives of patients with coeliac disease. Gut. 1993;34:354–357. DOI: 10.1136/gut.34.3.354.
24. Kumar V., Gutierrez-Achury J., Kanduri K., Almeida R., Hrdlickova B., Zhernakova D.V., Westra H.J., Karjalainen J., Ricano-Ponce I., Li Y. et al. Systematic annotation of celiac disease loci refines pathological pathways and suggests a genetic explanation for increased interferon-gamma levels. Hum Mol Genet. 2015;24:397–409. DOI: 10.1093/hmg/ddu453.
25. Cardoso-Silva D., Delbue D., Itzlinger A., Moerkens R., Withoff S., Branchi F., Schumann M. Intestinal Barrier Function in Gluten-Related Disorders. Nutrients. 2019;11:2325. DOI: 10.3390/nu11102325.
26. Matysiak-Budnik T., Moura I.C., Arcos-Fajardo M., Lebreton C., Menard S., Candalh C., Ben-Khalifa K., Dugave C., Tamouza H., van Niel G. et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. J Exp Med. 2008;205:143–154. DOI: 10.1084/jem.20071204.
27. Menard S., Lebreton C., Schumann M., Matysiak-Budnik T., Dugave C., Bouhnik Y., Malamut G., Cellier C., Allez M., Crenn P. et al. Paracellular versus transcellular intestinal permeability to gliadin peptides in active celiac disease. Am J Pathol. 2012;180:608–615. DOI: 10.1016/j.ajpath.2011.10.019.
28. Schumann M., Richter J.F., Wedell I., Moos V., Zimmermann-Kordmann M., Schneider T., Daum S., Zeitz M., Fromm M., Schulzke J.D. Mechanisms of epithelial translocation of the alpha(2)-gliadin-33mer in coeliac sprue. Gut. 2008;57:747–754. DOI: 10.1136/gut.2007.136366.
29. Delbue D., Cardoso-Silva D., Branchi F., Itzlinger A., Letizia M., Siegmund B., Schumann M. Celiac Disease Monocytes Induce a Barrier Defect in Intestinal Epithelial Cells. Int J Mol Sci. 2019;20(22):5597. DOI: 10.3390/ijms20225597.

ЛИТЕРАТУРА

1. Vanuytsel T., Tack J., Farre R. The Role of Intestinal Permeability in Gastrointestinal Disorders and Current Methods of Evaluation. Front Nutr. 2021;8:717925. DOI: 10.3389/fnut.2021.717925.
2. Buchner A.M. Confocal laser endomicroscopy in the evaluation of inflammatory Bowel disease. Inflamm Bowel Dis. 2019;25:1302–1312. DOI: 10.1093/ibd/izz021.
3. Chang J., Ip M., Yang M., Wong B., Power T., Lin L. et al. The learning curve, interobserver, and intraobserver agreement of endoscopic confocal laser endomicroscopy in the assessment of mucosal barrier defects. Gastrointest Endosc. 2016;83:785–791. DOI: 10.1016/j.gie.2015.08.045.
4. Chang J., Leong R.W., Wasinger V.C., Ip M., Yang M., Phan T.G. Impaired intestinal permeability contributes to ongoing bowel symptoms in patients with inflammatory bowel disease and mucosal healing. Gastroenterology. 2017;153:723–731. DOI: 10.1053/j.gastro.2017.05.056.
5. Queneherve L., David G., Bourreille A., Hardouin J.B., Rahmi G., Neunlist M. et al. Quantitative assessment of mucosal architecture using computer-based analysis of confocal laser endomicroscopy in inflammatory bowel diseases. Gastrointest Endosc. 2019;89:626–636. DOI: 10.1016/j.gie.2018.08.006.
6. Farre R., Vicario M. Abnormal barrier function in gastrointestinal disorders. Handb Exp Pharmacol. 2017;239:193–217. DOI: 10.1007/164.2016.107.
7. Хавкин А.И., Богданова Н.М., Новикова В.П., Юдина Д.В. Зонулин: физиологическое и клиническое значение в перинатальном периоде. Вопросы гинекологии, акушерства и перинатологии. 2020;19(5):132–139. DOI: 10.20953/1726-1678-2020-5-132-139.
8. Łoniewska B., Węgrzyn D., Adamek K., Kaczmarczyk M., Skonieczna-Żydecka K., Adler G. et al. The Influence of Maternal-Foetal Parameters on Concentrations of Zonulin and Calprotectin in the Blood and Stool of Healthy Newborns during the First Seven Days of Life. An Observational Prospective Cohort Study. J Clin Med. 2019;8(4):473. DOI: 10.3390/jcm8040473.
9. Хавкин А.И. Богданова Н.М., Новикова В.П. Биологическая роль зонулина и эффективность его использования в качестве биомаркера синдрома повышенной кишечной проницаемости. Российский вестник

перинатологии и педиатрии. 2021;66(1):31–38. DOI: 10.21508/1027-4065-2021-66-1-31-38.
10. Linsalata M., Riezzo G., D'Attoma B., Clemente C., Orlando A., Russo F. Noninvasive biomarkers of gut barrier function identify two subtypes of patients suffering from diarrhoea predominant-IBS: a case-control study. BMC Gastroenterol. 2018;18(1):167. DOI: 10.1186/s12876-018-0888-6.
11. Wegh C.A.M., de Roos N.M., Hovenier R., Meijerink J., Besseling-van der Vaart I. et al. Intestinal Permeability Measured by Urinary Sucrose Excretion Correlates with Serum Zonulin and Faecal Calprotectin Concentrations in UC Patients in Remission. J Nutr Metab. 2019;2019:2472754. DOI: 10.1155/2019/2472754.
12. DaFonte T.M., Valitutti F., Kenyon V., Locascio J.J., Montuori M., Francavilla R., Passaro T., Crocco M., Norsa L., Piemontese P., Baldassarre M., Fasano A., Leonard M.M. CD-GEMM Study Group. Zonulin as a Biomarker for the Development of Celiac Disease. Pediatrics. 2024;153(1):e2023063050. DOI: 10.1542/peds.2023-063050.
13. Martínez Gallego M.Á., Crespo Sánchez M.G., Serrano Olmedo M.G., Buño Soto A., Álvarez Casasempere S., Nozal P., Martínez-Ojinaga E., Molina Arias M., Losantos-García I., Molero-Luis M. Trends in Faecal Zonulin Concentrations in Paediatric Patients with Celiac Disease at Baseline and on a Gluten-Free Diet: Exploring Correlations with Other Faecal Biomarkers. Nutrients. 2024;16(5):684. DOI: 10.3390/nu16050684.
14. Slifer Z.M., Krishnan B.R., Madan J., Blikslager A.T. Larazotide acetate: a pharmacological peptide approach to tight junction regulation. Am J Physiol Gastrointest Liver Physiol. 2021;320(6):G983–G989. DOI: 10.1152/ajpgi.00386.2020.
15. Paterson B.M., Lammers K.M., Arrieta M.C., Fasano A., Meddings J.B. The safety, tolerance, pharmacokinetic and pharmacodynamic effects of single doses of AT-1001 in coeliac disease subjects: a proof of concept study. Aliment Pharmacol Ther. 2007;26:757–766. DOI: 10.1111/j.1365-2036.2007.03413.x.
16. Kivelä L., Caminero A., Leffler D.A., Pinto-Sanchez M.I., Tye-Din J.A., Lindfors K. Current and emerging therapies for coeliac disease. Nat Rev Gastroenterol Hepatol. 2021;18:181–195. DOI: 10.1038/s41575-020-00378-1.
17. Barrett K.E. Claudin-2 pore causes leak that breaches the dam in intestinal inflammation. J Clin Invest. 2020;130(10):5100–5101. DOI: 10.1172/JCI140528.
18. Garcia-Hernandez V., Quiros M., Nusrat A. Intestinal epithelial claudins: Expression and regulation in homeostasis and inflammation. Ann NY Acad Sci. 2017;1397:66–79. DOI: 10.1111/nyas.13360.
19. Luettig J., Rosenthal R., Barmeyer C. et al. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. Tissue Barriers. 2015;3(1–2):e977176. DOI: 10.4161/21688370.2014.977176.
20. Schumann M., Gunzel D., Buergel N. et al. Cell polarity-determining proteins Par-3 and PP-1 are involved in epithelial tight junction defects in coeliac disease. Gut 2012;61(2):220–228. DOI: 10.1136/gutjnl-2011-300123.
21. Szakal D.N., Gyorffy H., Arato A. et al. Mucosal expression of claudins 2, 3 and 4 in proximal and distal part of duodenum in children with coeliac disease. Virchows Arch. 2010;456(3):245–250. DOI: 10.1007/s00428-009-0879-7.
22. Schumann M., Siegmund B., Schulzke J.D., Fromm M. Celiac Disease: Role of the Epithelial Barrier. Cell Mol. Gastroenterol. Hepatol. 2017;3:150–162. DOI: 10.1016/j.jcmgh.2016.12.006.
23. van Elburg R.M., Uil J.J., Mulder C.J., Heymans H.S. Intestinal permeability in patients with coeliac disease and relatives of patients with coeliac disease. Gut. 1993;34:354–357. DOI: 10.1136/gut.34.3.354.
24. Kumar V., Gutierrez-Achury J., Kanduri K., Almeida R., Hrdlickova B., Zhernakova D.V., Westra H.J., Karjalainen J., Ricano-Ponce I., Li Y. et al. Systematic annotation of celiac disease loci refines pathological pathways and suggests a genetic explanation for increased interferon-gamma levels. Hum Mol Genet. 2015;24:397–409. DOI: 10.1093/hmg/ddu453.
25. Cardoso-Silva D., Delbue D., Itzlinger A., Moerkens R., Withoff S., Branchi F., Schumann M. Intestinal Barrier Function in Gluten-Related Disorders. Nutrients. 2019;11:2325. DOI: 10.3390/nu11102325.
26. Matysiak-Budnik T., Moura I.C., Arcos-Fajardo M., Lebreton C., Menard S., Candalh C., Ben-Khalifa K., Dugave C., Tamouza H., van Niel G. et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. J Exp Med. 2008;205:143–154. DOI: 10.1084/jem.20071204.
27. Menard S., Lebreton C., Schumann M., Matysiak-Budnik T., Dugave C., Bouhnik Y., Malamut G., Cellier C., Allez M., Crenn P. et al. Paracellular versus transcellular intestinal permeability to gliadin peptides in active celiac disease. Am J Pathol. 2012;180:608–615. DOI: 10.1016/j.ajpath.2011.10.019.
28. Schumann M., Richter J.F., Wedell I., Moos V., Zimmermann-Kordmann M., Schneider T., Daum S., Zeitz M., Fromm M., Schulzke J.D. Mechanisms of epithelial translocation of the alpha(2)-gliadin-33mer in coeliac sprue. Gut. 2008;57:747–754. DOI: 10.1136/gut.2007.136366.
29. Delbue D., Cardoso-Silva D., Branchi F., Itzlinger A., Letizia M., Siegmund B., Schumann M. Celiac Disease Monocytes Induce a Barrier Defect in Intestinal Epithelial Cells. Int J Mol Sci. 2019;20(22):5597. DOI: 10.3390/ijms20225597.