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РАЗНООБРАЗИЕ *Escherichia coli*: ПРЕДСТАВИТЕЛЬ МИКРОБИОМА ИЛИ ПАТОГЕН ДЛЯ ОБЩЕСТВЕННОГО ЗДРАВООХРАНЕНИЯ?

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Escherichia coli является одним из представителей кишечного микробиома. Структура популяции преимущественно клональная, однако наличие генов патогенности переводит синантропную Escherichia coli в патоген, способный вызывать развитие инфекционного процесса. В зависимости от генетического фона (наличия факторов вирулентности и генов, их кодирующих) Escherichia coli подразделяют на внекишечный и диарейный патотипы. К последним относятся энтеротоксигенные, энтеропатогенные, энтероинвазивные, энтероадгезивные и энтерогеморрагические E. coli, вызывающие геморрагический колит и/или гемолитико-уремический синдром, в том числе продуцирующие шига-токсин. Есть E. coli, способные прикрепляться к стенкам кишечника и вызывать нарушение процессов всасывания — энтероагрегационный и диффузно-агрегационный патотипы соответственно.

Ключевые слова: *Escherichia coli; диарея; заболевания; энтеротоксины; патогенность; молекулярно-генетические исследования; патогенность*

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DIVERSITY OF *Escherichia coli*: A REPRESENTATIVE OF THE MICROBIOME OR A PATHOGEN FOR PUBLIC HEALTH?

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Escherichia coli is one of the representatives of the intestinal microbiome. The population structure is predominantly clonal, however, the presence of pathogenicity genes translates synanthropic Escherichia coli into a pathogen capable of causing the development of an infectious process. Depending on the genetic background (the presence of virulence factors and the genes encoding them), Escherichia coli is divided into extra-intestinal and diarrhoeal pathotypes. The latter includes enterotoxigenic, enteropathogenic, enteroinvasive, enteroadhesive and enterohemorrhagic E. coli, which causes hemorrhagic colitis and/or hemolytic-uremic syndrome, including producing Shiga toxin. There is E. coli capable of attaching to the intestinal walls and causing a violation of the absorption processes – enteroaggregative and diffuse-aggregating pathotypes, respectively.

Key words: *Escherichia coli; diarrhea; diseases; enterotoxins; pathogenicity; molecular genetic studies; pathogenicity*

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The main habitat of *Escherichia coli* is the digestive system – the gastrointestinal tract, where, being an aerobic organism, this microorganism is in symbiosis with other representatives of the microflora, being part of the intestinal microbiome. Despite the possibility of genetic recombination, the population structure of E. coli is predominantly clonal, which makes it possible to identify the main phylogenetic groups. The literature data indicate seven phylogenetic groups A, B1, B2, D, E, F and C within each population, which is determined by geographical, socio-economic and medical data, including the genetic relationship of synanthropic *E. coli* to the host organism [4]. The analysis of the occurrence indicates that A, B1, B2, D are the main groups, and in A, B1 and D the determinants of virulence are rarely detected, while in synanthropic and pathogenic strains belonging to B2 their detection is the same [5,6]. It should be understood that in order to become etiologically significant agents determining the development of acute intestinal infection or another type of pathology, synanthropic *E. coli* must acquire virulence factors and vice versa, the identification of strains of the phylogenetic group B2 is potentially classified as pathogenic. Thus, the population structure of *E. coli*, depending on the genetic background (the presence of virulence factors and genes encoding them), can cause both diarrheal diseases (DEC) and extra-intestinal infections (ExPEC) [7,8,9]. Moreover, ExPEC phylogenetically differ from synanthropic E. coli or DEC and, depending on the course of the pathological process, are divided into uropathogenic (UPEC), septicemic (SEPEC) and meningitis-associated (MNEC) infections. ExPEC, like diaregenic colibacteria, have a wide range of virulence factors, which are often found in synanthropic E. coli living in the intestine [10]. This is possible due to the horizontal transfer of virulence determinants that determine the development of diarrheal diseases [11]. It is likely that in the future, the loss and acquisition of genes will continue to lead to the appearance of pathogenic isolates that do not correspond to the current definitions of DEC. In hospital settings, ExPEC having virulence genes, including resistance to antibacterial drugs, contribute to infection associated with medical care.

DEC has specific combinations of virulence signs, due to which they are grouped into pathotypes, each of which has unique genetic data, biological features and other characteristics [12]. Determining the pathotype is necessary both for the effectiveness of diagnosis and for understanding the burden of the disease, including the choice of drug therapy. It is known that DECs are genetically heterogeneous, for some there is no data on molecular genetic factors of pathogenicity [14]. The determination of pathotypes is also complicated by the frequent release of pathogenic *E. coli* in individuals with an asymptomatic course of infection [15], including the existence of hybrid strains [16]. Grouping DEC based on the general characteristics of a particular pathotype is useful for understanding the breadth of the variety of virulence mechanisms that determine the development of pathology. In this case, it is optimal to study genomic data – the search for new pathotype-specific and diarrhea-associated genes, including their unique ability to produce thermolabile and thermostable enterotoxins, a variety of colonization factors and other biological properties specific to pathogenic populations [17]. Molecular genetic research also makes it possible to determine the relationship with synanthropic *E. coli.* It is extremely important that DEC detection methods be as sensitive and specific as possible, which determines the accuracy of a comprehensive assessment and subsequent description of the characteristics of each isolate.

DEC pathotypes include enterotoxigenic *E. coli* (ETEC); enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC) and enteroadhesive strains (EAggEC), E. *coli* capable of attaching to intestinal walls and causing disruption of intestinal absorption processes – enteroaggregative *E. coli* (EAEC) and diffuse aggregating (DAEC), respectively. There is also enterohemorrhagic *E. coli* (EHEC), which causes hemorrhagic colitis and hemolytic-uremic syndrome, including Shiga toxin-producing (STEC) [49].

Enterotoxigenic Escherichia coli (ETEC)

Enterotoxigenic ETEC includes 22 serological variants (O6, O8, O11, O15, O20, O25, O27, O63, O78 and others) and more than 16 serovars, mainly causing "traveler's diarrhea" [3], especially the increasing etiological role of O128 and O167 in third world countries is noted. To date, the O157:H7 serovar has been and remains the most important one causing an outbreak of human diarrheal infections [3].

The diagnosis is based on the presence of colonization factors or the detection of thermolabile (lt) and thermostable (ST) enterotoxins [18], which determine electrolyte imbalance in intestinal epithelial cells, causing the development of secretory diarrhea. The presence of one or both of the above-mentioned toxin genes serves as an identification characteristic of the ETEC strain [19]. The contribution of both hemolysins to the pathogenicity of ETEC has been demonstrated in numerous epidemiological studies indicating the development of colibacteriosis (enterotoxigenic escherichiosis) both in humans and animals [20].

According to the literature, two classes of thermolabile toxin are distinguished: lt1, isolated from humans and lt2, similar in functional, immunogenic and biological properties, but found only in *E. coli* isolated from animals. The latter differs from the human in primary amino acid sequences [21]. For lt2, it is known that the genes responsible for its production are encoded not in the plasmid, as for example for lt1, but in chromosomal DNA. The immediate difference is that antiserums against lt do not neutralize lt2.

Two types of enterotoxin are distinguished among ST: STa (ST-I) and STb (ST-II), which have different structures and mechanisms of action. STa-enterotoxin is divided into two subtypes: STa-H, available in ETEC human isolates, and STa-P-associated *E. coli*, isolated mainly from animals: pigs, calves, lambs, chickens and horses, respectively [22].

Enteropathogenic Escherichia coli (EPEC)

Like most other DECs, EPEC is often the cause of diarrhea in infants and young children in economically and socially disadvantaged countries in low- and middle-income families, including travelers traveling to endemic regions. HERES includes 22 serological variants (serogroups O18, O44, O55*, O86, O111, O112, O114, O119, O125ac, O126, O127, O128ab, O142) and more than 29 serovars (O:H), representing a heterogeneous group of strains characterized by the variability of virulent signs, which determines their ability to cause the development of the disease [23]. It is known that there are both asymptomatic carriers and evidence that certain serogroups cause diarrhea more often than others (O55, O125, O111, O126, O18). This fact can be explained by a number of reasons, one of which is dif-

ferences in the immune status, the presence of IgA received by children with breast milk from their mother and preventing the colonization of the EPEC pathotype [24].

The EPEC virulence genes are encoded in the chromosomal locus of the enterocyte pathogenicity island (LEE) [25], and their centers are in the intimate protein gene encoded by LEE – eae [26]. Some EPEC strains carry the plasmid of the EPEC adhesion factor (pEAT) encoding the pilus gene, which forms a bundle-like unit of bfp [27]. Isolates in which bfp+ is detected are called typical EPEC (tEPEC) strains, and bfp− are defined as atypical EPEC (aEPEC) pathogens. Currently, there are no tests to detect highly virulent strains.

Enterohemorrhagic E. coli (EHEC) EHEC of the STEC subtype (shigatoxigenic EHEC type) is associated both with outbreaks of life–threatening foodborne diseases - severe bloody diarrhea caused by serotype O157:H7 or O157HNM, and can cause mild impairment, often accompanied by fever, vomiting or chills and caused by serotypes of other groups (O26, O111, O113, O117 and O145, respectively) [28].

STEC strains are determined by the presence of verotoxin production and a Shiga-like toxin encoded (shigatoxin-producing *E. coli* – STEC), and EHEC strains have additional virulence factors, the expression of which leads to hemorrhagic colitis and, in some cases, life-threatening hemolytic-uremic syndrome. All EHEC pathotypes are STEC, but not all STEC are EHEC. The diagnosis of STEC is based on the molecular identification of variants of the Shiga toxin (stx gene) and auxiliary virulence genes, including markers encoded by the LEE island of pathogenicity, also present in EPEC. Diagnostic methods for EHEC strains often target the hemolysin genes encoded by the plasmid [29]. Serotyping is used both to identify *E. coli* O157:H7 and other EHEC strains [30].

Enteroinvasive Escherichia coli (EIEC)

EIEC, also known as enteroinvasive E. coli, includes 9 serogroups (O28ac, O29, O124, O136, O143, O144, O152, O164, O167 and O173, respectively) and a limited number of serovars are associated, the most important of which are the serogroups O124, O144 and O152, respectively. They differ in the ability to damage and multiply in the cells of the intestinal epithelium, thereby causing the development of inflammation, and the clinical manifestations and mechanisms of virulence are indistinguishable from the mechanisms initiated by closely related Shigella species [31,32]. EIEC, like Shigella, carries an F-type pINV plasmid encoding genes responsible for the development of dysentery [33]. Molecular detection of the pINV-encoded ipaH gene, a type III effector protein, is used to differentiate Shigella and EIEC from other pathotypes [34]. EIEC also differ from Shigella in biochemical characteristics, molecular genetic data - the presence of a specific lacY gene [35], present in all EIEC, but absent in Shigella spp. There is a β-glucuronidase (uidA) gene present in both EIEC and Shigella spp [36].

Enteroaggregative E. coli (EAEC/EAgEC) EAEC is a new extra–intestinal diarrhoeal pathogen that causes diseases in people regardless of age and is common in both industrialized countries and low-income regions. There is evidence of the occurrence of EAEC in the microbiota of healthy individuals [37]. Studies of diarrhea using the example of different regions have shown their genetic diversity. The pathogenicity and clinical significance of EAEC are also questionable, since asymptomatic carriage is common, and studies do not indicate a direct link with diarrhea [38]. For example, when simulating infection on volunteers with various strains of EAEC isolated from patients, only one strain caused diarrhea, and not in every subject [37]. This fact can be explained by the fact that not all EAEC are able to adhere to intestinal epithelial cells.

EAEC includes 8 serotypes (O3, O15, O44, O77, 086, O111 and O127, respectively) [32], and the best definition of EAEC is the identification of an aggregative pattern on cell culture with the absence of markers associated with other pathotypes [39].

In this case, laboratory testing on the HEp-2 cell line is considered the gold standard of EAEC diagnostics. Recently, it has been proposed to differentiate the strains of EAgEC into typical (t-EAgEC) and atypical (a-EAgEC), differentiated by the presence or absence of the aggR gene. It has been suggested that aggR/t-EAgEC has a greater pathogenicity than a-EAgEC [3]. Several molecular targets can also be used to detect EAEC, but given that the subtypes differ significantly, there is no consistent molecular definition yet [40]. The most commonly used marker genes for EAEC include aatA, a plasmid–encoded gene important for biofilm formation, aggR; a transcription activator encoded by a plasmid; and the aaiC gene located on a genomic island with a type VI secretion system [41]. Genome-wide studies of EAEC isolates are necessary for further identification of gene targets and molecular epidemiology of EAEC.

Diffuse-aggregating (diffuse-attaching) E. coli (DAEC) Epidemiological data linking DAEC to diarrhea in children in the CIS countries are available, but, like EAEC, its status as a causative agent of diarrheal diseases remains uncertain due to inconclusive evidence regarding studies on asymptomatic carriage [42]. It is important to note that the global prevalence of DAEC is difficult to determine, since the target genes used to identify this pathotype are not specific. The first definition of DAEC is associated with the distinctive nature of diffuse adhesion on cell culture, however, this study is not suitable for diagnosis, since atypical EPEC (aEPEC) also have this property [43]. Later, DAEC strains were detected due to the presence of F1845 adhesion genes encoded by afa, dra, or daa operons and being structurally and functionally similar [44]. Despite the existence of molecular genetic studies regarding the determination of daaC, daaE, afaB, afaC and other genes in the afa, dra and daa operons, it has been shown that they are also present in well-characterized EAEC strains. Thus, despite the use of molecular genetic studies, gene identification is not 100% of the DAEC identification methods from other DECs. As in the case of EAEC, to identify DAEC, whole genome sequencing studies are needed, including taking into account epidemiological data. Hybrid strains Separate studies indicate the identification of hybrid strains with genes associated with the identification of several DECs at once. These include strains producing the Shiga–EAEC toxin, which caused an outbreak of diseases in Europe; ETEC, detected in livestock and EPEC strains carrying the ETEC lt hemolysin gene, including aEPEC, which has a gene usually found in extra-intestinal pathogenic *E. coli* (ExPEC) [45,46,47,48]. Hybrid strains are relatively rare, which is apparently due to the low transmission (mobility)

of virulence genes, but their existence is an important example of the existence of other DECs that do not fall under the classical description.

Resume. Unfortunately, molecular diagnostics are not always effective for determining DEC, in particular, due to problems with identifying molecular targets for EAEC and DAEC. In addition, epidemiological studies of asymptomatic carriage indicate a contradictory relationship between the presence of a marker gene and symptoms of diarrhea. Continuing this work, combined with well-designed epidemiological studies, will help us better understand disease outcomes with the possibility of developing a treatment strategy related to DEC. It is important to recognize and understand the exceptions in the ability to cause the development of the disease, including continuing research using the example of molecular genetic research methods to understand the breadth of diversity DEC. Since it is believed that synanthropic intestinal isolates are reservoirs of pathogenic strains, it remains an open question whether there is a relationship between them, including taking into account geographical, socio-economic and medical data providing further understanding of the occurrence of diarrhoeal and other *E. coli* pathotypes.

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