MAURÍLIO FERNANDES DOS SANTOS

Análise do perfil plasmidial e dos fatores de virulência de amostras de *Escherichia coli* enteropatogênicas atípicas (a-EPEC)

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RESUMO

SANTOS, M.F. **Análise do perfil plasmidial e dos fatores de virulência de amostras de *Escherichia coli* enteropatogênicas atípicas (a-EPEC).** Tese (Doutorado em Biotecnologia – Biotecnologia) – Instituto de Ciências Biomédicas da Universidade de São Paulo, São Paulo, 2009.

Escherichia coli enteropatogênica (EPEC) é um dos principais agentes de diarréia em crianças nos países em desenvolvimento. Esse patótipo pode ser classificado em dois grupos: EPEC típica (t-EPEC) e EPEC atípica (a-EPEC). Amostras de ambos os grupos de EPEC possuem em comum a capacidade de causar uma lesão no epitélio intestinal conhecida como "Attaching and Effacing" (A/E). A principal característica que distingue as a-EPEC é o fato das amostras desse grupo não possuírem o plasmídio pEAF ("EPEC Adherence Factor"). O pEAF contém os genes que codificam a fímbria tipo IV BFP ("Bundle Forming Pillus") e confere as t-EPEC o fenótipo de adesão localizada (LA) às células epiteliais. As a-EPEC apresentam geralmente uma adesão caracterizada como localizada-like (LAL), mas também podem apresentar adesão difusa (DA), adesão agregativa (AA), podem ser não aderentes (NA) ou mesmo apresentarem uma adesão indeterminada (IND). As amostras de a-EPEC também são conhecidas por comporem um grupo extremamente heterogêneo de patógenos que são capazes de expressar fatores de virulência descritos em outros patótipos de *Escherichia coli* diarreiogênicas (DEC). O objetivo principal deste estudo foi traçar o perfil plasmidial de 78 amostras de a-EPEC bem como investigar em 72 amostras a presença de genes de virulência descritos em outros patótipos de DEC para procura de um marcador de virulência específico deste grupo de amostras. Foi detectada a presença de alguns genes de virulência como: *pet* (5,5%), *pic* (2,7%), *astA* (18%), *efa1/lifA, toxB* (2,7%), *ldaH* (8,3%) e *ehly1* (4,2%). Os perfis plasmidiais obtidos permitiram verificar que entre as 78 amostras analisadas, 12 não possuem plasmídio, 33 possuem plasmídios entre 50 a 90 kb e 38 possuem plasmídios entre 90 a 124 kb. A pesquisa dos grupos de incompatibilidade revelou que os grupos IncFIB e IncF são os mais freqüentes entre as amostras de a-EPEC. Os resultados de RFLP do DNA plasmidial das amostras do sorotipo O55:H7 sugeriu que existem seqüências de nucleotídeos comuns entre os plasmídios. Os dados obtidos também permitiram inferir a existência de fragmentos de DNA plasmidial comum entre amostras de EHEC O157:H7 e amostras de a-EPEC O55:H7. A função biológica dos plasmídios de a-EPEC e a relação com o plasmídio pO157 necessitam de estudos complementares.

Palavras-chave: *Escherichia coli*. Diarréia. Virulência. Plasmídio.

ABSTRACT

SANTOS, M.F. **Plasmid profile and virulence factors analysis of atypical enteropathogenic *Escherichia coli* (a-EPEC) strains.**Tese (Doutorado em Biotecnologia – Biotecnologia) – Instituto de Ciências Biomédicas da Universidade de São Paulo, São Paulo, 2009.

Escherichia coli (EPEC) is one of the main agents of diarrhea in children in developing countries. This pathotype can be classified in two groups: typical EPEC (t-EPEC) and atypical EPEC (a-EPEC). Strains of both groups have in common the ability to cause a characteristic lesion in the intestinal epithelium known as Attaching and effacing (A/E). The main feature distinguishing a-EPEC is the fact that samples of this group do not have the plasmid pEAF ("EPEC Adherence Factor"). The pEAF contains the genes encoding the type IV fimbriae BFP ("Bundle Forming Pillus") and confers the phenotype of localized adherence (LA) to epithelial cells. The a-EPEC generally are characterized as localized-like adherence (LAL), but may also exhibit diffuse adherence (DA), aggregative adherence (AA), non-adherent (NA) or indeterminate adherence pattern (IND). Strains of a-EPEC compose a very heterogeneous group of pathogens that are capable of expressing virulence factors described in other pathotypes of diarrheagenic *Escherichia coli* (DEC). The aim of this study was to determine the plasmid profile of 78 strains of a-EPEC and investigate 72 strains for the presence of virulence genes described in other DEC. It was detected the presence of some virulence genes: *pet* (5,5%), *pic* (2,7%), *astA* (18%), *efa1/lifA, toxB* (2,7%), *ldaH* (8,3%) e *ehly1* (4,2%). The plasmid profiles obtained allowed us to verify that among the 78 samples analyzed, 12 did not have plasmids, 33 strains have plasmids ranging between 50 and 90 kb, and 38 have plasmids ranging between 90 to 124 kb. Incompatibility groups analysis revealed that IncFIB and IncF groups are the most frequent among the samples of a-EPEC. RFLP analysis of plasmid DNA of strains of serotype O55:H7 suggested that there are nucleotide sequences common to the plasmids. The data also allowed inferring the existence of fragments of plasmid DNA common to EHEC O157:H7 and a-EPEC O55:H7. The biological function of aEPEC plasmid and the relationship with pO157 requires further studies.

Key words: Escherichia coli. Diarrhea. Virulence. Plasmid.

1 INTRODUÇÃO

A família *Enterobacteriaceae* compreende um grande e heterogêneo grupo de bacilos Gram-negativos cujo habitat natural é o trato intestinal de seres humanos e animais. São anaeróbios facultativos, fermentam um grande número de carboidratos e possuem uma estrutura antigênica complexa constituída por lipopolissacarídeos, uma variedade de toxinas e outros fatores de virulência. Dentre as espécies incluídas na família, a ***Escherichia coli*** além de estar presente em diferentes nichos ecológicos, destaca-se como um dos mais importantes microrganismos entéricos relacionados à manutenção da fisiologia intestinal (EWING, 1986) e a um grande número de infecções intestinais e extraintestinais decorrentes da expressão de fatores de virulência específicos que algumas cepas possuem (HOLT, 1984).

Apesar da complexidade antigênica, a *E. coli* apresenta antígenos de superfície que possibilitam a sua classificação em sorogrupos e sorotipos bem definidos. Estudos realizados por Kauffmann (1947), já demonstravam a participação de determinados tipos de *E. coli* em surtos de diarréia em crianças, ressaltando a importância da identificação desse microrganismo através da caracterização dos seus antígenos de superfície. Esses antígenos são designados de somático ou antígeno O, capsular ou antígeno K e flagelar ou antígeno H (KAUFFMANN, 1947). Através de estudos sorológicos empregando reações de aglutinação com antisoros específicos, já foram identificados mais de 180 antígenos O em *E. coli*. Em adição, 100 antígenos K e pelo menos 60 antígenos H também foram descritos, possibilitando uma grande variedade de combinações. (CAMPOS; FRANZOLIN; TRABULSI, 2004).

Os antígenos O determinam os sorogrupos O e a combinação destes com os antígenos H determinam os sorotipos. Os antígenos K, com algumas exceções, não são usados na identificação de sorogrupos O ou de sorotipos. Além disso, alguns sorogrupos podem ser divididos em subgrupos em virtude de apresentarem frações antigênicas comuns e diferentes, do tipo ab/ac, por exemplo: *E. coli* O111ab, O111ac (EWING; DAVIS; MONTAGUE, 1963; ZULIANI; TRABULSI, 1969, SANTOS; 2002).

As amostras causadoras de infecções intestinais, chamadas *E. coli* diarreiogênicas (DEC), são atualmente classificadas em 6 patótipos: *E. coli* enteropatogênica (EPEC), *E. coli* enterotoxigênica (ETEC), *E. coli* enteroinvasora (EIEC), *E. coli* produtoras da toxina de Shiga (STEC), *E. coli* enteroagregativa (EAEC) e *E. coli* que apresenta padrão de adesão difusa em células epiteliais (DAEC) (KAPER; NATARO; MOBLEY, 2004). Esta classificação tem por base os mecanismos de patogenicidade (fatores de virulência específicos), síndromes clínicas, características epidemiológicas e/ou interação com linhagens celulares (NATARO; KAPER, 1998).

Essa classificação é capaz de distinguir grupos específicos de DEC, mas vários estudos têm demonstrado que um patótipo possui amostras com distintos perfis de virulência. Assim, as EPEC e as EAEC são atualmente divididas em típicas e atípicas e as STEC (*E. coli* produtoras da toxina de Shiga) contém a subcategoria conhecida como *E. coli* enterohemorrágica (EHEC) (KAPER; NATARO; MOBELEY, 2004).

A denominação *E. coli* enteropatogênica (EPEC) foi dada por Neter et al. (1955) a um grupo de cepas identificadas como o agente etiológico de diarréia em crianças, com base somente em dados epidemiológicos, resultados de tipagem sorológica e estudos em voluntários. Foi em 1995, no segundo Simpósio Internacional de EPEC realizado na cidade de São Paulo, Brasil, que estas passaram a ser classificadas como EPEC típicas ou

EPEC atípicas respectivamente, de acordo com a presença ou ausência do plasmídio "EPEC adherence factor" (EAF) (KAPER, 1996).

Tradicionalmente, as amostras de EPEC são inseridas nos seguintes sorogrupos: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142 e O158 (WORLD HEALTH ORGANIZATION, 1987). Estudos fenotípicos e moleculares demonstraram que esses sorogrupos são bastante heterogêneos, uma vez que amostras de um mesmo sorogrupo apresentam propriedades de virulência distintas que as colocam dentro de outras categorias de *E. coli* diarreiogênicas (CAMPOS et al., 1994; RODRIGUES et al., 1996; GOLÇALVES et al., 1997). De fato, atualmente sabe-se que esses clássicos sorogrupos compreendem amostras de EPEC típicas (t-EPEC) e EPEC atípicas (a-EPEC), assim como outros patótipos de DEC (TRABULSI; KELLER; GOMES, 2002). Um exemplo típico dessa heterogeneidade é o sorogrupo O111 que compreende amostras de EPEC típica, EPEC atípica, EHEC e EAEC (CAMPOS et al., 1994).

Desde a década de 40, as EPEC são apontadas como um dos principais agentes de diarréia em crianças com idade inferior a um ano nos países em desenvolvimento, causando morte de milhões de crianças na Ásia, África e nas Américas (LEVINE et al., 1993; ALBERT et al., 1995; ALBERT, 1996; CRAVIOTO et al., 1996; TORRES et al., 2001). No Brasil, as EPEC são responsáveis por mais de 30% dos casos de diarréia (TOLEDO et al., 1983; TRABULSI et al., 1985; LEVINE, 1987; GOMES et al., 1998).

A patologia das EPEC é caracteristicamente marcada pela produção de uma lesão histopatológica na célula intestinal denominada "attaching and effacing" (A/E) (MOON et al., 1983; NATARO; KAPER, 1998). A lesão A/E se manifesta na destruição das microvilosidades intestinais, adesão íntima e acentuada reorganização das proteínas do citoesqueleto dos enterócitos, culminando com o surgimento de estruturas na forma de pedestais sobre as quais a EPEC encontra-se intimamente aderida

(NATARO; KAPER, 1998). As moléculas efetoras responsáveis por todos esses processos são proteínas codificadas por genes localizados em uma ilha de patogenicidade chamada LEE ("locus of enterocyte effacement") (McDANIEL et al., 1995).

As t-EPEC são definidas como amostras de *E. coli* diarreiogênicas capazes de produzir a lesão A/E, por possuírem o gene *eae* ("EPEC attaching and effacing") localizado em LEE, por não expressarem a toxina de Shiga (Stx) e por possuírem o plasmídio EAF ("EPEC adherence factor") contendo os genes que codificam a fímbria BFP ("Bundle-Forming Pillus"). Além disso, as t-EPEC não apresentam fatores de virulência adicionais aos genes de LEE, exceto amostras do sorotipo O86:H34 que produzem citotoxina letal distensora – CDT (GHILARDI, 1999) e os sorotipos O55:H6 e O127:H6, que expressam a toxina EAST-1 ("enteroaggregative *E. coli* heat-stable toxin"). Outra importante característica das t-EPEC é o padrão de adesão às células epiteliais, conhecido como aderência localizada (LA). Os principais representantes das t-EPEC são os sorotipos O55:H6, O111:H2, O114:H2, O119:H6, O127:H6 e O142:H34 (TRABULSI; KELLER; GOMES, 2002).

As a-EPEC são definidas pela ausência do plasmídio EAF e presença do gene *eae* (KAPER, 1996). Diferentemente das t-EPEC, podem expressar fatores de virulência não codificados na região LEE (TRABULSI; KELLER; GOMES, 2002; HERNANDES et al., 2009). Segundo Trabulsi; Keller; Gomes (2002), há dois grupos de a-EPEC: um grupo que expressam fatores de virulência codificados exclusivamente na região LEE e outro que expressa fatores adicionais aos codificados em LEE. Cita-se como exemplo a expressão da toxina EAST-1 por amostras dos sorotipos O26:H11, O128ac:H2, O55:H7 e O119:H2 e enterohemolisinas E-hly ("EHEC hemolysin") por amostras dos sorotipos O119:H9, O26:H11, O111:H8 e O128:H2 (TRABULSI; KELLER; GOMES, 2002; CAMPOS et al., 2004).

Outra característica que distingue as a-EPEC é o padrão de adesão em cultura de células epiteliais. Enquanto as t-EPEC apresentam unicamente o padrão de adesão AL, as atípicas podem apresentar a adesão conhecida como LAL ("localized-like adherence") (RODRIGUES et al., 1996), DA ("diffuse adherence") ou AA ("aggregative adherence") (TRABULSI; KELLER; GOMES, 2002; ABE et al., 2009; HERNANDES et al., 2009). O padrão de aderência LAL é característico da maioria dos sorotipos de a-EPEC e é mediado principalmente pela adesina intimina, codificada pelo gene *eae* (PELAYO et al., 1999). Os principais sorotipos de a-EPEC, pertencentes aos sorogrupos clássicos de EPEC, são: O26:H11, O55:H7, O55:H34, O86:H8, O111:H8, O119:H9, O111:H25, O119:H2, O125:H6, O128:H2 (TRABULSI; KELLER, GOMES, 2002).

Estudos recentes demonstraram um relativo aumento na incidência de a-EPEC no Brasil e um declínio na freqüência de sorotipos EAF positivos (TRABULSI; KELLER; GOMES, 2002). De fato, estudos epidemiológicos recentes demonstraram que as a-EPEC configuram um grupo emergente de patógenos (FERNANDES-FILHO, 2004; GOMES et al., 2004; FRANZOLIN et al., 2005; BUERIS et al., 2007; ARAUJO et al., 2007).

Estudos filogenéticos apontam as a-EPEC como evolutivamente mais próximas de EHEC (TRABULSI; KELLER; GOMES, 2002; BANDO et al., 2009), o que sugere a possibilidade de que genes plasmidiais ou cromossômicos homólogos aos de EHEC possam ser encontrados em a-EPEC. Salvo alguns estudos que procuraram caracterizar fatores ou mecanismos de virulência das a-EPEC (PELAYO et al., 1999; VIEIRA et al., 2001; DULGUER et al., 2003; SCALETSKY et al., 2005; BAl et al., 2007; HERNANDES et al., 2008; MOREIRA et al., 2008), a maioria dos estudos sobre a-EPEC restringem-se a caracterizações epidemiológicas, determinação de sorotipos e potenciais fatores de virulência.

Apesar dos vários estudos, até o momento não foi descrito nenhum marcador de virulência específico das a-EPEC, bem como nenhum plasmídio comum entre amostras desse grupo de patógenos foi identificado. Sabe-se que amostras de a-EPEC não possuem EAF ou pelo menos não o possuem em sua completa seqüência genética. Algumas amostras abrigam plasmídios contendo grupos de genes similares ao EAF, mas os genes *bfp* e *per,* requeridos para o estabelecimento da adesão AL estão mutados ou inativos (OKEKE et al., 2000; NWANESHIUDU et al., 2007). Esses plasmídios podem, além da resistência a antibióticos, conferir vantagens adaptativas ou de virulência as a-EPEC, mas não existem muitos estudos na literatura sobre o perfil ou caracterização de plasmídios de a-EPEC, o que poderia vir a ser uma importante contribuição para o entendimento da patogênese deste grupo de patógenos.

7 CONCLUSÃO

Em relação às amostras de a-EPEC estudadas, os resultados apresentados neste estudo permitiram as seguintes conclusões:

- Genes de virulência descritos em outros patótipos de DEC podem ser detectados em a-EPEC e não foi encontrado nenhum marcador genético específico para as amostras de a-EPEC estudadas.
- A maioria das a-EPEC possui plasmídios de alto peso molecular.
- Os grupos de incompatibilidade IncF e IncFIB foram os mais freqüentes nas amostras analisadas.
- Amostras do mesmo sorotipo possuem perfil plasmidial muito similar.
- Plasmídios de a-EPEC podem conter sequências de DNA similares ao pO157.
- Existem sequências homólogas entre o plasmídio pMFS320 e os plasmídios de diferentes amostras de a-EPEC.
- O plasmídio pMFS320 e pO157 possuem sequências homólogas.

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