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大肠杆菌鞭毛调控基因 flhDC 与生物材料植入感染的研究进展 *

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摘要:随着生物材料被广泛应用于临床,生物材料植入感染成为令人棘手的常见医院内感染,有报道占院内感染的 50%,大肠杆菌是临床以生物材料为中心感染的优势菌种。生物材料表面的细菌生物膜使其膜内细菌能有效抵御抗生素治疗和机体的防御反应,是导致生物材料为中心感染难以控制的根源。大肠杆菌的运动性与细菌生物膜形成密切相关,鞭毛是大肠杆菌的运动器官,鞭毛的生成需要三级基因的表达,操纵子 flhDC 编码鞭毛生成的一级主调控基因。我们推测:"鞭毛调控基因 flhDC 的表达→鞭毛的生成→细菌的运动性→细菌生物膜形成"之间存在着一一对应的关系,这为临床防治生物材料植入感染提供新思路。本文就以大肠杆菌鞭毛调控基因 flhDC 与生物材料植入感染做一简要综述。

关键词:大肠杆菌;flhDC;生物材料植入感染;细菌生物膜

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Progress on Biomaterial Centered Infection and *Escherichia coli*'s Flagella Regulator Genes flhDC*

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ABSTRACT: As Biomaterials has been widely used in clinical, BCI (Biomaterial centered infection) has already become a serious problem in Nosocomial Infection. It was reported that, the BCI accounts for 50% Nosocomial Infection. *Escherichia coli* (*E.coli*) is one of the most common microorganisms associated with BCI. The formation of Bacterial biofilm (BF) on the surface of Biomaterials is the main reason that BCI can't be controlled. In the BF state, microorganisms are relatively immune to antibodies and resistant to conventional antimicrobial agents. The motility of *E.coli* is closely related to BF formation, and flagella is the sport organs of *E.coli*. The generation of flagella need 3 levels gene expression, and operon flhDC is the first level and master control gene. We speculate that: There are one-to-one relationship with The expression of operon flhDC→The generation of flagella→The motility of *E.coli*→Bacteria biofilm formation, which provides new ideas for clinical prevention and treatment of IAI. In this paper, in order to make a brief review on the relationship of *E.coli*'s flagella regulator genes flhDC and Implant-Associated Infection caused by *E.coli*..

Key words: *Escherichia coli* (*E.coli*); flhDC; Implant-Associated Infection (IAI); Bacterial biofilm (BF)

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前言

随着生物材料广泛应用于临床, 生物材料植入感染(Biomaterial centered infection.BCI)成为常见医院内感染[1]。细菌可伴随生物材料(Biomaterials)的植入侵入机体,黏附于生物材料表面形成生物膜,由于生物膜的存在,一旦发生 BCI,抗生素难以渗透至膜内,造成感染反复发作,是临床 BCI 难以控制的主要原因[2]。

大肠杆菌是人体肠道中的条件致病菌,在手术控制性降压或失血性休克期间,大肠杆菌可侵入血液,在生物材料表面黏附形成生物膜,是临床 BCI 的优势菌种。鞭毛是大肠杆菌的运动器官,其介导的运动性和黏附性在大肠杆菌生物膜形成过程中发挥重要作用[3]。鞭毛的生成需要三级基因的表达,操纵子 flhDC 编码鞭毛生成的最高级调控基因 flhDC[4]。我们推测:flhDC 通过调控鞭毛的生成,影响大肠杆菌的运动性进而对生物膜形成产生影响。这为本课题研究提供新思路:以 flhDC 基因及其调控途径为靶点,抑制 flhDC 表达,影响鞭毛的生成,减少细菌生物膜形成。

1 大肠杆菌导致的生物材料植入感染(Biomaterial centered infection caused by *Escherichia coli*)

生物材料(Biomaterials)是指一类与人体组织、体液或血液直接接触和相互作用,不凝血、不溶血以及不引起细胞突变、畸

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变和癌变，能对机体的细胞、组织和器官进行诊断、治疗、替代、修复、诱导再生或增进其功能的材料[5-7]。

随着材料科学的不断发展，生物材料被广泛应用于临床，以生物材料为中心的感染（BCI）已经成为医院内感染领域非常棘手的问题，有报道占医院内感染的 50%，常常给患者带来灾难性后果[8,9]。大肠杆菌是临床生物材料植入感染的优势菌种，在心脏瓣膜置换术、关节置换术、脑室腹腔分流术等术后生物材料植入感染中大肠杆菌检出率为 3～10%[10-13]。

大肠杆菌是人体肠道中的条件致病菌，心脏大血管手术体外循环期间、神经外科或骨科等手术控制性降压期间、以及临床上常见的失血性休克，均可导致肠道屏障作用减弱、肠通透性升高，大肠杆菌穿透肠壁进入淋巴系统或血液系统，形成肠道大肠杆菌移位，造成菌血症，血液中的细菌为细菌在生物材料表面黏附提供菌源[14,15]。大肠杆菌在生物材料表面一旦形成生物膜，就为大肠杆菌提供保护膜，使其能有效抵御机体的防御反应和抗生素的治疗，导致临床大肠杆菌相关的 BCI 难以控制[16]。

2 大肠杆菌鞭毛调控基因 flhDC 与细菌生物膜形成

2.1 大肠杆菌生物膜的形成

细菌生物膜（Bacterial biofilm, BF）是指细菌在生长过程中附着于物体表面，其内分泌多种蛋白多糖复合物（主要是胞外多糖），使细菌相互粘连并包裹其中而行成的具有一定功能的膜状结构复合体[17]。细菌生物膜形成是一个动态的过程，研究[18,19]发现：细菌生物膜的形成要经历 " 黏附→聚集及生长→成熟→脱落 " 四个阶段。细菌黏附是细菌生物膜形成的第一步，细菌黏附于生物材料是造成生物材料植入感染的始动环节。见图 1。

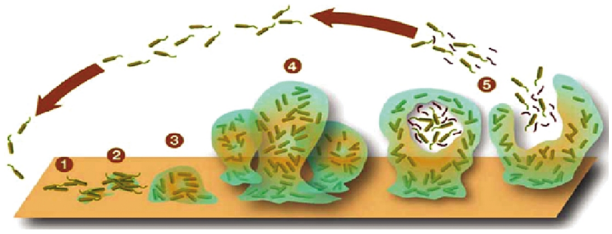

图 1 细菌生物膜的形成过程及活动周期

Fig.1 The formation of bacterial biofilm

Note: ① Attachment of bacteria;② Swarming of bacteria;③ Growth of biofilm ;④ Mature biofilm;⑤Bacterial shedding.

Fig.1 is quoted from P stoodley.et al.Ann.Rev.in Micro 2002.56

2.2 大肠杆菌鞭毛在生物膜形成中的作用

细菌的运动性具有重要的生态学和病理学意义，对于大肠杆菌来说，其运动性在细菌生物膜形成中是必需的[20,21]。鞭毛是大肠杆菌最主要的运动器官，介导大肠杆菌的黏附、运动和趋化，帮助细菌附着于宿主体内并迁移到营养物质丰富的位置去。Thomas K 等通过构建大肠杆菌鞭毛调控及结构蛋白缺失菌株，证实鞭毛缺失的大肠杆菌运动性大幅下降[22]。此外，多个研究发现除了运动性，鞭毛对于很多胃肠道致病菌的侵袭来说也是必须的，细菌鞭毛既可以作为粘附的动力装置，又能分泌毒力因子，其介导的运动性在细菌移位中起到重要作用[23]。

2.3 flhDC 操纵子调控细菌鞭毛的生成

有超过 50 个基因参与调控细菌鞭毛的生成以及细菌的运动，这些基因分布在 10 多个操纵子上，通过 3 个等级进行调控，只有在上一级调控基因的激活的条件下，下级调控基因才能够表达。flhDC 操纵子位于鞭毛运动调节子三级调控系统的最高等级。flhDC 是调控鞭毛基因表达的主调控因子[4,24]。还有研究[25]表明，flhDC 不仅是调控鞭毛基因表达的主调控因子，而且是一个具有广泛调节功能的调控蛋白，是控制鞭毛生物合成，细菌细胞分裂和毒力因子表达的整体调节因子。

3 大肠杆菌鞭毛调控基因 flhDC 表达的调控

3.1 温度调控大肠杆菌鞭毛调控基因 flhDC 的表达

大肠杆菌鞭毛调控基因 flhDC 的表达受到各种生理及环境因素的调控[26-29]。温度是非常重要的环境因素。研究表明：人类正常体温（37℃）促进大肠杆菌鞭毛调控基因 flhDC 的表达，低体温（≤ 23℃）抑制其表达[30,31]。

3.2 密度感应系统（QS）调控 flhDC 的表达

密度感应系统（Quorum sensing system. QS）可以调控多种细菌的运动性[32]。大肠杆菌密度感应调节子 C(quorum sensing E.coli regulator C, QseC) 是双组分调控系统 QseBC 的一部分，QseC 与自诱导物 -3（AI-3）、肾上腺素（EPI）或者去甲肾上腺素（NE）结合后，发生自身磷酸化作用，磷酸化后的 QseC 与 QseB 相互作用，QseB 将激酶上的磷酸基团转移到自身天冬氨酸位点上，发生自身磷酸化，并激活效应区，使其构象改变而暴露 DNA 结合位点，结合靶 DNA 序列，从而激活鞭毛主调控操纵子 flhDC 的转录[33-35]。

我们的研究项目：81260228- 大肠杆菌密度感应调节子 C (QseC)在生物材料植入感染中的作用研究[36]发现：① 大肠杆菌 QseC 基因与鞭毛泳动能力相关，QseC 缺失后运动能力显著下降，同时 QseC 信号链中断，细菌对肠粘膜的侵袭力和穿透力减弱，导致细菌移位发生率下降；② 大肠杆菌 QseC 对生物材料表面细菌生物膜的形成具有促进作用，QseC 缺失后，生物材料表面大肠杆菌的细菌群落减少、生物膜厚度降低。

4 总结与展望

综上所述，大肠杆菌鞭毛介导的运动性在大肠杆菌生物膜形成中发挥重要作用，操纵子 flhDC 是编码鞭毛生成的一级主调控基因 flhDC，将来有望以大肠杆菌 flhDC 基因及其调控途径为靶点，通过抑制 flhDC 基因表达，影响大肠杆菌鞭毛的生成，下调细菌的运动性，从而抑制大肠杆菌在生物材料表面形成生物膜，这为临床防治大肠杆菌相关生物材料植入感染提供新的思路。

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