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Niche Factors of Nondiphtherial Corynebacteria in Invasive Human Infections: Traitors Rather Than Friends

Panagiota Xaplanteri[1]* and Charalampos Potsios[2]

[1]*General Hospital of Eastern Achaia, Department of Microbiology, Aigio, Greece.*

[2]*Department of Internal Medicine, University General Hospital of Patras, Patras, Greece.*

***Correspondence:**
Panagiota Xaplanteri, General Hospital of Eastern Achaia, Department of Microbiology, Aigio, Greece.

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ABSTRACT

Background: *The genus Corynebacterium includes Nondiphtherial Corynebacterium species, mostly opportunistic human pathogens. Different virulence factors have been described for, like pili, microcapsule, cell wall structure, pathogenicity enzymes, and toxins. The aim of this article is to quote the major niche factors of Corynebacterium jeikeium, Corynebacterium ulcerans, Corynebacterium pseudotuberculosis, and Corynebacterium amycolatum strains isolated from invasive human infections.*

Conclusions: *Different components of nondiphtherial corynebacteria can act as potent virulence factors dependent on host-bacterium interactions. Their surface proteins lead to successful colonization of human host cells. Their ability to uptake genes that promote multidrug antibiotic resistance renders them a threat under specific milieu. Identification to species level is also crucial to monitor invasive human infections.*

Keywords

Nondiphtherial *Corynebacteria*, Invasive human infections, Opportunistic pathogen, *Corynebacterium jeikeium*, *Corynebacterium ulcerans*, *Corynebacterium pseudotuberculosis*, *Corynebacterium amycolatum*.

Introduction

The genus *Corynebacterium* includes gram-positive bacteria with more than 110 species. These species show different metabolic requirements, shape, and milieu preference [1,2]. As most strains are opportunistic human pathogens, their virulence factors are better described as niche factors that is they play significant role in the microbe pathogenicity in a certain environment and in combination with other proteins of the bacterium [3].

Nondiphtherial *Corynebacteria* are often misidentified or underestimated when isolated from human samples, thus leading to insufficient phenotypic profiles and inappropriate therapeutic interventions [4]. As some members of the genera demonstrate multidrug resistance to antibiotics, accurate phenotypic profiles of antimicrobial susceptibility are crucial [4]. Different virulence factors have been described for Nondiphtherial *Corynebacterium* species, like pili, microcapsule, cell wall structure, pathogenicity enzymes, and toxins [5]. The aim of this article is to quote the major niche factors of *Corynebacterium jeikeium, Corynebacterium ulcerans, Corynebacterium pseudotuberculosis*, and *Corynebacterium amycolatum* strains isolated from invasive human infections.

Main text

2a. *Corynebacterium jeikeium* is part of the normal flora of human skin. Nowadays it is considered the culprit of severe nosocomial infections. Most labile to *C. jeikeium* infections are immunocompromised patients in nosocomial settings, especially the Intensive Care Unit, with underline malignancies, and therapy with broad-spectrum antibiotics. These strains express a multiresistant phenotype. Worldwide, these strains are reported to be susceptible only to glycopeptides, such as vancomycin and teicoplanin [3,6]. Surface proteins surA and surB, encoded by *jk2032* and *jk0220* genes respectively, are like surface proteins of

group A and group B *Streptococcus*. Their role is binding of the bacterium to human epithelial cells. These proteins in *C. jeikeium* K411 promote phenotypic diversity. As a result, the microbe changes its antigenicity and escapes host immune system [6].

C. jeikeium K411 also possesses the genes (*jk1700 [srtA] and jk0103 [srtB])* class II encoding sortases leading to the formation of adhesive pili anchored to the bacterial cell wall. This enhances adhesion and colonization of the bacterium in the initial stage of bacterial infection [1,6]. The CbpA protein of *C. jeikeium* K411, product of the *cbpA* gene and member of the microbial surface components recognizing adhesive matrix molecules family, promotes adhesion to host collagen-rich tissues and is thus related to initialization of colonization [6]. The *jk0448 (nanA)* gene encodes NanA protein which has similar action to neuraminidases of *Streptococcus pneumoniae*, leading to host tissue damage [6]. The *jk1103 (asa) gene* encodes an alkaline ceramidase, a lipolytic enzyme that promotes the release of sphingosine from ceramides. Sphingosine is related to downregulation of macrophages and provides the bacterium sufficient fatty acids as nutrients [6]. The *jk0629 (choE)* gene encodes a cholesterol oxidase that is a cytotoxic and macrophage-destroying factor of *Rhodococcus equi*. Cholesterol oxidation leads to disorganization of the eukaryotic plasma membrane [6]. The *jk2054 (che)* gene encodes a secreted cholesterol esterase that hydrolyses the long-chain fatty acid esters from cholesterol [6]. The *jk0010 (acpA)* encodes an acid phosphatase with phospholipase C activity, that shows similarity to the AcpA protein of *Francisella tularensis*. Acid phosphatases suppress the respiratory burst of human neutrophils of intracellular pathogens, but their role in extracellular pathogens needs further elucidation [6]. Plasmid pKW4 of C. jeikeium K411 encodes a bacteriocin-like substance with a narrow spectrum of bactericidal activity against other *Corynebacteria species* giving the bacterium predominance over host skin colonization [6].

2b. *C. ulcerans*: virulence factors other than diphtheria toxin (DT) The encoding gene of the putative ribosome-binding protein with significant structural similarity to the A chain of Shiga-like toxin (SLT-1) from *Escherichia coli* has been described in the *C. ulcerans* strain 809 isolated from an 80-year-old woman with fatal pulmonary infection [7]. This *rbp* gene encodes a putative conserved ribosome-binding protein (Rbp). This protein displays the catalytic N-glycosidase activity of Shiga-like toxin, which is cleavage of an adenine from the 28S rRNA of the 60S ribosome. As a result, the 28S rRNA is unable to interact with the elongation factors EF-1 and EF-2, which leads to interruption of protein synthesis and cell death by apoptosis [7,8]. Data support acquisition of the *rbp* gene by *C. ulcerans* 809 by horizontal transfer [7].

Phospholipase D (PLD) is a major virulence factor of *C. ulcerans*, encoded by *pld* gene for phospholipase D [3,7]. It is a secreted exotoxin that functions as a sphingomyelinase, hydrolyzing albumin-bound lysophosphatidylcholine [3]. Lysophosphatidic acid that occurs induces pro-inflammatory responses [8]. Sphingomyelin depletion has catastrophic effects on infected erythrocytes and neutrophils [9]. Moreover, PLD increases vascular permeability, thus enabling bacterial dissemination [3].

The *cpp* gene *(CULC809, 01974* and *CULC22_02125)* encodes corynebacterial protease CP40. The amino acid sequences of *C. ulcerans* Cpp is similar to the a-domain of the extracellular endoglycosidase EndoE from *Enterococcus faecalis*, which hydrolyses the conserved glycans on IgG [8].

C. ulcerancs's neuraminidase H (NanH) shows neuraminidase and trans-sialidase activities enabling the invasion of host cells [8]. *C. ulcerance* sialidase modifies host sialic acids and use them to decorate their own cell surface. In this way the bacterium fools the host immune mechanisms [10].

Subunits of adhesive pili of the SpaDEF type: Interaction of adhesive pili with receptors of the host cell surface facilitates intracellular invasion. Two gene clusters are involved. The first gene cluster is like the *spaDEF* gene region of *Corynebacterium diphtheriae NCTC 13129* encoding the Spa-DEF pilus [8].

Serine proteases: The *tspA, vsp,* and *vsp2* genes encode serine protease type proteins that help the bacterium survive in unfavorable milieu [8]. C.ulcerans also expresses a protein with 58% similarity to the RhuM virulence factor of *Salmonella enterica*. Inactivation of this protein reduces the virulence of the strain [10]. *C. ulcerans* can proliferate in macrophages within the first hours of internalization [7]. Interaction with human THP-1 macrophages with *C. ulcerans* strain 809 revealed that the microbe can survive in macrophages for at least 20 hours by delaying phagolysosome maturation. The underlying mechanism still needs elucidation [10].

2c. *C. pseudotuberculosis*

Phospholipase D (PLD) is a potent virulent factor of *C. pseudotuberculosis*. *C. pseudotuberculosis* and *C. ulcerans* are the only members of *Corynebacteria* to possess phosholipase D. PLD promotes invasion of the bacteria from the initial infection sites and is involved in macrophages killing [10,11]. Phospholipase D is expressed at a high level by *C. pseudotuberculosis* within macrophages [12]. Intracellular Pld destructs macrophage membranes and activate host cell signaling pathways that lead to macrophage malfunction and death [12]. Antibodies against PLD can inhibit the bacterial spread in host tissues and induce protection via vaccination [13,14].

C. pseudotuberculosis also possesses sialidases with the same characteristics as *C.ulcerans*'s [10]. These proteins detach host sialic acids and display them on their cell surface to evade host immune mechanisms [10].

The endo-b-N-acetylglucosaminidase protein (CP40) is detected in *C. pseudotuberculosis* culture supernatants [11]. Mice vaccination with this protein revealed high protection rates [15,16]. Neuraminidase H (NanH) is present on the surface of many *C.*

pseudotuberculosis strains and can be secreted [11]. Sortases are related to the adhesive pili synthesis in *C. pseudotuberculosis* FCR41. These pili are constructed by the major pilin, SpaA and SpaD; minor pilin, SpaB and SpaE; and tip pilin, SpaC, SpaF [3]. SpaC is a protein located at the tip of the pili of *C. pseudotuberculosis strains* and shares similarities in structure and physiology with the respective one of *C. diphtheriae*. The same protein promotes adhesion of *C. diphtheriae* to human pharyngeal epithelial cells [2]. *C. pseudotuberculosis* FCR41 also expresses a housekeeping sortase (srtD), responsible for the pili anchorage to the cell wall [1]. The *phoP* gene encodes the PhoP protein from *C. pseudotuberculosis* Cp1002, that enhances host cell adhesion [17]. The *Cp1002_0988 gene*, during adhesion process is located within one of the pathogenicity islands and displays high expression levels in comparison to control [18].

2d. C. amycolatum is normally human skin and mucosal membranes flora [4]. The *rpsL* gene, containing mutations similar to those of streptomycin-resistant *Mycobacterium tuberculosis* isolates has been identified in many studied strains [4].

C. amycolatum strains possess 17 genes involved in iron acquisition. *C. amycolatum* strain NCTC7243 possesses the operon ciuABDE, coding for an ABC-type siderophore transporter system [19]. Other strains possess the fagABCD operon, coding for iron-siderophore transport through the membrane [20]. The *gene hmuU* involved in the heme-transporter system hmuTUV of *C. diphtheriae* and *C. Ulcerans* is present in all *C. amycolatum* strains [21]. The *vctC* gene that belongs to vctPDGC heme-transportation system in *Vibrio cholerae* is also part of *C. amycolatum* genome [22]. The *genes mbtI* from *Mycobacterium tuberculosis* and *fxbA* from *Mycobacterium smegmatis* involved in siderophore biosynthesis pathways have also been described in *C. amycolatum* strains [4]. Genes encoding SpaD-like pili are present in most *C. amycolatum* isolates. Proteins SpaD, SpaE, and SpaF represent the adherence structure that is anchored to the bacterial surface with the help of sortases SrtB and SrtC [23]. The same machinery is used for biofilm formation [4].

Conclusions

Different components of nondiphtherial *Corynebacteria* can act as potent virulence factors dependent on host-bacterium interactions. Their surface proteins lead to successful colonization of human host cells. Their ability to uptake genes that promote multidrug antibiotic resistance renders them a threat under specific milieu. Identification to species level is also crucial to monitor invasive human infections.

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