



Insight of Genus *Corynebacterium*: Ascertaining the Role of Pathogenic and Non-pathogenic Species

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This review gathers recent information about genomic and transcriptomic studies in the *Corynebacterium* genus, exploring, for example, prediction of pathogenicity islands and stress response in different pathogenic and non-pathogenic species. In addition, is described several phylogeny studies to *Corynebacterium*, exploring since the identification of species until biological speciation in one species belonging to the genus *Corynebacterium*. Important concepts associated with virulence highlighting the role of Pld protein and Tox gene. The adhesion, characteristic of virulence factor, was described using the sortase mechanism that is associated to anchorage to the cell wall. In addition, survival inside the host cell and some diseases, were too addressed for pathogenic corynebacteria, while important biochemical pathways and biotechnological applications retain the focus of this review for non-pathogenic corynebacteria. Concluding, this review broadly explores characteristics in genus *Corynebacterium* showing to have strong relevance inside the medical, veterinary, and biotechnology field.

Keywords: *Corynebacterium*, bacterial genomics, bacterial biochemistry, pathogenesis related genes, biotechnology of microorganisms

INTRODUCTION

This review is limited to a general discussion of the genus *Corynebacterium* and its species. It includes specific information on the genes that are found in pathogenic strains compared to those that are non-pathogenicity. Various studies describe these bacteria as gram-positive (Hard, 1975; Dorella et al., 2006) but with shape, oxygen requirement, and environment of preference divergent dependent on specie, that constitute a very heterogeneous group. The genus *Corynebacterium*, which currently has more than 110 validated species, is highly diversified. It includes species that are of medical, veterinary, or biotechnological relevance (Bernard, 2012; Soares et al., 2013; Eikmanns and Blombach, 2014). In an examination of the diverse group to which these bacteria belong, this study describes the structural organization, function, and dynamism of genome. This review It also explores some important process, such as cell division, in order to improve the understanding of

this genus, the pathogenic processes that is directly associated with several diseases and symptoms and some biochemical pathways associated with biotechnology industry explored by the non-pathogenic species. In addition, this work explores genes and pathways that may play a role in pathogenesis, and compare them to those found in non-pathogenic strains. **Table 1** provides a list of the main species and important information about them, showing some species studied currently.

GENOMICS AND TRANSCRIPTOMICS

Next-generation high-throughput DNA sequencing techniques (Ansorge, 2009) combined with new computational advances in assembly, annotation, and comparative analysis have resulted in an explosion of data available for research biologists. This wealth of information has pushed the field of genomics beyond the examination of sequences from single isolates to the ability to look across hundreds of genomes simultaneously. This new comparative ability adds significant advantages, not only for looking at differences that may exist within specific isolates, but can also shed light on the evolutionary process at broad taxonomic levels (Alfo and Lindblad-toh, 2013). This increases our understanding of chromosomal structure and the role played by horizontal transfer (Ochman et al., 2000). Broad comparisons between bacteria that cause disease with their closest relatives can highlight the genes and sequences that play a role in pathogenicity (Cohen et al., 2015; Papaventsis et al., 2017).

The genus *Corynebacterium* includes a diverse number of species and strains. As of April 2017, the PATRIC database (Wattam et al., 2017) had 466 genomes from 83 separate species (**Supplementary Table 1**). Some characteristics that unite these different species include having a single, circular chromosome, originally projected to range from 2.5 to 3.1 Mb in size (Dorella et al., 2006), and a high GC content (Pinto et al., 2014). A close examination of the current data shows that the size of the genomes within *Corynebacterium* range from 1.84 (*C. caspium* DSM 44850, ARBM00000000.1) to 15.8 Mb (*C. striatum* strain BM4687, CTEG00000000.1). There is also a striking range in the GC content, from a low of 10.7 (*C. striatum* strain BM4687, CTEG00000000.1) to 74.7% (*C. sphenisci* DSM 44792, CP009248.1). Generally, *Corynebacterium* lack plasmids, although there are several strains that have 1 or 2 plasmids as part of their genome (**Supplementary Table 1**). They also vary in the number of coding sequences (CDSs) that they have. An examination of all available genomes (Wattam et al., 2017) shows an average of 2480.6 CDSs, with *C. caspium* DSM 44850 as the strain with the fewest called genes (1647) and *C. aurimucosum* strain 118_CAUR have the most (9489). These various genomes have been isolated both from environmental sources as well as from individual hosts, and has several important pathogenic members that include *C. diphtheriae*, *C. pseudotuberculosis*, and *C. ulcerans*.

Several studies have looked at the phylogeny of *Corynebacterium*, but only across a limited number of strains. A study (Pascual et al., 1995) did the first examination using 16S rRNA sequences and gave a direct comparison

of *Corynebacterium* to its closest relatives, that included *Mycobacterium*, *Gordona*, *Rhodococcus*, and *Norcardi*. This was followed by a study of 56 species (Khamis et al., 2004) that looked at examined phylogeny two separate genes (16S and *rpoS*) to try to identify the best method to define *Corynebacterium* species. A later study by the same authors showed that a partial *rpoB* sequence provided the best method for identification of corynebacteria (Khamis et al., 2005). Gao and Gupta expanded the number of sequences used to build a tree when they created looked at patterns across the phylum Actinobacteria, including 14 *Corynebacterium* isolates, using the RpoB, RpoC, and gyrase B proteins joined into a single consensus sequence (Gao and Gupta, 2012). None of the studies showed the same branching patterns, but there were similarities across each study, with the pathogenic species *C. diphtheriae*, *C. pseudotuberculosis*, and *C. ulcerans* all grouped together into a “pathogenic clade”. Including more genes in a similarity matrix also grouped these three species together (Soares et al., 2013). A strong phylogenetic analysis across this genus using a larger analysis including many more genes would resolve some of the differences seen between the earlier studies, and provide more insight into the evolution of the genus. Particularly, Phylogenetic approaches can be applied as methods for the identification of new species formation. It was a goal of a recent work showing events of biological speciation (Oliveira et al., 2016), among strains of the *C. pseudotuberculosis* species, in which it was proposed these strains could be under anagenesis process checking information such as: presence of biovar equi or ovis, evolutionary divergences, number of transition, and transversion substitutions and protein structure analysis.

Phylogenetic studies typically examined genes that are shared across all member, but several papers have described horizontal gene transfer as playing an important role in the evolution of *Corynebacterium*, particularly in terms of pathogenicity and virulence. A study of *C. pseudotuberculosis* identified seven islands that appeared to be linked to the pathogenicity of this species (Rocha et al., 2011). These islands included genes that have traditionally been associated with virulence, and these included iron uptake, secreted toxins, fimbrial subunits, and adhesion factors. This study was expanded, and six more islands were detected (Soares et al., 2013). Examination of *C. diphtheriae* also identified a number of pathogenicity islands (Trost et al., 2012), and these islands, which include the *tox* gene (Efstratiou et al., 2003), CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) regions (Vivian et al., 2012), and pilus gene clusters (Trost et al., 2012), are suggested to be a driving force in evolution and pathogenesis of this species (Sangal and Hoskisson, 2016). While most of the studies involving horizontal transfer have examined pathogenic strains, it has also been identified in non-pathogenic strains (Kalinowski et al., 2003). Surprisingly, an incidence of horizontal transfer of a region containing a prophage was found in *C. glutamicum* ATCC 13032, a non-pathogenic strain of industrial importance, whose source seemed to be *C. diphtheriae* (Kalinowski et al., 2003). This begs the question of whether the island is ancestral and lost in some members of *Corynebacterium*, or if it is a true transfer. A detailed genomic

TABLE 1 | A list of well-known *Corynebacterium* species and some of the significant features that define them.

Taxonomy	Pathogenesis	Number of genomes	Oxygen requirement
<i>C. accolens</i> (Ang and Brown, 2007; Wong et al., 2010)	Pelvic Osteomyelitis; Granulomatous Mastitis	2	Facultative
<i>C. ammoniagenes</i>		3	Anaerobic
<i>C. amycolatum</i>	Endocarditis; Sepsis	3	Aerobic
<i>C. argentoratense</i> (Riegel et al., 1995)	Tonsillitis	3	Unknown
<i>C. atypicum</i>		1	Facultative
<i>C. aurimucosum</i> (Lo et al., 2015)	Urinary tract infection	15	Facultative
<i>C. auriscanis</i> (Collins et al., 1999)		1	Aerobic
<i>C. bovis</i> (Burr et al., 2012)	Hyperkeratosis; Mastitis	1	Facultative
<i>C. callunae</i> (Persicke et al., 2015)	Non-pathogenic Amino acid production	2	Aerobic
<i>C. camporealensis</i>	Mastitis	2	Facultative
<i>C. capitovis</i> (Collins et al., 2001)		1	Anaerobic
<i>C. casei</i>	Non-pathogenic Food production	2	Facultative
<i>C. caspium</i>		1	Facultative
<i>C. ciconiae</i>		1	Anaerobic
<i>C. crenatum</i> (Xu et al., 2012; Su et al., 2015)	Non-pathogenic Amino acid production	2	Aerobic
<i>C. deserti</i>		1	Aerobic
<i>C. diphtheriae</i>	Diphtheria	86	Aerobic
<i>C. doosanense</i>		2	Facultative
<i>C. durum</i> (Riegel et al., 1997; James et al., 2011)		2	Facultative
<i>C. efficiens</i> (Odeniyi et al., 2017)	Non-pathogenic Laccases and Amino acid production	2	Facultative
<i>C. epidermidicanis</i> (Frischmann et al., 2012)		1	Facultative
<i>C. falsenii</i>		2	Facultative
<i>C. freiburgense</i>		1	Facultative
<i>C. freneyi</i> (Auzias et al., 2003; Funke and Frodl, 2008)	Bacteremia	1	Anaerobic
<i>C. genitalium</i>		1	Facultative
<i>C. glucuronolyticum</i>		2	Facultative
<i>C. glutamicum</i>	Non-pathogenic Food and Amino acid production	28	Facultative
<i>C. glycinophilum</i>	Non-pathogenic Amino acid production	1	Aerobic
<i>C. halotolerans</i> (Rückert et al., 2012)	Non-pathogenic	3	Aerobic
<i>C. humireducens</i>		2	Facultative
<i>C. imitans</i>		1	Unknown
<i>C. jeikeium</i>	Nosocomial infections	24	Facultative
<i>C. kropfenstedtii</i>		4	Facultative
<i>C. kutscheri</i>	Lung abscess	1	
<i>C. lactis</i> (Antunes et al., 2015)		1	Facultative
<i>C. lipophiloflavum</i>		1	
<i>C. lubricantis</i>		1	
<i>C. marinum</i>		1	Facultative
<i>C. maris</i>		1	Aerobic
<i>C. massiliense</i>		1	
<i>C. mastitidis</i>	Subclinical mastitis	1	
<i>C. matruchotii</i>	Oral infections	2	Aerobic
<i>C. minutissimum</i> (Granok et al., 2002)	Erythrasma	3	Facultative
<i>C. mustelae</i> (Funke et al., 2010)		1	Aerobic
<i>C. nuruki</i> (Shin et al., 2011)	Non-pathogenic Alcohol fermentation	1	Aerobic

(Continued)

TABLE 1 | Continued

Taxonomy	Pathogenesis	Number of genomes	Oxygen requirement
<i>C. pilosum</i>	Cystitis	2	
<i>C. propinquum</i> (Abdolrasouli and Roushan, 2013)	Urethritis	1	Facultative
<i>C. pseudodiphtheriticum</i> (Manzella et al., 1995; Martaresche et al., 1999)	Nosocomial Pneumonia; Bronchitis	2	
<i>C. pseudotuberculosis</i>	Caseous Lymphadenitis	71	Facultative
<i>C. pyruviciproducens</i> (Tong et al., 2010, 2012)	Non-pathogenic Pyruvic acid and ovalbumin production	1	Facultative
<i>C. renale</i> (Honda and Yanagawa, 1973)	Cystitis; Pyelonephritis	1	Facultative
<i>C. resistens</i> (Schröder et al., 2012)	Bacteremia	1	
<i>C. riegelii</i> (Funke et al., 1998)		1	Facultative
<i>C. simulans</i> (Wattiau et al., 2000)		3	Facultative Anaerobic
<i>C. singulare</i>		1	Facultative
<i>C. sp. ATCC</i>		124	
<i>C. sputi</i>		1	Anaerobic
<i>C. stationis</i>		4	
<i>C. striatum</i> (Sheldon and Coudron, 1990)	Endocarditis	3	
<i>C. terpenotabidum</i> (Rückert et al., 2013)	Non-pathogenic Squalene production	1	Aerobic
<i>C. testudinoris</i>		1	
<i>C. timonense</i> (Henrique et al., 2011; Merhej et al., 2016)		2	Facultative
<i>C. tuberculostearicum</i>		1	Anaerobic
<i>C. tuscaniense</i>		1	
<i>C. ulcerans</i> (De Zoysa et al., 2005b)	Pharyngeal Diphtheria	17	
<i>C. ulceribovis</i>	Ulceration	1	Anaerobic
<i>C. urealyticum</i>	Urinary tract infection	3	Aerobic
<i>C. ureicelerivorans</i>	Septicemia	1	Facultative
<i>C. uterequi</i>		1	Facultative
<i>C. variabile</i> (Schröder et al., 2011)	Non-pathogenic Food production	3	Aerobic
<i>C. vitaeruminis</i> (Al-Dilaimi et al., 2014)		3	Facultative
<i>C. xerosis</i>		2	

The source of information were obtained by PATRIC Database (Wattam et al., 2014) and updated with new bibliographical sources.

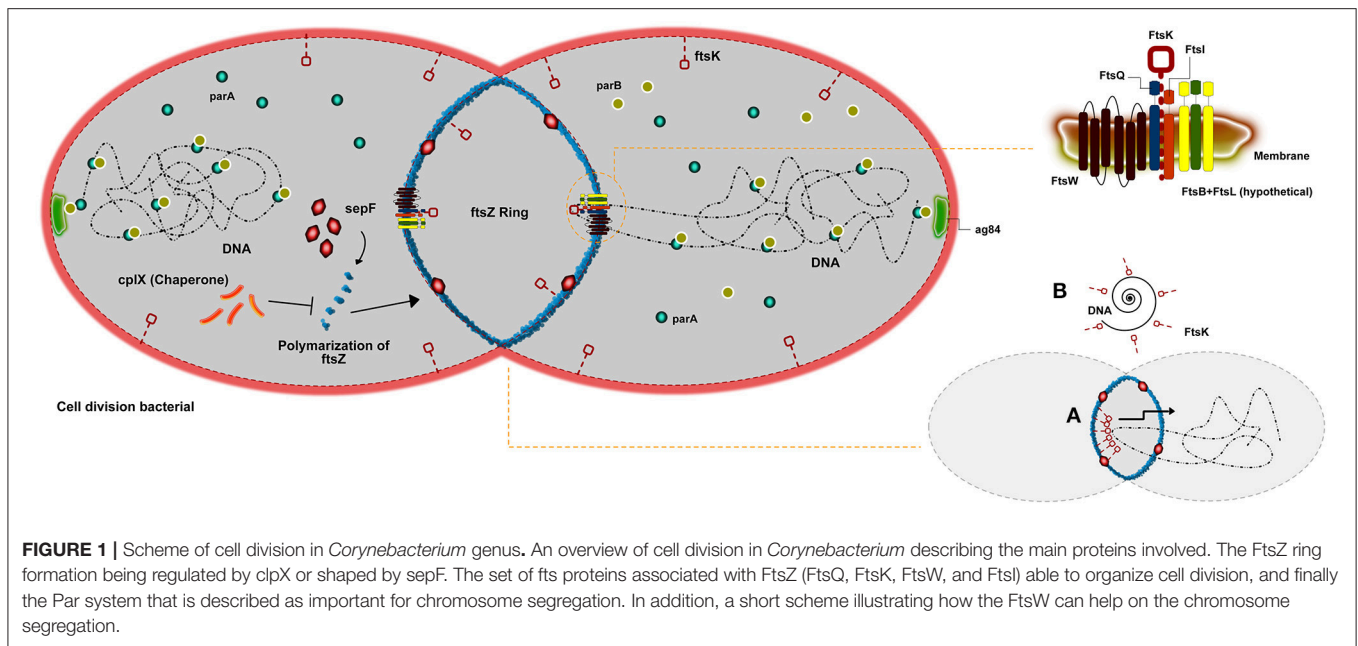
analysis across the genome could shed light on these types of incidents.

Studies that examine transcriptome in this genus are somewhat sparse, the majority of them examining the gene expression in *C. glutamicum*, which is not surprising considering the role it plays in the industrial production of amino acids (Lee et al., 2016). There are a number of microarray studies, a few that use RNA-Seq to examine transcription (Jiyoon et al., 2013; Mentz et al., 2013; Neshat et al., 2014; Sun et al., 2016; Albersmeier et al., 2017) and a single experiment that uses CHiP-seq (Jungwirth et al., 2013). There is a single study that looks beyond *C. glutamicum*. In order to analyze strains from *C. glutamicum* by RNA-seq in different degree of dissolved oxygen (DO) conditions in bioreactors, a recent work (Sun et al., 2016) showed how the DO effect could influence in the energy metabolism in this species. At a low DO rate, the glycolysis pathway was up-regulated effecting the over-production of amino acids, such as cysteine, arginine, and valine. This work has provided good ways to improve the oxygen acceptance by *C. glutamicum* in order to enhance the heterologous protein expression and amino acid production. In addition, (Pinto et al.,

2014) a work examined gene expression patterns that were altered by three different conditions such as acid, osmotic, and thermal shock stress of abiotic stress in *C. pseudotuberculosis*. Several genes were observed to be at the minimum a 2-fold change in expression levels, which could describe important genes associated with infectious function associated in virulence, defense against adhesion, regulation, and oxidative stress.

CELL DIVISION

Bacterial reproduction can be understood by ordered process in which cells increase in volume, duplicate genetic material, and isolate the newly formed DNA molecules (chromosomes) before detach the DNA to two daughter cells. Divisome is a known bacterial event resulting from the macromolecular machinery promoted by the order of DNA replication, chromosome segregation, and cytokinesis (Wu and Errington, 2011). A principal player involved in bacterial cell division in all bacteria is FtsZ. This protein initiates the polymerization of tubulin into a ring-like structure to start the divisome (Goehring and Beckwith, 2005). Some studies have demonstrated that FtsZ works in a



cooperative assembly, creating in a polymeric form, such as rings, bundles, tubules, and sheets that were observed depending on the experimental conditions used (Romberg et al., 2001; Caplan and Erickson, 2003; Chen et al., 2005). A pivotal factor of the Z ring cluster is the interaction between FtsZ and the cell membrane. However, FtsZ is a protein unable to interacting with the membrane alone, until more recent results. Because of this, all proposed models for Z ring assembly depend upon a setup of other molecules in order to attach it to the membrane (Erickson, 1997, 2001; Goehring and Beckwith, 2005; Dajkovic et al., 2008) (**Figure 1**). A study (Pichoff and Lutkenhaus, 2002) in *Escherichia coli* proposed that two proteins, FtsA and ZipA, work together in order to anchor FtsZ to the membrane. This evidence FtsZ-ZapA-ZipA could be observed in other bacterial types, such as *Bacillus subtilis* (Gamba et al., 2009). However, species from the genus *Corynebacterium* do not present sequences of either FtsA or ZipA in their genomes nor do they present homologs to them (Letek et al., 2007; Fiuza et al., 2008), which suggests that FtsZ assembly is accomplished by another protein or set of proteins. A study, using fluorescence and differential interference contrast micrographs, describes how FtsZ is able to interact with a setup of proteins in *Corynebacterium*, such as FtsQ, FtsW, FtsK, and FtsL. These proteins form a cluster of molecules on the membrane that recruit FtsZ in order to promote cytokinesis (Hale and De Boer, 2002). Although FtsA is essential for viability in *E. coli*, it is absent in *Corynebacterium* species. Another FtsZ-interacting protein, SepF (also named YlmF), is able to supersede FtsA in genus *Corynebacterium*, suggesting that FtsA and SepF have overlapping functions (Ishikawa et al., 2006). In *B. subtilis*, is mentioned that SepF protein is not pivotal for cell division, in which its overproduction could balance for the lack of FtsA (Ishikawa et al., 2006). However, another work exploring the role of SpeF in *Mycobacterium*—A homologous

genus to *Corynebacterium*—showed it is indeed essential for division (Gola et al., 2015). Nevertheless, the complete absence of SepF can harm the normal morphology of cells. The absence of both proteins is described as lethal to the cell (Ishikawa et al., 2006). The setup of proteins FtsQ-FtsW-FtsK-FtsL described, are membrane proteins with transmembrane domains. The function of some of these molecules on septum-formation is still not completely clear, although it has been proposed to be associated with shape formation, elongation, division, and sporulation (Alvarez et al., 1997; Mohammadi et al., 2011). Particularly, FtsK shows to act at the cell division septum in order to translocate DNA into the correct cellular compartment. Differently, associated regulation proteins cell division under stress conditions play a role on inhibits Z-ring formation are mentioned as highly conserved in a high amount of bacteria. In *Corynebacterium* the protein Clpx, that is a ATP-dependent protease, has been proposed inhibiting FtsZ polymer dynamics, either through degradation of the FtsZ monomers and polymers (Camberg et al., 2009) or by disassembling FtsZ polymers (Sugimoto et al., 2010). Chromosome segregation can also be explained by the genes parA and parB, which were previously described as important in cell control (Ginda et al., 2013). The same study showed that parA is able to interact with the polar growth determinant DivIVA, required for polar localization of the chromosome during sporulation (Sieger and Bramkamp, 2015), which in *Corynebacterium* is ag84. It is suggested that the Par system present an additional function in the replication procedure of DNA and too in the precision of the divisions sites, regarding the ParA-ParB Interactions already described during plasmid partitioning (Volante and Alonso, 2015). In addition, DNA damage can promote the inhibition of Z-ring formation, preventing the production of offspring with damaged genomes. Two proteins are responsible to control a response induced under

such conditions. When activated, the RecA protein is able to stop the DNA-binding capacity in connecting with LexA, causing its activation and leading to DNA autocatalytic cleavage.

MAIN FEATURES OF PATHOGENIC SPECIES

Associate Diseases and Epidemiology

Among all *Corynebacterium* species isolated from humans, a group of potentially toxigenic microorganisms associated to different infectious processes stands out: *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, and *Corynebacterium pseudotuberculosis*. These species can produce potent exotoxins, i.e., diphtheria toxin (DT) and/or phospholipase D. These exotoxins can be associated with a large number of diseases, for example diphtheria and caseous lymphadenitis (Tauch and Sandbote, 2014). The species *C. diphtheriae* is the most significant pathogen of this group, in which it was the primary cause of diphtheria, a disease that is almost eradicated from developed countries due to a universal vaccine that targets the diphtheria toxin (Galazka and Dittmann, 2000; Wagner et al., 2012). This toxin can also be produced by *C. ulcerans* and *C. pseudotuberculosis*. These species are zoonotic agents, historically thought to induce diseases in humans after contact with contaminated animals (Wagner et al., 2010; Dias et al., 2011; Bernard, 2012). Other *Corynebacterium* species associated with animal diseases include: *Corynebacterium amycolatum*, *Corynebacterium aquilae*, *Corynebacterium auriscanis*, *Corynebacterium bovis*, *Corynebacterium camporealensis*, *Corynebacterium canis*, and others (Tauch and Sandbote, 2014).

Diphtheria

Diphtheria is a notifiable disease and needs public health response to limit spread among patients (Bernard, 2005). This is a toxin-mediated disease which affects the region of the respiratory tract, generally characterized by the presence of an inflammatory pseudomembrane on the tonsils, oropharynx, and pharynx manifesting sore throat, fever, and some cases able to achieve death (Hadfield et al., 2000). The classic symptoms associated with the disease are lymphadenitis, dysphagia, headaches, sore throat, low-grade fever, and malaise (Bernard, 2005). This disease can cause kidney disease, neuritis, hearing loss, and myocarditis (Funke et al., 1997; Roux et al., 2004). The most common type of diphtheria can be caused by toxigenic strains of *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*. Zoonotic infection in humans is generally caused by *C. ulcerans* and *C. pseudotuberculosis*, whereas *C. diphtheriae* appears to be generally human specific (Wagner et al., 2010; Sangal et al., 2014). These are the only species in the genus capable of harboring a bacteriophage that carries DT-specific *tox* gene and potentially express DT (Holmes, 2000). *Tox* gene sequence is described highly conserved which confers the quality of toxoid vaccine response. The regulation of *tox* gene transcription is made by the DtxR regulon, which controls the balance of iron homeostasis (De Zoysa et al., 2005a; Trost et al., 2012). Some strains of *C. diphtheria*, *C. ulcerans*, or *C. pseudotuberculosis* lack *tox* gene, or have *tox* gene but no DT detectable, are

considered to be non-toxigenic (Efstratiou and George, 1999; Sangal and Hoskisson, 2016). Even considered as non-toxigenic, these strains, especially *C. diphtheriae*, can cause diseases, like pharyngitis and tonsillitis, endocarditis, septic arthritis, and osteomyelitis, in certain vulnerable populations (Funke and Bernard, 2011; Sangal and Hoskisson, 2016).

Caseous Lymphadenitis

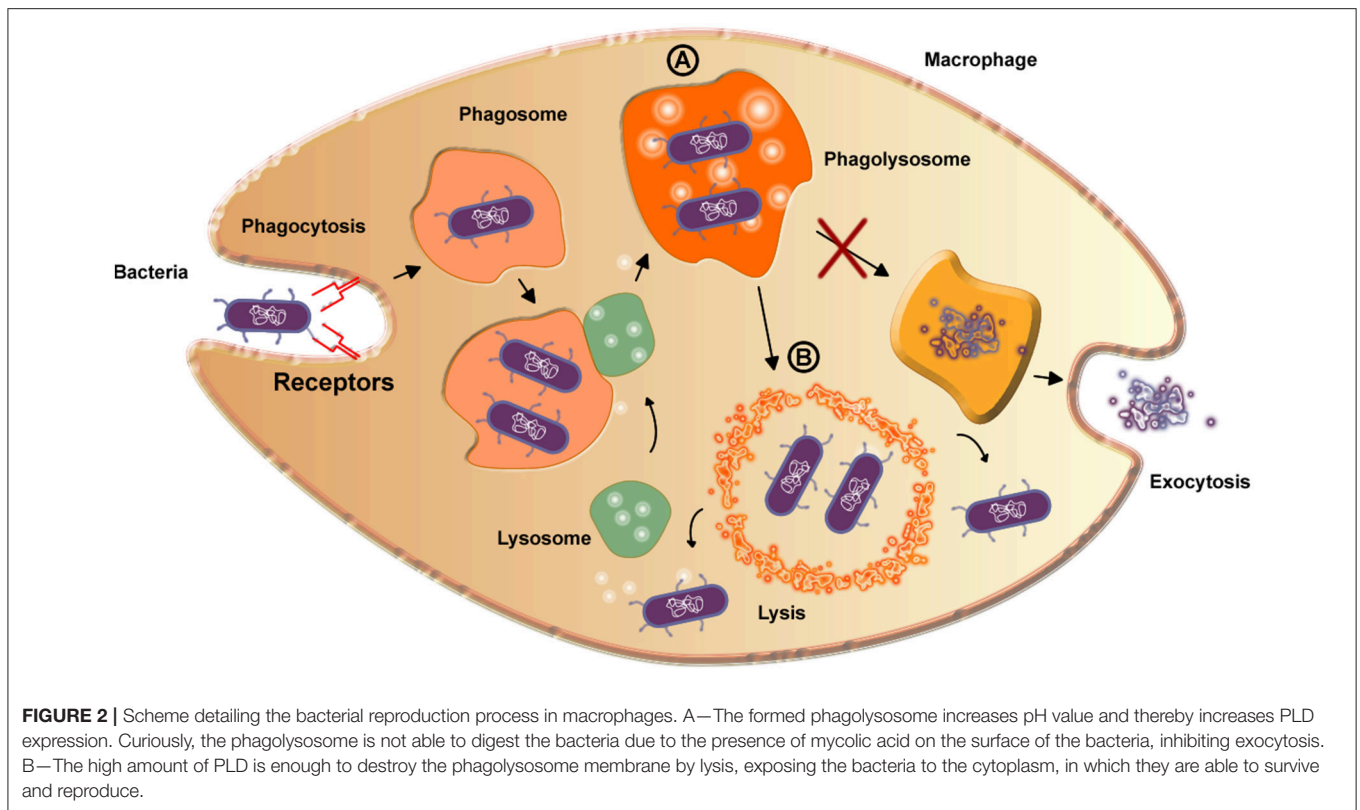
The etiologic agent of caseous lymphadenitis is *C. pseudotuberculosis*. This disease is common in small ruminant populations throughout the world and can cause a significant economic impact for producers. *C. pseudotuberculosis* infection in humans is not common, but has been reported on several occasions, making the disease a potential zoonosis (Peel et al., 1997; Dorella et al., 2006; Fontaine and Baird, 2008; Mills et al., 2009). The infectious process occurs mainly in animals, with clinical symptoms or asymptomatic, and the bacterial transmission that promotes the disease is usually spread by superficial wounds (Windsor and Bush, 2016). The primary virulence factor of *C. pseudotuberculosis* is Phospholipase D (Dorella et al., 2006), an exotoxin that promotes the hydrolysis and degradation of sphingomyelin in endothelial cell membranes (Figure 2), increasing the vascular permeability, which then facilitates to the spread and persistence of the bacterium in the host (Williamson, 2001).

There are two biovars of *C. pseudotuberculosis*: biovar ovis and biovar equi. The biovar ovis strains are responsible for causing infection mainly in sheep and goats. The principal characteristics of caseous lymphadenitis in these animals are the formation of caseous necrosis on the lymphatic glands or abscess formation in superficial lymph nodes and subcutaneous tissues (Baird and Fontaine, 2007). *C. pseudotuberculosis* biovar equi also can infect horses manifesting different disease patterns like external abscesses, ulcerative lymphangitis of the limbs, and some internal organs can be affected as called the visceral form Pratt et al. (2005).

VIRULENCE FACTORS

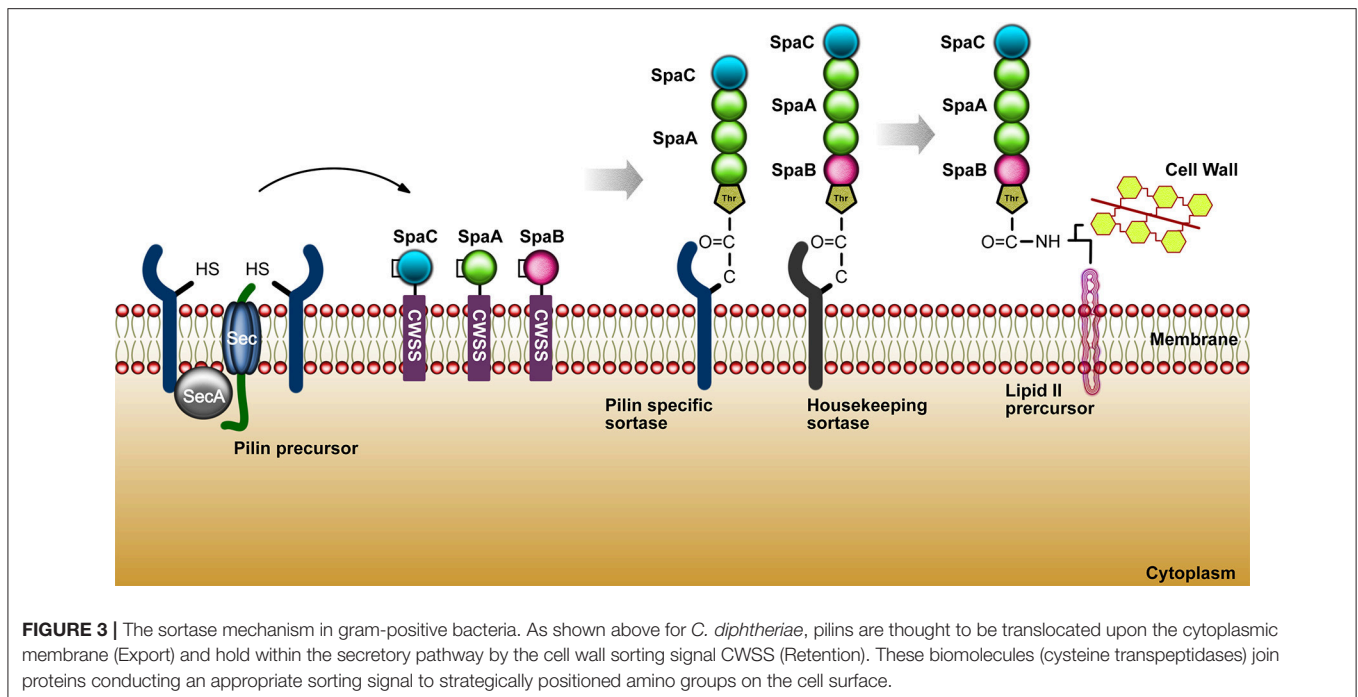
Adhesion Mechanisms

The bacterial adhesion process to the host cells was firstly elucidated through research with *E. coli* in 1908, in which it was shown that these bacteria, via multimeric pili, could hemagglutinate animal cells. In order to better understand important features associated to bacterial adhesion, some studies has been focusing on specific proteins as the pili, monomeric adhesins and bacterial tissue tropism ability. Research intended to explore the different manners by which bacteria may adhere to their host and how the host respond to it has opened a big field of study. Nowadays, it is known that pathogenic and commensal bacteria are able to express molecules that can help their interaction with eukaryotic host cells. Under this process, the underlying mechanism may be either beneficial for bacterial colonization or disadvantageous when the adhesion activates specific processes that may eliminate bacteria from the environment through phagocytosis and immune cell infiltration (Kline et al., 2009). The species from the genus *Corynebacterium* have in common a rich variety of lipoglycans, such as



lipoarabinomannans (LAM) and lipomannans (LM) (Brennan and Nikaido, 1995). *C. diphtheriae* presents a lipoglycan surface component called CdiLAM, a novel LAM variant that contributes to adhesion through an interaction with human respiratory epithelial HEp-2 cells (Moreira et al., 2008). Another adhesive component in *C. diphtheriae*, identified as surface-associated protein DIP1281 and annotated as hypothetical invasion-associated protein, was investigated by atomic force microscopy and fluorescence staining. The DIP1281 gene product seems to be related to the organization of the outer protein layer of *C. diphtheria* (Ott et al., 2010). The bacterial adhesins may recognize and colonize through of a differential regulation of genes either by the activation of structures such as hair-like, characteristic named pili or fimbriae, or identified as non-pilus adhesin, when are related with microbial cell surface (Soto and Hultgren, 1999). Gram-positive bacteria possess several surface proteins anchored to the cell wall through a sortase-dependent mechanism. The class II of sortase (minor class, formed by sortases with N-terminal signal peptide and a C-terminal membrane anchor) are the most frequent in corynebacteria, streptococci, and enterococci (Cossart and Jonquières, 2000; Ton-That et al., 2004). The first description of the pili molecule in gram positive bacteria, dates to around 1967 with a study of 45 *Corynebacterium renale* strains. The fibrils identified presented a great similarity to pili protein structures, previously described in gram negative bacteria. Using electron microscopy, the pilus characteristics of *C. renale* were observed based in morphological analyses of quantity and length (Yanagawa et al.,

1968). According to Trost et al. (2010), there are gene clusters encoding sortase genes related to the adhesive pili synthesis from *C. pseudotuberculosis* FCR41. The pili structures are comprised of the major pilin, SpaA and SpaD; minor pilin, SpaB and SpaE; and tip pilin, SpaC, SpaF. A complete pilus structure or even the minor pilins may perform an initial contact to the host cell receptors facilitating the delivery of virulence factors. *C. pseudotuberculosis* FCR41 presents a housekeeping sortase (*srtD*), responsible for the pili anchorage to the cell wall and located in another region of the genome (Trost et al., 2010). In the research of Ton-That and Schneewind (2003), it was observed that *C. diphtheriae* strain NCTC13129 also shows pili regions. This work showed three pili clusters: SpaA, major pilin protein; SpaB, minor pilin; and, SpaC, as a pilus tip protein. The housekeeping gene of *C. diphtheriae* is *srtF*, localized elsewhere on the chromosome (Ton-That and Schneewind 2003). In 2006, a second and third pilus were characterized, in which the second pilus cluster was identified as presenting a major pilin protein (SpaD) and minor pilus protein (SpaE and SpaF), and the third pilus cluster contains a major pilin (SpaH) and two minor pili proteins (SpaG and SpaI) (Gaspar and Ton-That, 2006). Moreover, the length of the filament is directly proportional to the abundance of the SpaH pilus (Swierczynski and Ton-That, 2006). In 2011, Trost et al. worked with two *C. ulcerans* strains to search for candidate virulence factors. The proteomes of *C. ulcerans* 809 and *C. ulcerans* BR-AD22 were analyzed and they found twelve virulence factors (*cpp*, *pld*, *spaF*, *spaE*, *spaD*, *spaC*, *spaB*, *rpfl*, *cwIH*, *nanH*, *vpsI*, and *tspA*) commonly shared by both



strains, and two exclusive to *C. ulcerans* 809 (*rbp* and *vsp2*). Both *C. ulcerans* strains present the genes *srtB* and *srtC* in the *spaDEF* region. Moreover, a second pilus gene cluster was observed, the *spaBC*, in which *spaB* gene is responsible for minor pilus protein coding and *spaC* codes a tip protein (Trost et al., 2011). **Figure 3** summarizes the sortase mechanism in gram-positive bacteria.

In addition to these molecules associated to anchorage to the cell wall, the bacteria have shown a system of others molecules able to control a large number of physiological functions including sporulation, competence, antibiotic resistance, and the transition to stationary phase (Mitrophanov and Groisman, 2008), called two-component systems (TCS). These systems are also able to mediate the adaptive responses to the environment (Koretke et al., 2000), including the pathogen virulence ability (Pérez et al., 2001).

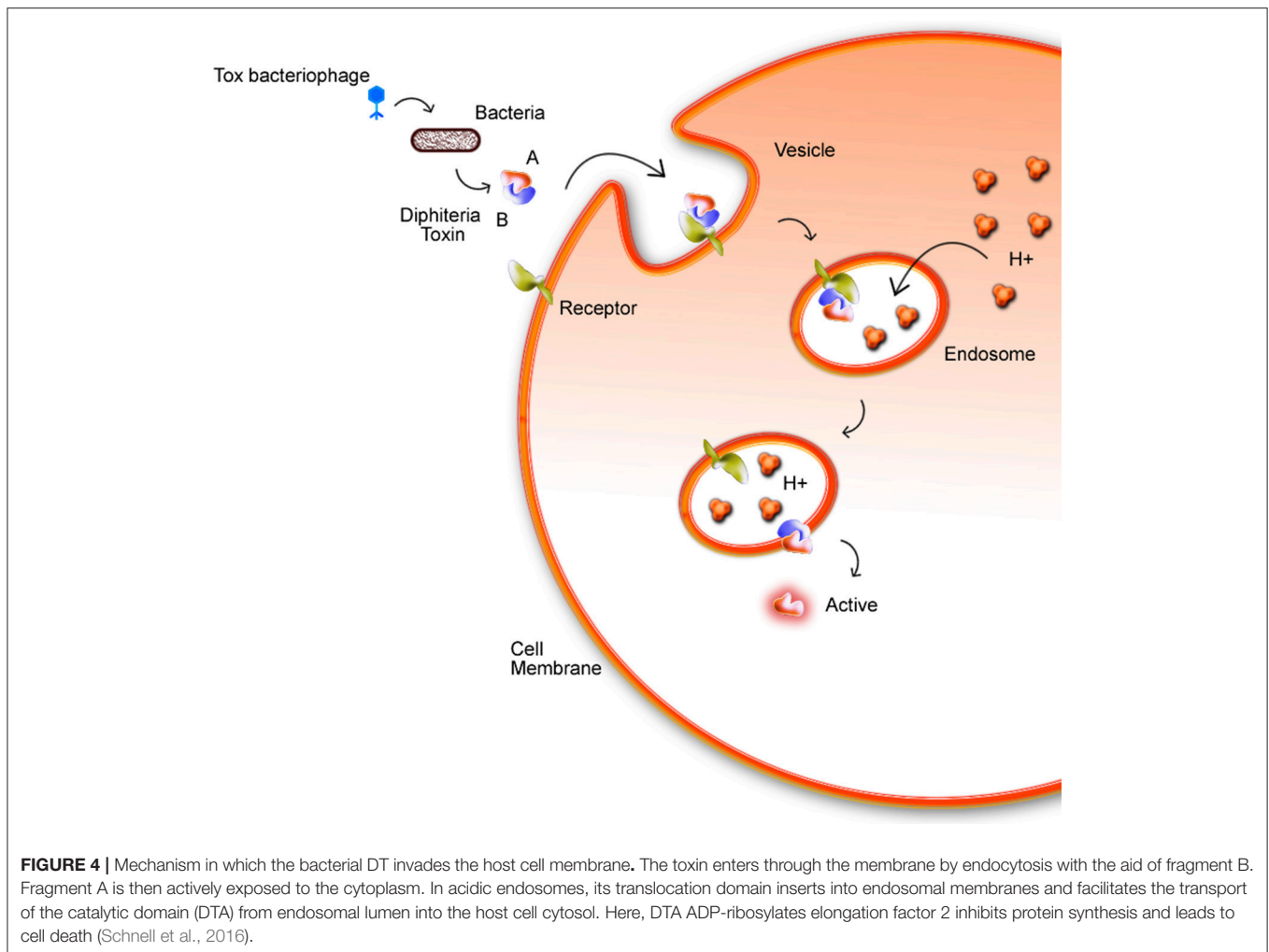
Furthermore, some studies have described the characterization of virulence factors of *Corynebacterium* species by means of host model, such as *Caenorhabditis elegans*. Studying 42 isolates of *C. diphtheriae*, Broadway et al. showed that most of them expressed the heterotrimeric SpaA pili, characterizing the bacterial adherence to pharyngeal epithelial cells. In addition, they observed that both non-toxicogenic and toxicogenic strain of *C. diphtheriae* (lack pili) aggravated the death of the nematode comparing with the control NCTC13129, toxicogenic and pilated strain (Broadway et al., 2013). Recently, a work using the same model, investigated other characteristics related with the pathogenicity of *C. diphtheriae*, *C. ulcerans*, and *C. glutamicum*, in addition of pili and nematode killing analysis (Antunes et al., 2017).

Another element associated as virulence factor is the *phoP* gene, that takes part in the PhoPR two-component system regulation, in which Tiwari et al. analyzed the role of the

PhoP protein from *C. pseudotuberculosis* Cp1002. Curiously, the mutant Cp1002 strain produced with absence to *phoP* gene, showed a reduction of cell adhesion rates that affects the surface properties (Tiwari et al., 2014).

Toxicity of Corynebacteria

Phages are widely found in the environment, such as soil, and they present a multiple cycles repeated daily by cellular lysis. The presence of phages in corynebacteria is described since 1970s (Ogata et al., 1980; Annie et al., 1987). Freeman's studies identified that some *C. diphtheriae* strains, using a mechanism of phage-mediated conversion, could produce the diphtherial toxin (Freeman and Morse, 1951; Hard, 1975). This discovery caught the attention for future works about corynebacteriophages, such as one of the first described comparative analysis of tox^+ and tox^- performed by Randall and Lane (Holmes and Barksdale, 1970). The *tox* gene is found in corynebacteriophage regions: βtox^+ , γtox^+ , and ωtox^+ , inside the chromosomes of *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*, but in this last one just in the biovar equi. Chromosomal genes interfere directly in Diphtheria Toxin (DT) expression and may cause, for example, an increase of DT production resulting from a low intracellular amount of iron due to inhibition of the regulatory *dtxR* gene (Guaraldi et al., 2014). *C. diphtheriae* strains produce DT, which is responsible for inhibiting protein synthesis in eukaryotic cells. DT is composed of two subunits, A and B fragments. DT binds to a specific receptor via B fragment while the A fragment, that is the active region, is translocated by an endosome into the host cell cytoplasm (**Figure 4**). The tox^+ phage may convert non-toxicogenic *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis* to toxicogenic bacteria (Buck et al., 1985; Naglich et al., 1992). In a recent work (Schnell et al., 2016),



diphtheria toxin (DT, 58 kDa), which is the causative agent of diphtheria is efficiently taken up into human cells and its catalytic domain (DTA, 21 kDa) acts as an extremely potent enzyme in the cytosol. Histidines residues (diphthamide) are modified by DTA covalently transfers, inhibiting protein synthesis and causing cell death.

Sing et al. demonstrated in 2003 that there are differences between the *tox* genes from *C. ulcerans* and *C. diphtheriae* strains. The DT from both species are about 95% identical in nucleotide and amino acid sequences, where the differences corresponding around to one and three amino acids located in the signal and catalytic region of the A fragment, respectively and 23 amino acids of DT are different between *C. diphtheriae* and *C. ulcerans* in B fragment (Sing et al., 2003).

Another toxin related to species from genus *Corynebacterium* is phospholipase D (PLD). This toxin, which is encoded by the *pld* gene, has been indicated as the leading virulence factor for this bacteria. Furthermore, studies suggest that PLD activity facilitates the dissemination and infiltration process into host tissues (Hodgson et al., 1992). Through pan-genomic analyses, Soares et al. identified the presence of *pld* in 14 of 15 *C. pseudotuberculosis* strains. One of these strains, *C. pseudotuberculosis* 31, presents a frameshift mutation near

the 3'-end of the *pld* gene that could be implicated with a minor ability of this strain to interact with the host. However, from all strains, *C. pseudotuberculosis* strain 31 was the only one in this study to harbor the *tox* gene (Soares et al., 2013). In *C. ulcerans* there is an extracellular neuraminidase (NanH), a potential virulence factor. This same NanH also occurs in *C. diphtheriae*, *C. pyogenes*, *C. pseudotuberculosis*, and *C. belfanti* (Trost et al., 2010). The two *C. ulcerans* studied by Trost et al. also presented PLD (Trost et al., 2011).

Survival Inside the Macrophage

Inside macrophages, bacteria are exposed to a broad range of different environmental stresses that may affect the metabolism, interfere with the structure and, consequently, the function of macromolecules. The intracellular medium may be altered by a nitrosative surface, oxidative/thermal osmotic shock, and starvation stresses that will trigger survival mechanism of the bacteria (Kazmierczak et al., 2005).

C. pseudotuberculosis, the causative agent of caseous lymphadenitis (CL), presents a lipidic surface associated with pathogenicity and virulence. In a study with this lipidic surface, it was demonstrated that the toxicity observed in extracted lipid may cause a high susceptibility to mouse peritoneal macrophages,

due to the necrotizing action of the *C. pseudotuberculosis* surface lipids, whereas this same cytotoxic effect was not observed in macrophages from rabbits and guinea pigs (Hard, 1975).

In order to understand how *C. pseudotuberculosis* 1002 is able to survive in the environment to infect the host, Pinto et al. analyzed it through transcriptional profile with regards to acid osmotic and thermal shock stresses. The most relevantly expressed genes were related to the adhesion process, stress response, and oxidoreduction, where the genes involved in virulence ability were affected. In the adhesion process, the Cp1002_0988 gene, one of the three genes comprising this mechanism was very relevant under osmotic stress because it was located within one of the pathogenicity islands predicted for *C. pseudotuberculosis* 1002. Besides that, this gene presented 6.8-fold change in expression levels in comparison with the control, whereas the other two genes, Cp1002_1764 and Cp1002_1765 presented 2.7- and 4-fold changes in expression. Regarding the genes that constituted the cellular oxidoreduction processes, they observed that some genes showed functions related to bacterial persistence in this environment. Curiously, some genes are involved in both adhesion and oxidoreduction and were fundamentally important due to the relevance in virulence (Pinto et al., 2014).

In addition, a *phoP* gene study was performed to analyze the adhesion importance and invasion in a wild type and a *phoP* mutant strain of *C. pseudotuberculosis* 1002. There was a change in genes possibly involved in the metabolism of lipids composing the cell envelope that may affect the *phoP* mutant interaction with the macrophages (Tiwari et al., 2014).

In analysis of osmotic stress response of *C. glutamicum*, it was demonstrated that the bacteria might adapt its metabolism according to the adverse conditions, meaning the osmolarity may only affect the cells if a variation in this coefficient exists. Besides that, the production of lysine increased in low dilution rates and with glucose consumption (Varela et al., 2004). Regarding the oxidative stress, carbon fluxes in the central metabolism of *C. glutamicum* were affected under deletion of the regulatory protein McbR, redirecting from the pentose phosphate pathway into glycolysis in response to the deletion. Furthermore, the deletion resulted in the increasing of pyruvate dehydrogenase (Krömer et al., 2008).

The activity and regulation of a zinc uptake regulated (*Zur*), in *C. diphtheriae*, Smith et al. identified three genes whose transcription is repressed by *Zur*: *cmrA*, *zrg*, and *troA*. Besides, they showed that *zur* gene transcription is made by a promoter, and it one is regulated by *zur* gene product, being its product modulate by zinc presence in the environment, also indicating the ability of *C. diphtheriae* to integrate different signals from a variety of metals to survive (Smith et al., 2009).

Host-Pathogen Relationship in the Infection by *C. pseudotuberculosis* and Immune Response

As a major *C. pseudotuberculosis* virulence factor, the exotoxin *pld* has already been described as an important molecule in the host-pathogen relationship, since it is implicated in

the dissemination of the bacteria from the original area of the infection to other organs, through the hydrolysis of sphingomyelin from the host's tissues and cell membranes (Pépin et al., 1989). The *pld* protein is seen to be associated with infection although is described with a small role but it seen important for the viability after the infection (McKean et al., 2007), and recently it was described that lymphocyte activation is inhibited by the *C. pseudotuberculosis* sphingomyelinase through the suppression of the ORAI receptors (Combs and Lu, 2015). The importance of the *pld* exotoxin in the host-pathogen relationship can be understood by the observation that anti-*pld* antibodies can inhibit the bacterial dissemination in the host and is related to the protection induced by vaccination (De Rose et al., 2002; Moura-Costa et al., 2008). The endo- β -N-acetylglucosaminidase CP40 is a secreted molecule that have been recently described as an important *C. pseudotuberculosis* virulence factor (Shadnezhad et al., 2016) and the vaccination of mice with this protein showed high protection rates (Droppa-Almeida et al., 2016). Other molecules that are involved in the establishment of the infection and to its dissemination to other organs are the lipids that are found in the bacterial wall, since the amount of these lipids in different bacterial strains were closely related to the virulence presented by each isolate (Muckle and Gyles, 1983).

Since *C. pseudotuberculosis* is a facultative intracellular pathogen, the protective immune response to the bacterium is based on a Th1 cellular response, and the infection with virulent strains of the bacteria induces the production of Th1 response-related cytokines such as IFN- γ (Meyer et al., 2005; Vale et al., 2016). Indeed, it was seen that the production of IFN- γ and TNF following the stimulation of murine splenocytes with the bacterium is driven by the activation of MAPK p38 and ERK 1/2 signaling pathways (de Souza et al., 2014). Mice inoculated with anti-IFN- γ antibodies showed an increased bacterial proliferation in the organs (Lan et al., 1998), but this work also shown that the innate immune response is also important, since the inoculation of anti-TNF antibodies also led to a higher bacteremia. It has also been observed that *C. pseudotuberculosis*-infected small ruminant' peripheral mononuclear blood cells are capable to produce significant amounts of IFN- γ when stimulated *in vitro* with bacterial antigens, and goats have a more intense production of this cytokine than sheep (Rebouças et al., 2011). This situation can be related to the fact that caseous lymphadenitis lesions in sheep are more disseminated and can be found in organs like spleen, lungs, and liver, and in goats these lesions are more likely to be found in superficial lymph nodes (Moura-Costa et al., 2008; Bastos et al., 2011).

The humoral immune response is also activated in the infection by *C. pseudotuberculosis*. In a murine model, it was observed that there is a peak in the production of IgG1 and IgG2a 60 days after an experimental infection with a pathogenic strain of the bacteria (Vale et al., 2016). Recent experiments on the development of vaccines against the bacteria showed that the production of IgG2a is correlated with a higher protection against a virulent challenge in mice that were previously inoculated with *C. pseudotuberculosis* recombinant proteins (Silva et al., 2014; Brum et al., 2017). Bastos et al. (2011-2013) observed that

sheep that produced higher amounts of specific IgM in the acute phase of the disease present a better prognostic in the clinical progression of caseous lymphadenitis and are more likely to develop asymptomatic infections. Among the several bacterial antigens that induces the production of specific antibodies, the exotoxin pld is considered a major immunodominant antigen, and it was observed that 100% of goats that were infected with the bacteria present specific IgG against pld, but only 70% of the infected sheep present this same pattern of antibody production (Hoelzle et al., 2013). Anti-pld antibodies are considered good biomarkers in the serodiagnosis of the infection in small ruminants, and satisfactory specificity and sensitivity levels were seen when recombinant pld or bacterial culture supernatants were employed as antigens in the development of immunodiagnosis assays (Sutherland et al., 1987; Menzies et al., 2004; Rebouças et al., 2011).

Mechanisms of Antibiotic Resistance in *Corynebacterium*

Studies point out that different species can show antibiotic resistance to different chemical compounds. Additionally, these results could to explain that extrachromosomal genetic elements are associated in the transmission of resistance genes in both pathogenic and potentially pathogenic (Adderson et al., 2008; Fernandez-Roblas et al., 2009). Usually, in species of *Corynebacterium*, the antibiotic resistance genes are located on large plasmids, e.g., resistance to tetracycline, chloramphenicol, erythromycin, and streptomycin on plasmid pTP10 described in *C. xerosis*. Others elements as the fluoroquinolones are described associated to the mechanism of resistance, also the tetracyclines are observed in phenotypic studies being found in 97% of the tested strains. Some glycopeptides can be described as component of the antibiotic resistance such as the vancomycin, an antibiotic recommended by many authors in the empirical treatment of invasive infections.

On the basis of phenotypic and genotypic studies is possible to understand the mechanism of antibiotic resistance that are proper to each species of the genus *Corynebacterium* associated with infections. These same studies could improve the knowledge about the sensitivity to antibiotics of different multidrug-resistant species of the genus *Corynebacterium*. Currently, some candidates are indicated as highest efficacy in treatment of infections such as tigecyclin, chinupristin/dalphopristin, glycopeptides, daptomycin, and linezolid (Olender, 2012).

MAIN FEATURES OF NON-PATHOGENIC SPECIES

Biotechnology Applications

Microorganisms produce several things that are useful for mankind and that is the reason behind importance of these tiny creature (Demain, 1990). These material could be explained as small molecules, usually described as metabolites that are broadly explore to vegetative growing (primary) and those that are described as inessential (secondary) or large molecules explained as nucleic acids, proteins, carbohydrates). For centuries, these

organisms have been utilized for the production of daily goods such as beer, bread, and wine. For example, filamentous fungi have been extensively used for the commercial production of organic acids, with, 1 billion pounds of citric acid with a market value of US\$1.4 billion produced annually. The Embden-Meyerhof pathway's product followed by the tricarboxylic acid cycle for the production of citric acid; the process is controlled by the inhibition of phosphofructokinase by citric acid. *Aspergillus niger* is used in iron and manganese deficient media for commercial processes. High level citric acid production is proportional to high intracellular concentration of fructose 2,6-biphosphate, a potential glycolysis activator (Demain, 2000).

At present, the net annual global expenditure of amino acids production is valued to be more than 2 million tons. The yearly demand for amino acids like MSG-based flavor enhancers or food additives including D,l-methionine, l-lysine, and l-threonine is around to be considerably higher than 1 million tons each. It is estimated that the pharmaceutical industry uses, mainly for intravenous and enteral nutrition, demand a value per year around 15,000 tons of amino acids (Kusumoto, 2001).

The genomic structure and metabolism of *C. glutamicum* are well characterized making this a microorganism better targeted for biotechnological utilization among this genus. This organism is frequently employed to production of L-amino acids (Becker and Wittmann, 2012b). However, some works already described this microorganism can be engineered for production of several "first-class" chemicals like succinate (Litsanov et al., 2012) or isobutanol (Blombach et al., 2011). Regarding these l-amino acids, the most relevant are l-glutamate and l-lysine based on production scales (Becker and Wittmann, 2012a). Furthermore, there are the expectation to create qualified producers for others amino acids such as l-leucine, l-serine, and l-methionine, which are uphold by a detailed knowledge into the corresponding regulation and their amino acid biosynthetic pathways in *C. glutamicum*.

Fermentation

The fermentation process can create almost 1,200 million pounds of monosodium glutamate per year, using different species of the genera *Corynebacterium* (e.g., *C. glutamicum*) and *Brevibacterium* (e.g., *B. flavum* and *B. lactofermentum*) (Demain, 2000). Additionally, these microorganisms can be utilized for the amino acid production, for example the l-glutamic acid, which is a commercially very important, frequently used as a food preservative in order to flavor enhancer, such as sodium salt (Shyamkumar et al., 2014). In addition, another one amino acid, with strong commercial importance, is the l-lysine that also is produced by batch fermentation. Usually, the industrial process looks for efficient approaches with short cost and time, using immobilized cells for aerobic processes or free cells. However, such type of applicability is still defiant. A current work (Razak and Viswanath, 2015) trying figuring out the better way to ascertain whether free cells or immobilized cells were useful for l-lysine production, showed that immobilized cells of the strain *C. glutamicum* MH 20-22 B, were more prominent as they yield more l-lysine compared to free cells.

IMPORTANT BIOCHEMICAL PATHWAYS

Lysine Biosynthesis Pathway

The amino acid L-lysine is produced by fermentative processes, conducted by bacteria can be produced together with methionine, threonine, and isoleucine by a branched of biochemical pathways. This pathway is harshly controlled for *E. coli* species, which includes a set of kinases proteins that are able to regulate its production. Additionally, when a large amount of the final product is abundant the initial enzyme is inhibited, in which no overproduction occurs.

Nevertheless, in some lysine-fermentation organisms (e.g., several mutants of *C. glutamicum* and its relatives), the only protein kinase able to act in the regulation is the aspartate kinase, which its presence is regulated via coordinated feedback inhibition by threonine and lysine. Curiously, some strains of *C. glutamicum* cannot to grow up unless methionine and threonine are present in the medium, its due to some of these strains are absent to the homoserine dehydrogenase. This observation was described that while the threonine supplement is maintained at a limiting concentration, the intracellular concentration of threonine will be used as the limiting factor and feedback inhibition of aspartate kinase will be bypassed (Demain, 2000). On the other hand, recently Pérez-García et al. (2016) reported the modification in phosphotransferase system (PTS) in *C. glutamicum* strain *GRLys1* produced l-lysine and l-pipecolic acid quickly. That can also be an alternative way for the production of l-lysine through *C. glutamicum* (Pérez-García et al., 2016).

Carotenoids Biosynthesis Pathway

The literature describe the carotenoids are yellow to red colored pigments originating from the terpenoid biosynthetic pathway. They are very abundant in plants and microorganisms, where they can have diverse functions such as photo protection or light harvesting molecules or as membrane stabilizers (Lee and Schmidt-Dannert, 2003; Sandmann and Yukawa, 2005). Carotenoids are derived from the universal precursor isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP) (Rodríguez-Villalón et al., 2008). Moreover, IPP and DMAPP can influence the yield and rates of isoprenoid production by its enhancing of cellular metabolic flux, using them as strategy to the improvement of these molecules (Martin et al., 2003; Leonard et al., 2010).

The C50-terpene decaprenoxanthin and its glucosides are described as the predominant carotenoids in *C. glutamicum* (Krubasik et al., 2001a). Currently, just three different C50 carotenoid biosynthetic pathways have been described: the biosynthetic pathways of the ϵ -cyclic C50 carotenoid decaprenoxanthin in *C. glutamicum* (Krubasik and Sandmann, 2000; Krubasik et al., 2001b), the β -cyclic C50 carotenoid C.p. 450 in *Dietzia* sp. CQ4 (Tao et al., 2007) and the γ -cyclic C50 carotenoid sarcinaxanthin in *Micrococcus luteus* NCTC2665 (Netzer et al., 2010). In addition, only five species of *Corynebacterium* genus have been identified to include carotenoid pigments i.e., *C. michiganense* (Saperstein and Starr, 1954), *C. erythrogenes* (Hodgkiss et al., 1954), *C. fascians*

(Prebble, 1968), and *C. poinsettiae* (Starr and Saperstein, 1953). *C. poinsettiae* (*Curtobacterium flaccumfaciens*) e.g., is known to produce the C50 carotenoids bacterioruberin, bisanhydrobacterioruberin, and C.p. 450 (Sandmann and Yukawa, 2005).

As described in some works, *C. glutamicum* possesses a carotenogenic gene cluster, observed based on transposon mutant analysis and biochemical evidence, that encodes responsible enzymes for the entire decaprenoxanthin biosynthesis starting from DMPP (Krubasik and Sandmann, 2000; Krubasik et al., 2001a). The farnesyl pyrophosphate (FPP, C15) and geranylgeranyl pyrophosphate (GGPP, C20) are suggested to be the promptly pioneers of the C30 and C40 carotenoids biosynthesis are generated from DMPP by prenyl transferase CrtE (Krubasik and Sandmann, 2000). Subsequently, the colorless carotenoid phytoene is produced by phytoenesynthase (CrtB) activity. Finally, the red-colored lycopene is produced by four subsequent desaturation reactions by phytoene desaturase (CrtI) (Krubasik and Sandmann, 2000; Krubasik et al., 2001b). The crtEb gene that produce the lycopene elongase enzyme is able to catalyze the reaction of the elongation of lycopene to the acyclic C50 carotenoid flavuxanthin. Posteriorly, the reaction of flavuxanthin to decaprenoxanthin is catalyzed by heterodimeric carotenoid- ϵ -cyclase, encoded by crtYf and crtYe genes (Krubasik et al., 2001b; Eggeling and Bott, 2005; Netzer et al., 2010). Despite the mono/diglucosylated decaprenoxanthin can be explored in *C. glutamicum*, the genes and enzymes for glucosylation of decaprenoxanthin are still unidentified (Netzer et al., 2010).

Histidine Biosynthesis Pathway

The first genetic studies on histidine biosynthesis were targeted using the *C. glutamicum* AS019, which was derived of *C. glutamicum* ATCC 13059. The genes hisA, that is able to codify the 1-(5-phosphoribosyl)-5-[(5phosphoribosylamino)methylideneamino]imidazole-4carboxamide (5^oProFAR) isomerase, and the gene hisF encoding one subunit of the imidazole glycerol phosphate synthase, were analyzed by aggregation of analogous histidine auxotrophic *E. coli* mutants (Jung et al., 1998). The gene hisH, that is able to codify the second subunit of imidazole glycerol phosphate synthase (Kim and Lee, 2001), and the genes hisG and hisE, to the ATP phosphoribosyltransferase and phosphoribosyl-ATP pyrophosphatase, were respectively analyzed using the same methodology (Kwon et al., 2000). With the access to complete genome sequence of *C. glutamicum* (strain ATCC 13031) (Ikeda and Nakagawa, 2003; Kalinowski et al., 2003), several metabolic pathways were able to be reconstructed and better understood, including histidine biosynthesis. Nine of the 10 enzymatic activities needed for histidine biosynthesis were identified by genome annotation, these were the genes hisAEFGH, already known from *C. glutamicum* AS019, the genes hisI, encoding phosphoribosyl-AMP cyclohydrolase, hisB, coding for imidazoleglycerol-phosphate dehydratase, hisC, coding for histidinol-phosphate aminotransferase, and hisD, encoding histidinol dehydrogenase, which catalyzes the final two steps of histidine biosynthesis in *C. glutamicum*.

It been more than three decades that we are introduced with modern biotechnology. With the birth of recombinant DNA technology in 1972, biotechnology has been driven to new heights that headed toward the constitution of a new industry. Along with recombinant DNA technology, new microbial biotechnology including fermentation, high-throughput screening for drug target and novel metabolites, microbial physiology, and strain improvement, bioreactor design and downstream processing, cell fusion, cell immobilization, protein engineering, metabolic engineering, and evolutionary characterization of enzymes (Wendisch et al., 2016).

The genomics, transcriptomics, proteomics considered as application of high-throughput technologies have been used in the development of *C. glutamicum* strains by the use of the biotechnology industry. These new technologies helped immensely in the strain development production of *C. glutamicum*. For example, the genome-reduced of *C. glutamicum* strain MB001 was biotechnologically modeled for the production of the decaprenoxanthin, carotenoids lycopene, and astaxanthin (Heider et al., 2014), and the amino acids L-citrulline (Eberhardt et al., 2014) (Eberhardt et al., 2014). Correspondingly, MB001-based strains were developed for the production of the amino acids L-arginine, L-ornithine, L-proline, and the diamine putrescine (Jensen et al., 2015). In recent times, CRISPR interference (CRISPRi) technology using the inactive Cas9 protein was performed on L-lysine and L-glutamate production to determine the effects of target gene repression (Cleto et al., 2016). Effects on amino acids produced by CRISPRi/dCas9-mediated target gene repression were comparable to levels achieved by target gene deletion. For many target genes, this robust methodology may potentially be operated in parallel. The use of signal peptide is one of the approach identified for enhancing secretion efficiency. However, when compared with *E. coli*, *C. glutamicum* has some disadvantages, such as lower efficiency of transformation and a low number of available expression systems. To achieve and overcome such challenges, it is needed to the development of extraordinary approaches for expression and secretion systems that leads to gain a deeper understanding and increase production workhorse in the field of microbial biotechnology (Lee et al., 2016; Wendisch et al., 2016).

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CONCLUSION

We conclude that the proposed work adds significantly information in the medical, veterinary, and biotechnology area to *Corynebacterium* genus and its species. Additionally, the review explores general important contributions such as the cell division and Genomic/Transcriptomic. Also, specific details to pathogenic for example highlighting the virulence factors and curiosities about the host-pathogen relationship, an infamous context extremely important to be discussed to these species and non-pathogenic species, such as the amino acid production strongly important to the food production.

AUTHOR CONTRIBUTIONS

AO—Writing and reading of review; LO, LB, SJ, ST, FA, and RP—writing of specific parts of manuscript; HF, AS, and PG—Support in the manuscript development; RW, and VA—Leadership and supervision of work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmicb.2017.01937/full#supplementary-material>

Supplementary Table 1 | Detailed list of corynebacterium genomes.

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