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MINI-REVIEW

Genomics of iron acquisition in the plant pathogen *Erwinia amylovora*: insights in the biosynthetic pathway of the siderophore desferrioxamine E

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Abstract Genomics has clarified the biosynthetic pathway for desferrioxamine E critical for iron acquisition in the enterobacterial fire blight pathogen *Erwinia amylovora*. Evidence for each of the individual steps and the role of desferrioxamine E biosynthesis in pathogen virulence and cell protection from host defenses is presented. Using comparative genomics, it can be concluded that desferrioxamine biosynthesis is ancestral within the genera *Erwinia* and *Pantoea*.

Keywords Fire blight · Desferrioxamine · Ferrioxamine · Siderophore biosynthesis

Introduction

Iron is an essential nutritional factor for every living organism as a cofactor for numerous proteins. Even though iron is one of the most abundant micronutrients in nature, iron bioavailability under physiological conditions is fairly low. Under aerobic conditions, at neutral and alkaline pH, the most prevalent form is ferric iron (Fe^{III}), which is commonly precipitated to form iron minerals. In order to solubilize and acquire iron from their environment, living organisms utilize high-affinity uptake systems. Microorganisms excrete siderophores, usually low molecular weight molecules in the range of 400–1,000 Da, to increase the solubility of iron. Once an excreted siderophore has captured ferric iron, the resulting iron–siderophore complex is reabsorbed by the cell via highly selective membrane-associated ATP-dependent transport systems (Köster 1991).

Desferrioxamines (DFOs) consisting of alternating diamine and dicarboxylic acid building blocks linked by amide bonds are among the strongest hydroxamate siderophores known. Desferrioxamine E (DFO-E, also nocardamine) was first isolated from a *Streptomyces* sp. (Yang and Leong 1982) and subsequently found in many other bacteria, including *Pantoea agglomerans* (formerly *Erwinia herbicola*), *Pseudomonas stutzeri* and *Hafnia alvei* (Meyer and Abdallah 1980; Berner et al. 1988; Reissbrodt et al. 1990).

Biosynthesis of DFO by *Erwinia amylovora*

It has been reported that enterobacterial plant pathogenic *E. amylovora* strains produce DFOs (Feistner et al. 1993; Kachadourian et al. 1996). This pathogen is the major global threat to sustainable pome fruit production (i.e., apple, pear and quince), and it also causes economic, amenity and ecological damage to a wide range of ornamental, landscape and forest *Rosaceae* species (Bonn and van der Zwet 2000; Duffy et al. 2005; Rezzonico et al. 2011). The major product of DFO biosynthesis in *E. amylovora* is DFO-E, while minor amounts of other DFOs (D_2, X_{1-7} and G_1) are also produced (Feistner et al. 1993; Kachadourian et al. 1996). Using transposon mutagenesis, a DFO-negative mutant of *E. amylovora* CFBP 1430 was obtained (Kachadourian et al. 1996), in which the transposon was inserted in the *dfoA* gene (Dellagi et al. 1998). Additionally, a DFO uptake mutant

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with a transposon insertion in the TonB-dependent receptor gene *foxR* was also obtained. This mutant was able to synthesize DFO, but was deficient in its ability to use DFO as siderophore. Based on this, it was severely impaired in ability to grow under iron-limited conditions (Kachadourian et al. 1996; Dellagi et al. 1998). The *foxR* gene was subsequently cloned and sequenced (Kachadourian et al. 1996).

Using this *foxR* sequence, we searched the complete, annotated genome sequence of *E. amylovora* CFBP 1430 (Smits et al. 2010b) in order to localize the gene on the chromosome. As it is known that single cosmids complementing all *dfo* mutants in *E. amylovora* CFBP 1430 can be obtained, it was assumed that DFO biosynthetic genes are clustered on the *E. amylovora* genome (Dellagi et al. 1998). The flanking regions of the *foxR* gene were analyzed for the presence of potential DFO biosynthesis genes. Directly downstream of *foxR* and on the complementary strand (Fig. 1), three genes designated here as *dfoJAC* were identified and annotated as siderophore biosynthetic genes. They have significant sequence identity to the DFO biosynthesis genes from *Streptomyces coelicolor* A3(2) and to the alcaligin biosynthesis genes from *Bordetella* spp. The *dfoA* gene was identical to the previously unpublished *dfoA* sequence (Dellagi et al. 1998; Smits et al. 2010b).

The DFO biosynthetic gene clusters in closely related bacteria

The recent availability of genome sequences of related species and genera enables investigation into the dissemination of DFO biosynthesis genes within the enterobacteria. The DFO biosynthesis gene clusters in the genomes of all *E. amylovora* strains currently published (Sebaihia et al. 2010; Smits et al. 2010b; Powney et al. 2011; Smits et al. 2011a) have an identical arrangement (Fig. 1). Slightly lower sequence identities were observed between the *Spiraeoideae* isolates CFBP 1430 and Ea273 and the *Rubus* isolate ATCC BAA-2158. The same genetic arrangement was also found in the genomes of *Erwinia pyrifoliae* strains (Kube et al. 2010; Smits et al. 2010a), *Erwinia* sp. Ejp617 (Park et al. 2011) and *Erwinia tasmaniensis* (Kube et al. 2008; Fig. 1), species not previously reported to produce DFOs (Smits et al. 2010a).

However, the gene organization of the *dfo* gene cluster in the genome of *Erwinia billingiae* Eb661 (Kube et al. 2010; Fig. 1) is different in that a major facilitator superfamily (MFS) transporter, here designated DfoS, is present directly downstream of *dfoC* in the same transcriptional direction. An MFS transporter is also seen in the genomes of different *Pantoea* spp. (De Maayer et al. 2010; Smits et al. 2010c, 2011b) at the similar position (Fig. 1). Orthologues of this MFS transporter can also be identified in the genomes of *E. amylovora* CFBP 1430, *E. pyrifoliae* strains (Kube et al. 2010; Smits et al. 2010a), *Erwinia* sp. Ejp617 (Park et al. 2011) and *E. tasmaniensis* (Kube et al. 2008; Fig. 1), but located distantly from the *dfoJAC* cluster. It can be speculated that DfoS is responsible for cell export of DFO-E, analogous to the alcaligin transporter AlcS in *Bordetella bronchiseptica* (Brickman and Armstrong 2005; Fig. 1).

The closely related fire blight biocontrol agent *Pantoea vagans* C9-1 (Rezzonico et al. 2010; Smits et al. 2010c) produces DFOs (Feistner and Ishimaru 1996). In this antagonistic bacterium, the *dfoJACS* gene cluster is located on the megaplasmid pPag3, which can be lost under stressful, unfavorable growth conditions (Smits et al. 2010d). This gene cluster includes downstream of *dfoC* the *dfoS* gene, but not the gene encoding the TonB-dependent receptor for ferrioxamine. Examination of the genome for the *foxA* gene encoding the ferrioxamine TonB-dependent receptor of *P. agglomerans* K4 (Deiss et al. 1998) indicated that it is encoded on the chromosome (Smits et al. 2010c). The DFO biosynthesis clusters in the draft genomes of *P. agglomerans* E325 (Smits and Duffy, unpublished) and *Pantoea eucalypti* αB (Adams et al. 2009) have the same arrangement as in *P. vagans* C9-1. The chromosomally encoded DFO biosynthesis cluster of the *Eucalyptus* pathogen *Pantoea ananatis* LMG 20103 (De Maayer et al. 2010) also contains the *foxA* gene directly downstream of *dfoS* (Fig. 1). The genome of *Pantoea* sp. At-9b (Pinto-Tomás et al. 2009) lacks the DFO biosynthesis cluster. None of the former *Erwinia* spp. now included in the genera *Pectobacterium*, *Brenneria* and *Dickeya* or any other *Enterobacteriaceae* contain a DFO biosynthesis cluster although many of these produce alternative iron siderophores.

Phylogenetic analysis of concatenated DfoJAC (Fig. 2) revealed that the sequences from pathogenic *Erwinia* spp. are very closely related, whereas DfoJAC of *E. billingiae* Eb661 branched deeply within the tree. Additionally, the DfoJAC of three *Pantoea* spp., all previously incorrectly assigned to *P. agglomerans* (Ewing and Fife 1972; Gavini et al. 1989; Brady et al. 2009; Rezzonico et al. 2009), had a higher sequence identity to each other than compared with that of *P. ananatis* LMG 20103, which also deeply branched. However, pairwise distances are above 75% for all genes, indicating a common origin for the DFO biosynthesis cluster in *Erwinia* and *Pantoea*.

The putative pathway for DFO biosynthesis

Using cross-feeding experiments, Feistner (Feistner 1995) had proposed a pathway for DFO biosynthesis in

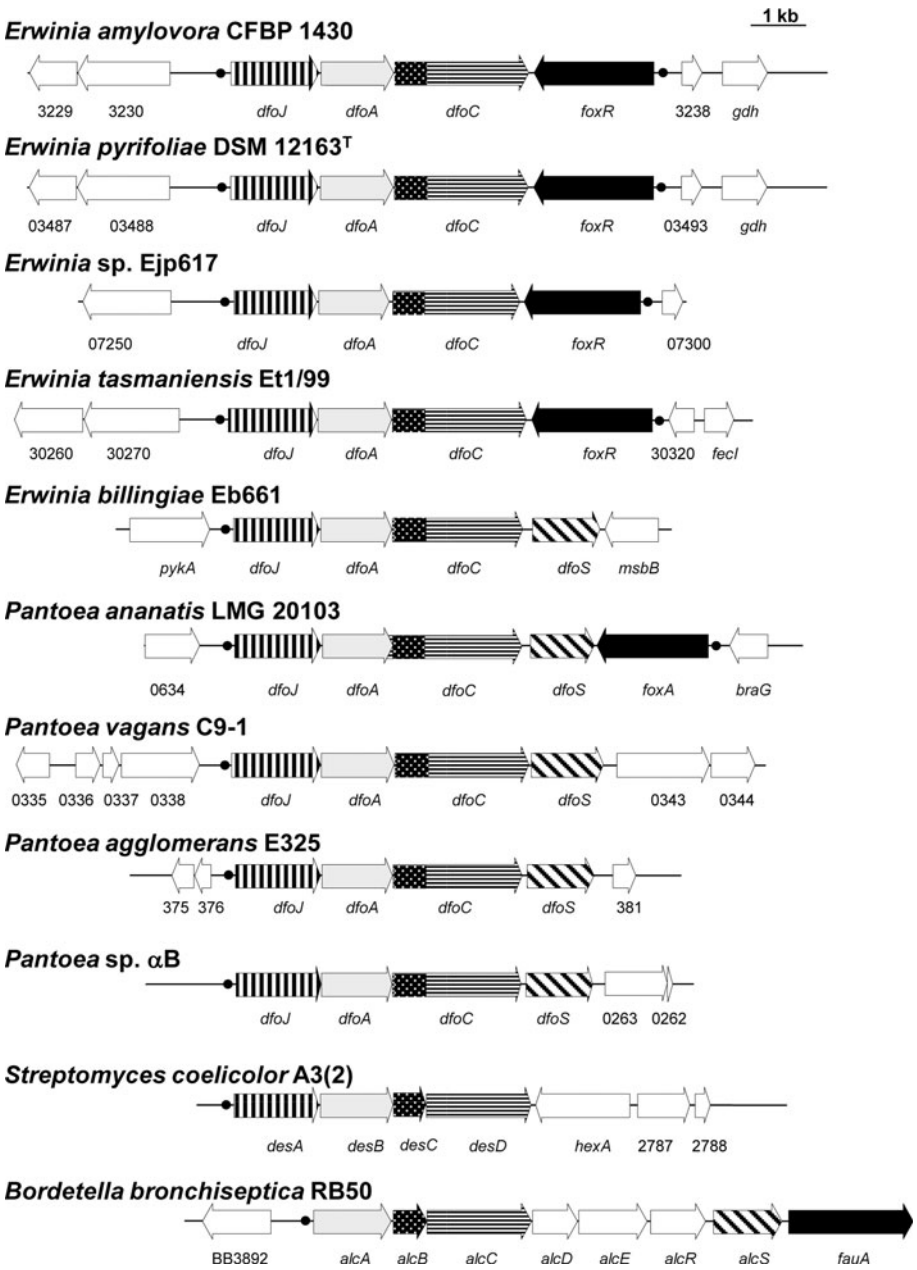

Fig. 1 Comparison of gene clusters for desferrioxamine biosynthesis. Genes with similar putative function are uniquely colored. The two domains in *dfoC* are indicated by different *shadings*. The position of *Fur boxes* are indicated by a *black dot*, wherever identified. White genes depict unrelated genes

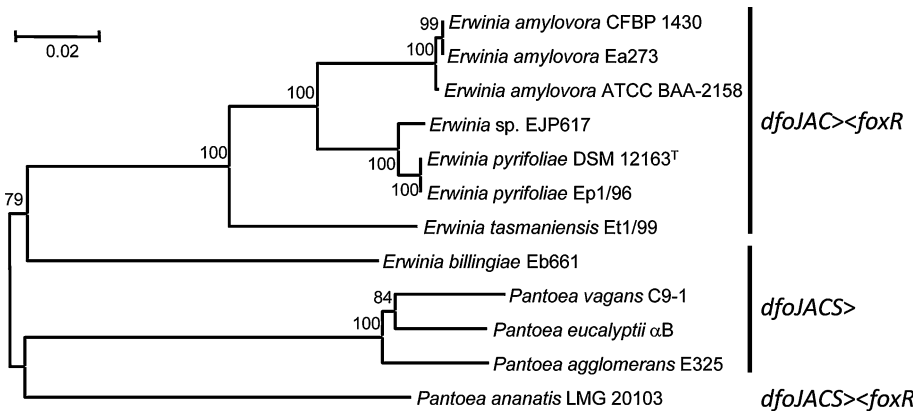

Fig. 2 Unrooted phylogenetic tree of concatenated amino acid sequences of DfoJ, DfoA and DfoC. Significant bootstrap values (1,000 repetitions) are indicated

E. amylovora (Fig. 3) that is essentially identical to the pathway as determined for *S. coelicolor* A3(2) (Challis 2005), for which some biochemical evidence is present (Schupp et al. 1987, 1988; Barona-Gómez et al. 2004). The individual steps and the enzymes involved are outlined below.

The putative first enzyme in the biosynthetic pathway for DFO is a pyridoxal-5'phosphate-dependent lysine/ornithine decarboxylase DfoJ (EC 4.1.1.-) (Expert et al. 2000). This enzyme has moderate sequence identity to DesA, the respective protein in the DFO biosynthesis pathway of *S. coelicolor* A3(2) (Schupp et al. 1988; Bentley et al. 2002), and therefore the putative function might be that of the lysine decarboxylase, yielding cadaverine (Fig. 3). Based on the incorporation of small amounts of putrescine into the DFO profile of *E. amylovora*

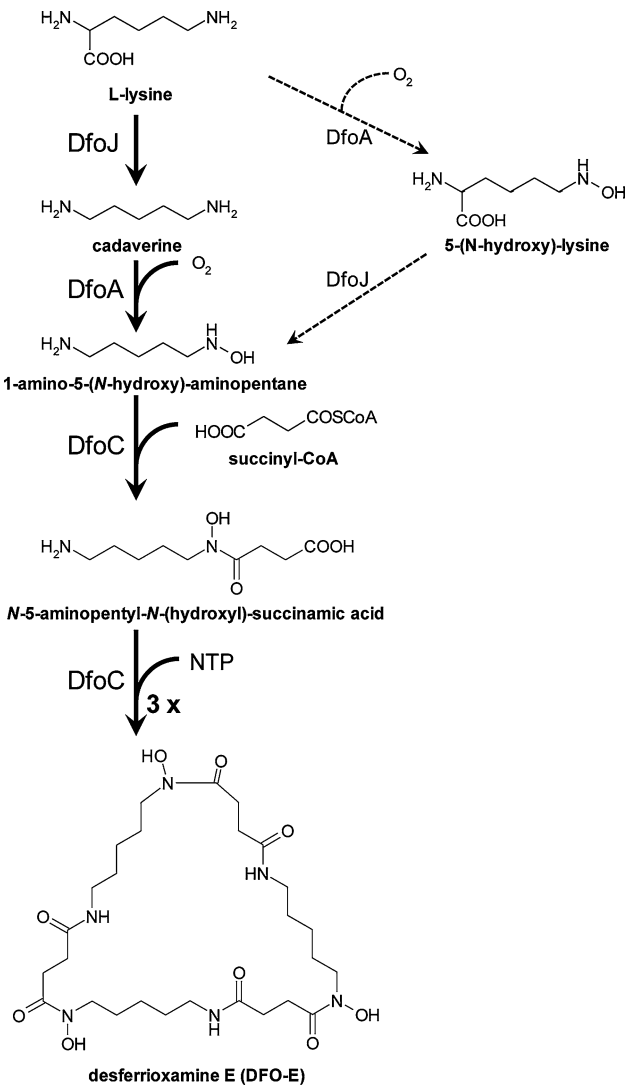

Fig. 3 Proposed biosynthetic pathway for desferrioxamine E in *E. amylovora* CFBP 1430 (*left*) and theoretical alternative pathway (*right*)

(Feistner et al. 1993), it is very well possible that this enzyme can also decarboxylate ornithine to putrescine.

In Bergey's manual of Systematic Microbiology, however, it is described that lysine/ornithine decarboxylase was not detected using Møller's method in *Erwinia* spp. (Hauben and Swings 2005). As Møller's assay is performed in a rich medium containing sufficient iron (Møller 1955), induction of the iron regulon will not have taken place, so that the result of this assay has to be taken with great care. The enzyme assays were never performed under low-iron conditions.

The second step of the proposed DFO biosynthetic pathway is an oxygenation on one of the terminal amino groups of cadaverine and, to minor extend, of putrescine to yield 1-amino-5-(*N*-hydroxy)-aminopentane and 1-amino-4-(*N*-hydroxy)-aminobutane, respectively (Fig. 3). The amine monooxygenase DfoA belongs to the IucD family of enzymes and is a flavin-dependent protein. Orthologues are present in many organisms that are able or hypothesized to produce hydroxamate-type siderophores (Challis 2005).

Theoretically, there is an alternative biosynthetic pathway over initial *N*-monooxygenation and subsequent decarboxylation (Feistner 1995), comparable to the pathway for aerobactin biosynthesis (Challis 2005). This alternative pathway (Fig. 3) corresponds to the current annotation of DfoA as a L-lysine *N6*-monooxygenase (EC 1.14.13.59). However, based on cross-feeding experiments (Feistner 1995), there is currently only evidence for an initial decarboxylation (Expert et al. 2000), indication that this enzyme has a hypothetical function as a cadaverine *N*-monooxygenase.

The protein encoded by *dfoC* is predicted to contain two domains: an acyl transferase domain of the AlcB family (PFAM 10331) within the first 150 amino acids and a siderophore synthase domain belonging to the IucA/IucC family (PFAM 04183). The latter domain belongs to the type C siderophore synthases (Challis 2005). The gene cluster encoding DFO biosynthesis in *S. coelicolor* A3(2) has two genes encoding the same functions as DfoC (Fig. 1): *desC* encodes the acyl transferase, while *desD* encodes the siderophore synthase (Barona-Gómez et al. 2004). DfoC is thus a natural fusion protein.

The first reaction performed by DfoC (Fig. 3) involves the coupling of succinyl-CoA to 1-amino-5-(*N*-hydroxy)-aminopentane to form the intermediate *N*-5-aminopentyl-*N*-(hydroxyl)-succinamic acid. This intermediate, described as being chemically instable (Barona-Gómez et al. 2004), is most probably not released into the medium, but is directly, in an ATP-dependent reaction, trimerized and cyclisized by DfoC to form DFO-E. The incorporation of one molecule of 1-amino-4-(*N*-hydroxy)-aminobutane will yield DFO-D_2 that was detected as second major DFO in *E. amylovora* (Feistner et al. 1993). Based on the minor DFOs that were

detected in cultures of *E. amylovora* (Feistner et al. 1993), we conclude that DfoC can accommodate a variety of precursors and ring sizes that are not known to be tolerated by *Streptomyces* spp.

The TonB-dependent ferrioxamine receptor FoxR

For the reabsorption of iron(III)-loaded siderophores, a TonB-dependent receptor is commonly employed, transporting the siderophores into the periplasmic space. For ferrioxamine, the respective receptors were named FoxR in *E. amylovora* (Kachadourian et al. 1996; Dellagi et al. 1998), FoxA in *P. agglomerans* (Deiss et al. 1998) and FauA in *Bordetella*. The gene encoding the FoxR receptor was cloned and characterized (Kachadourian et al. 1996). FoxR belongs to the TonB-dependent ferrihydroxamate receptors [TC 1.B.14.1.1] and may accept a broad spectrum of ferrioxamines, but not other siderophores (Deiss et al. 1998). In the *E. amylovora* CFBP 1430 genome (Smits et al. 2010b), the *foxR* gene is located on the complementary strand directly downstream of *dfoC* (Fig. 1).

In *E. amylovora* CFBP 1430, *foxR* mutants retain their ability to synthesize DFO but lose the ability to utilize this as an iron substrate, are impaired in growth under iron-limited conditions such as found on flower surfaces, have reduced virulence and are less resistant to plant defense responses (Kachadourian et al. 1996; Expert et al. 2000).

The genome of *E. amylovora* CFBP 1430 contains genes for three additional TonB-dependent receptors. One of these encodes a copper uptake receptor, while the other two encode for receptors with unknown specificity (Smits et al. 2010b). In the genome, remnants of an inactivated ferrichrome TonB-dependent receptor *fhuA* were identified, but it still contains its cognate ABC transporter *fhuCDB*. In contrast, the two closely related species *E. pyrifoliae* DSM 12163 and *E. tasmaniensis* Et1/99 contain a full *fhuACDB* system, indicating that they should be able to utilize this siderophore. Furthermore, the genome of *E. tasmaniensis* Et1/99 encodes a full iron(III) dicitrate uptake system, located downstream of the DFO gene cluster and an achromobactin-like siderophore uptake system (Kube et al. 2008; Smits et al. 2010b). The base for the limited utilization of siderophores by *E. amylovora* (Kachadourian et al. 1996) is thus determined by the lack of the corresponding systems.

Regulation

The DFO biosynthetic genes and the TonB-dependent receptor FoxR in *E. amylovora* CFBP 1430 are inducible under low-iron conditions (Kachadourian et al. 1996), indicating a global regulation by the ferric uptake receptor Fur (Hantke 1981; de Lorenzo et al. 1987), and the corresponding gene was identified in the genome (Smits et al. 2010b). A Fur box (de Lorenzo et al. 1987) was identified upstream of the *E. amylovora* CFBP 1430 *foxR* gene (Kachadourian et al. 1996), but could also be identified upstream of the *dfoJ* gene (Fig. 1), as in *S. coelicolor* A3(2) (Barona-Gómez et al. 2004). Based on the limited intergenic space between *dfoJ* and *dfoA* (10 bp) and between *dfoA* and *dfoC* (1 bp), it can be predicted that a single transcript spanning the *dfoJAC* region is generated.

Role of DFO in interaction with plants

The role of DFO biosynthesis in fire blight caused by *E. amylovora* has been well studied (Expert 1999; Expert et al. 2000). It has been shown that two outer membrane proteins with an apparent M_w of 70 and 80 kDa are induced under low-iron conditions, one of which corresponds to FoxR (Dellagi et al. 1998). A *foxR* mutant of *E. amylovora* CFBP 1430 accumulated DFO molecules in its external medium, decreasing the iron availability (Dellagi et al. 1998) and inhibiting its own growth. A gene knockout of *dfoA* in *E. amylovora* CFBP 1430 completely abolished production of DFO-E in this strain (Dellagi et al. 1998). Additionally, it was noted that this enzyme not only had a critical function for iron acquisition, but also played a role in cell protection against the host oxidative burst elicited during infection (Dellagi et al. 1998). However, unlike non-pathogenic mutants inactivated in the *hrp*-type III secretion system or in the amylovoran biosynthetic cluster (Oh and Beer 2005), *dfoA* mutants still caused fire blight when inoculated at high cell titer (Dellagi et al. 1998) indicating a limited role in virulence. Both types of mutants were handicapped in ability to colonize floral tissues and cause necrotic symptoms on apple flowers, indicating that iron availability is limited *in planta*. Considering the limited iron uptake determinants available to *E. amylovora* (Smits et al. 2010b), DFO plays a primary role in iron scavenging and fitness of the organism *in planta*.

Conclusions

We have identified the biosynthetic genes for DFO in *E. amylovora* CFBP 1430 (Smits et al. 2010b) and provide genomic clarification for the individual gene products. High conservation of the DFO biosynthetic proteins observed in genomes of currently sequenced members of the related genera *Erwinia* and *Pantoea* indicates the ancestral nature of this feature. In contrast, the pectolytic ex. *Erwinia* group (e.g., *Dickeya dadantii* Ech703 and

Pectobacterium atrosepticum SCRI1043) do not carry DFO biosynthetic genes.

The role of DFO in pathogenicity of *E. amylovora* is intimately related to the life cycle of the pathogen within its host. Evolution of DFOs fulfill a dual function for the pathogen as an efficient iron transporter to cope with iron-limited conditions within host tissues and also as a defense mechanism to protect against oxidative burst host reactions during early infection stages. Although not yet confirmed with mutational analysis, accumulating evidence anticipates a similar role for DFOs in closely related plant pathogenic and/or plant-associated *Erwinia* species.

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