The versatility and adaptation of bacteria from the genus *Stenotrophomonas*

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Abstract | The genus *Stenotrophomonas* comprises at least eight species. These bacteria are found throughout the environment, particularly in close association with plants. Strains of the most predominant species, *Stenotrophomonas maltophilia*, have an extraordinary range of activities that include beneficial effects for plant growth and health, the breakdown of natural and man-made pollutants that are central to bioremediation and phytoremediation strategies and the production of biomolecules of economic value, as well as detrimental effects, such as multidrug resistance, in human pathogenic strains. Here, we discuss the versatility of the bacteria in the genus *Stenotrophomonas* and the insight that comparative genomic analysis of clinical and endophytic isolates of *S. maltophilia* has brought to our understanding of the adaptation of this genus to various niches.

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The genus *Stenotrophomonas*, which is phylogenetically placed in the Gammaproteobacteria, was first described with the type species *Stenotrophomonas maltophilia*[1]. This species was originally named *Pseudomonas maltophilia* by Hugh and Ryschenko in 1961, but was later transferred to the genus *Xanthomonas*[2] before it was given its own genus[1]. The genus name (from the Greek 'stenos', meaning narrow, 'trophus', meaning one who feeds and 'monas', meaning unit) was intended to highlight the limited nutritional range of the bacterium[1]. However, several studies subsequently demonstrated that the genus is capable of great metabolic versatility and intraspecific heterogeneity[3–8] (FIG. 1). The genus currently comprises eight species, *S. maltophilia, Stenotrophomonas nitritireducens*[9], *Stenotrophomonas rhizophila*[10], *Stenotrophomonas acidaminiphila*[11], *Stenotrophomonas koreensis*[12], *Stenotrophomonas chelatiphaga*[13], *Stenotrophomonas terrae*[14] and *Stenotrophomonas humi*[14]. *Stenotrophomonas dokdonensis* was described in 2006 (REF. 15) but was transferred in 2008 to the genus *Pseudoxanthomonas*[16]. Phenotypic and genotypic studies as well as analysis of the ecological and metabolic diversity of these bacteria have revealed further differentiation at the species level.

Although *Stenotrophomonas* spp. occur ubiquitously in the environment, soil and plants are their main environmental reservoirs. *S. maltophilia* is a typical, often dominant member of the microbial communities that are found on or in plants and has a worldwide distribution (reviewed in REFS 17,18). Members of the genus *Stenotrophomonas* have an important ecological role in the nitrogen and sulphur cycles[19–21] and several *Stenotrophomonas* species, especially *S. maltophilia* and *S. rhizophila,* can engage in beneficial interactions with plants (FIG. 1). *S. maltophilia* is also an emerging human pathogen that is responsible for fatal infections in humans (reviewed in REFS 18,22). In contrast to the phylogenetically closely related genera *Xanthomonas* and *Xylella*, no *Stenotrophomonas* species are known to be phytopathogenic (FIG. 2).

Various molecular tools, including transposon mutagenesis, allelic exchange and reporter fusions, have been developed to facilitate the genetic analysis of the diverse activities of *Stenotrophomonas* spp. Furthermore, the full genome sequence of an environmental isolate, *S. maltophilia* R551-3, and a clinical isolate, *S. maltophilia* K279a, are now available. In this Review, we describe the versatility of bacteria from the genus *Stenotrophomonas*, using a comparison of these

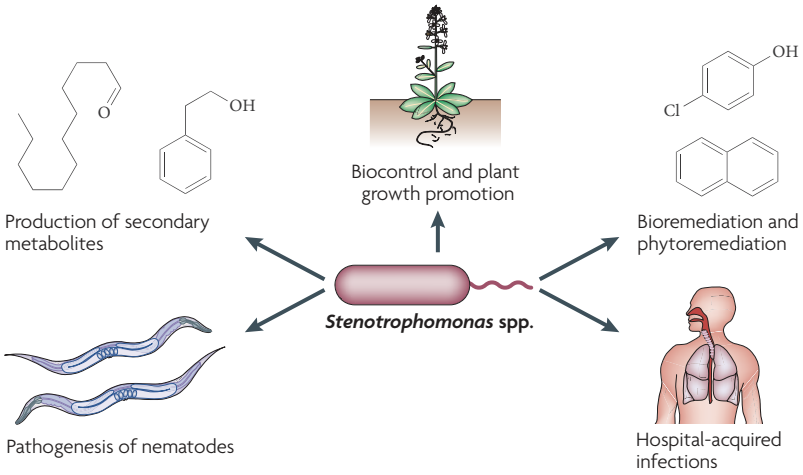

Figure 1 | **Biotechnological uses of *Stenotrophomonas spp.*** *Stenotrophomonas* spp. have many traits that could be used in different biotechnological processes. Some *Stenotrophomonas* spp. can produce antimicrobial compounds that protect plants, as well as generate factors that can promote plant growth. Also, many *Stenotrophomonas* spp. have a high level of intrinsic resistance to heavy metals and antibiotics and have been shown to degrade a wide range of compounds, including pollutants, and could potentially be used in bioremediation and phytoremediation. *Stenotrophomonas maltophilia* is also known to cause human disease as a result of its ability to colonize immunocompromised patients, and has been shown to be virulent in a nematode model.

recently sequenced genomes to highlight the possible genetic basis of adaptation to different niches.

Associations of *Stenotrophomonas* with plants

Stenotrophomonas species, especially *S. maltophilia* and *S. rhizophila*, are often found in association with plants. These bacteria can be isolated from the rhizosphere[23,24] or from internal plant tissues, particularly from the vascular tissues of the root and stem (FIG. 3; Supplementary information S1 (movie)). Endophytic strains of *S. maltophilia* have been isolated from the roots of many plant species, including cucumber (*Cucumis sativus*)[25], oilseed rape (*Brassica napus*)[26], potato (*Solanum tuberosum*)[26], strawberry (*Fragaria x ananassa*)[26], alfalfa (*Medicago sativa*)[27], sunflower (*Helianthus annuus*)[27], maize (*Zea mays*)[28], rice (*Oryza sativa*)[29], wheat (*Triticum astivum*)[30], various weeds, willow (*Salix herbacea*)[31] and poplar (*Populus*)[32].

Factors involved in plant colonization. Most *Stenotrophomonas* spp. are highly adaptable to hostile and nutrient-limited environments. Several factors have a known or suggested influence on the ability of *Stenotrophomonas* spp. to colonize and survive on plant surfaces. The establishment of interactions between plants and microorganisms in the rhizosphere is preceded by the movement of free-living microorganisms towards the plant roots and can involve chemotaxis towards attractants that are present in plant root exudates. In addition to flagellar motility, other contributing factors to the colonization of plant tissues include a high bacterial growth rate, vitamin B1 synthesis, the exudation of NADH dehydrogenase and bacterial lipopolysaccharides (LPSs), particularly the O antigen (reviewed in REFS 17,18). Furthermore, many *Stenotrophomonas* spp. can produce extracellular enzymes (proteases, lipases, nucleases, chitinases and elastases) that have been shown to be important in plant colonization by other rhizosphere microorganisms.

S. maltophilia produces various pili or fimbriae that have been implicated both in adhesion to surfaces[33] and in the formation of complex biofilms. Both adhesion and biofilm formation might contribute to the ability of *S. maltophilia* to compete with other microorganisms on the surface of plant roots, and are certainly important for the colonization of medical devices that leads to infection in humans[34]. de Oliveira-Garcia and colleagues[33] characterized SMF1 fimbriae from *S. maltophilia* strains SMDP92 and ATCC 1363. SMF1 fimbriae are composed of a 17 kDa fimbrin subunit that shares significant amino-terminal amino acid sequence similarity to the CupA fimbriae of *Pseudomonas aeruginosa* and to several fimbriae from pathogenic *Escherichia coli*. All of the clinical *S. maltophilia* isolates that were tested produced the 17 kDa fimbrin. The genomes of *S. maltophilia* strains K279a and R551-3 contain genes that encode type I pili (Sterm_0582-85, Sterm_1304-09 and Sterm_2358-66; based on R551-3 genome annotation), which have been implicated in adhesion and the early stages of biofilm formation, and type IV pili (Sterm_1417-22 and Sterm_3223–26), which have been implicated in adherence, auto-aggregation, twitching motility and biofilm formation. These gene clusters are distributed throughout each genome of the sequenced strains in a similar manner, which may indicate that there are some similarities in the plant and animal colonization strategies. Both *S. maltophilia* SMDP92 and ATCC 1363 carry *manA*, *manB*, *rmlB*, *rmlA*, *rmlC* and *rmlD* (also known as Stemr_0515-30), which encode enzymes involved in the biosynthesis of LPS and exopolysaccharides. Mutations in *manA*, *rmlA* and *rmlC* affect biofilm formation and twitching motility in *S. maltophilia* WR-C[35].

Epiphytic *Stenotrophomonas* bacteria can also alter the properties of the leaf surface to which they attach. Schreiber *et al.*[36] have demonstrated that *S. maltophilia* SaO5sm can increase the water permeability of *Hedera* and *Prunus* cuticles, which in turn should increase the availability of water and dissolved compounds in the phyllosphere, thereby enhancing the environmental growth conditions for the bacteria. The molecular mechanism (or mechanisms) responsible for the observed effects is as yet unknown, although it has been proposed that extracellular enzymes that degrade the cutin polymer and/or plasticizers, such as biosurfactants, could be responsible[37].

The synthesis of compatible solutes by bacteria contributes to their survival under the changing osmolarities that occur in the rhizosphere[38]. *S. maltophilia* accumulates trehalose as the only compatible solute, whereas *S. rhizophila* produces glucosylglycerol in addition to trehalose[39,40]. These sugars often accumulate intracellularly and protect against various stresses[41]. *S. maltophilia* K279a encodes the Smlt2757 and Smlt2759 proteins, which are involved in the biosynthesis of trehalose through the degradation of

Intraspecific heterogeneity
The quality of being diverse within a single species.

Rhizosphere
The zone around roots that is influenced by the plant and is a region of high microbial activity.

Endophytic
A microorganism that lives within a plant for at least part of its life cycle without causing apparent disease.

Epiphytic
Describes a bacterium that grows on or attaches to the surface of a living plant.

Phyllosphere
The micro-environment on the leaf surface of a plant.

Compatible solute
An organic compound that acts as a cytoplasmic solute to regulate water content for bacterial cells growing in environments of high osmolarity.

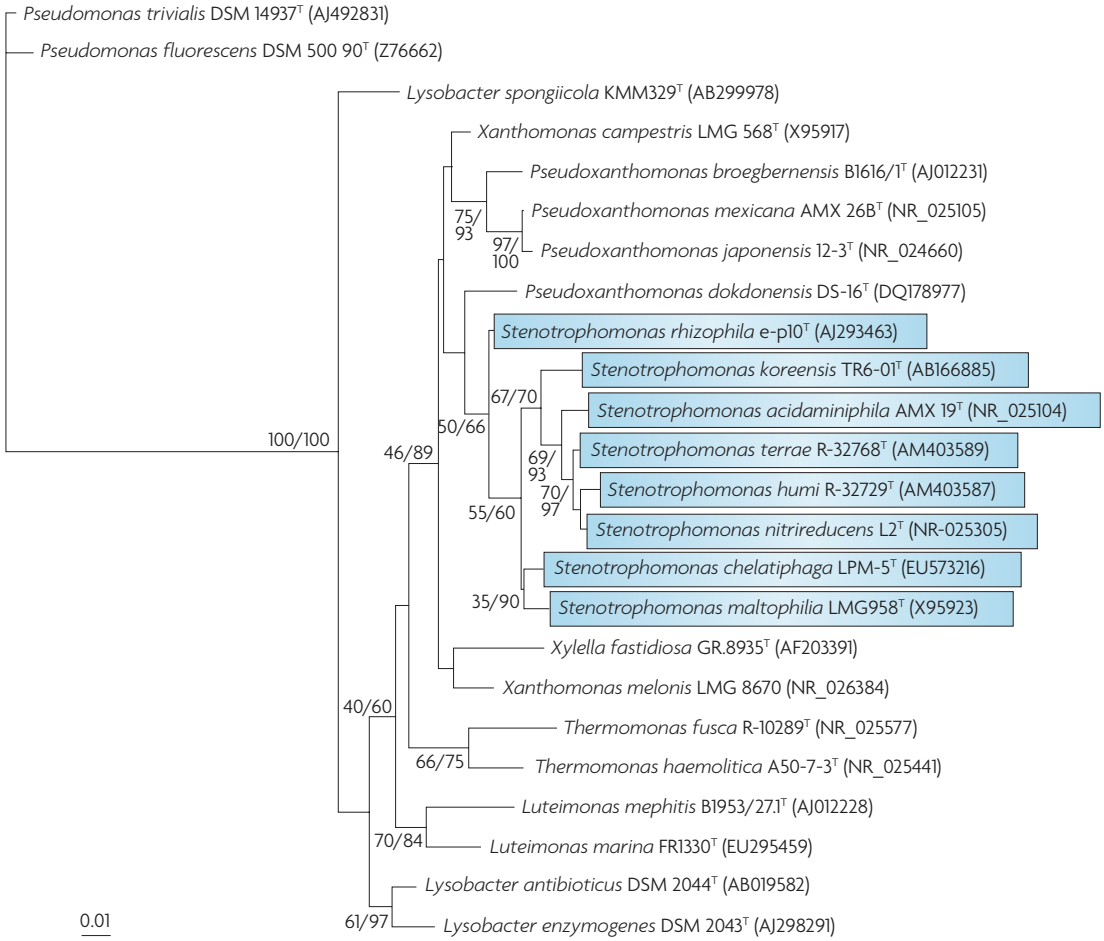

Figure 2 | **Phylogenetic analysis of the eight validly described *Stenotrophomonas* species and related taxa.** This neighbour-joining tree illustrates the maximum likelihood based on 16S rDNA sequences of *Stenotrophomonas* species and related taxa. Bootstrap values for >50% of 100 replicates (maximum likelihood/neighbour joining) are shown at the corresponding nodes. The scale bar represents 0.01 changes per nucleotide position.

glycogen by the TreY–TreZ pathway[42]. Genes encoding the enzymes in a second pathway for trehalose biosynthesis that involves the conversion of maltose (the trehalose synthase pathway), are carried on another region of the *S. maltophilia* K279a genome, which is absent from *S. maltophilia* R551-3 (Supplementary information S2 (table)). Both *S. maltophilia* K279a and *S. maltophilia* R551-3 can also produce trehalose from glucose through the trehalose-6-phosphate synthase–trehalose-6-phosphate phosphatase pathway (encoded by *otsA* and *otsB*). However, unlike the clinical isolate *S. maltophilia* K279a, the environmental isolate *S. maltophilia* R551-3 does not encode the pathway to use trehalose and therefore cannot use this sugar as a sole carbon source[32].

S. maltophilia might also have the capacity to protect itself from predation by soil protozoa, which could confer a selective advantage over other bacteria. The genome of the environmental isolate *S. maltophilia* R551-3 contains a cluster of six genes (Stemr_2139-44), which is absent from the *S. maltophilia* K279a isolate (Supplementary information S3 (table)). The *rebA–C* genes encode refractile inclusion bodies, known as R bodies, which are toxic to sensitive species of *Paramecium*[43], a genus of unicellular ciliate protozoa that live in freshwater environments. As similar *rebA* and *rebB* gene clusters are found in *Xanthomonas axonopodis* pv. *citri* str. 306 and in *Shewanella denitrificans* OS217, these proteins could conceivably have a role in the defence of bacteria against predation by protozoa in the rhizosphere or bulk soil.

Biotechnological uses of *Stenotrophomonas* spp.

Stenotrophomonas spp. are promising candidates for biotechnological applications in agriculture; treatment with *Stenotrophomonas* spp. can result in enhanced plant growth and can influence plant development on marginal soil (FIG. 1). For example, plant growth promotion of up to 180% was observed for wheat, tomato, lettuce, sweet pepper, melon, celery and carrot in the highly salinated soils of Uzbekistan[17]. *Stenotrophomonas* spp. also have promising applications in bioremediation and phytoremediation[44], as these bacteria can metabolize a large range of organic compounds that are present in the rhizosphere, including phenolic compounds found in plant root exudates. Accordingly, *S. maltophilia* can degrade *p*-nitrophenol and 4-chlorophenol[45], polycyclic aromatic hydrocarbons[46],

R body
A bacterial inclusion consisting of long proteinaceous ribbons rolled up inside the bacterial cell.

Phenolic compound
A chemical compound that is characterized by the presence of a hydroxyl group attached to a six-membered aromatic ring; many plants produce phenolic compounds.

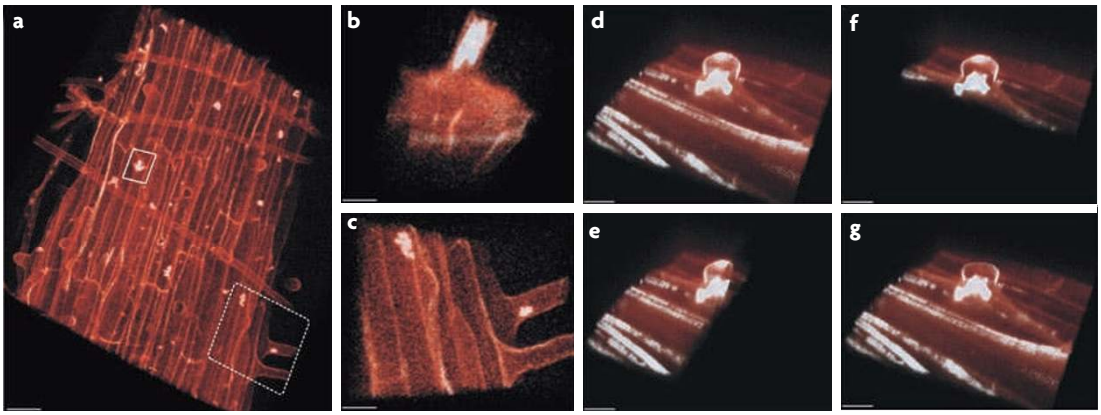

Figure 3 | **Root and endosphere colonization by *Stenotrophomonas rhizophila*.** Volume renderings of confocal laser scanning micrographs of DsRed-labelled *Stenotrophomonas rhizophila* DSM 14405^T cells in the rhizosphere of tomato plants. **a** | Colonization of 1-week-old tomato roots. The colonization pattern is characterized by small colonies that mainly grow inside the epidermal cells and the root hairs. **b**,**c** | Magnifications of the regions selected by the continuous line and dotted line, respectively, in part **a**, observed from a different angle. **d** | Seven *S. rhizophila* DSM 14405^T cells forming a cluster inside a new tomato root hair. **e**–**g** | Cutting planes of the image in panel **d** on the x, y and z axes, respectively. The scale bars represent 40 μm (**a**), 3 μm (**b**), 20 μm (**c**) and 5 μm (**d**–**g**). Images courtesy of C. Zachow, Graz University of Technology, Austria.

selenium compounds[47], benzene, toluene, ethylbenzene[48] and xenobiotics[44,48]. These broad metabolic properties could provide plants with protection against the phytotoxic effects of these compounds. *Stenotrophomonas* spp. can enhance plant productivity by several mechanisms, including the production of the plant growth hormone indole-3-acetic acid (IAA)[49], nitrogen fixation[21,50] and the oxidation of elemental sulphur, which in turn provides sulphate for the plants[19]. Examples of how *Stenotrophomonas* spp. have been used in such applications are provided in TABLE 1. In the following sections, we detail some of the traits of *Stenotrophomonas* spp. that make them amenable to such applications.

Metal tolerance. Many *S. maltophilia* strains have intrinsic resistance to various heavy metals[51,52]. For example, the *S. maltophilia* strains Sm777 and D457R have been shown to tolerate various toxic metals, such as cadmium, lead, cobalt, zinc, mercury and silver. When tested in tenfold diluted tryptic soy broth, strain Sm777 is additionally tolerant to 50 mM selenite, 25 mM tellurite and 50 mM uranyl salts. These properties of *S. maltophilia* have the potential to be exploited for bioremediation purposes or to aid phytoremediation. Furthermore, the tolerance of *S. maltophilia* strains to heavy metals could be useful in the bioremediation of soils that are polluted with heavy metals and xenobiotics.

A different complement of genes that specify metal tolerance has been identified in the *S. maltophilia* R551-3 and K279a genomes (Supplementary information S4 (table)). Genes coding for copper and mercury resistance, located on a genomic island in *S. maltophilia* K279a, were absent from the *S. maltophilia* R551-3 genome. Conversely, loci coding for arsenic resistance (*ars*, Stemr_2020-2024) and two tellurium resistance proteins (Stemr_2893-94) were identified in the *S. maltophilia* R551-3 genome but were absent from the *S. maltophilia* K279a genome.

Biocontrol properties. The potential of *Stenotrophomonas* spp. for the biocontrol of oomycete, fungal and bacterial pathogens has been demonstrated in several systems that include both monocotyledonous and dicotyledonous crops as hosts[53–61] (examples of these are provided in TABLE 1). *Stenotrophomonas* spp. can prevent the growth or activity of plant pathogens by several different mechanisms. *In vitro*, most *S. maltophilia* isolates have antifungal activity[7], and the new antifungal compounds maltophilin[62] and xanthobaccin[60] have been described. *Stenotrophomonas* spp. also produce volatile organic compounds (VOCs) with antifungal activity[63–65] (see below). *S. maltophilia* strains have an extraordinarily high hydrolytic potential; they produce diverse proteases, chitinases, glucanases, DNases, RNases, lipases and laccases[23,66,67]. Both chitinolytic and proteolytic activities contribute to the biocontrol activity of *S. maltophilia*[61,68–70]. Chitinases might protect plants against fungal pathogens through fungal cell wall lysis but might also have a role in triggering plant defence mechanisms[71]. A chitinase from *S. maltophilia* strain C5 was shown to suppress summer patch disease (caused by *Magnaporthe poae* Lanschoot and Jackson) in Kentucky bluegrass by the activation of disease resistance genes[72]. The precise roles of the other exoenzymes in the antagonistic activity of *S. maltophilia* remain to be elucidated and it is therefore likely that further bacterial products also control plant disease by inducing plant defences.

Another factor that is important for the control of fungal infection is competition for iron. *Stenotrophomonas* cells can efficiently capture siderophores that are produced by other microorganisms[73], such as ferrichrome, which is produced by fungi of several genera, including the phytopathogenic genus *Ustilago*[74]. Both of the sequenced *S. maltophilia* genomes encode many TonB-dependent receptors (TBDRs), outer membrane proteins that

Xenobiotic
A chemical that is only man-made, and otherwise is not found in the environment.

Biocontrol
The control of harmful pests and pathogens through the use of microorganisms.

Siderophore
A small organic molecule that is produced by bacteria to sequester iron.

Table 1 | **Applications of *Stenotrophomonas* spp. in biocontrol**

Strain	Pathogen and/or plant species	Refs
Stenotrophomonas maltophilia	Soil-borne pathogen	55
S. maltophilia	*Rhizoctonia solani* damping-off in bark compost media	58
S. maltophilia 3089	*Verticillium dahliae*; oilseed rape	54
S. maltophilia 34S1	Summer patch disease of turf grass	57,72
S. maltophilia C3*	Biocontrol of brown patch disease	56
Stenotrophomonas sp. strain SB-K88	Sugar beet damping-off disease	60
S. maltophilia C3*	*Bipolaris sorokiniana*; tall fescue	61
S. maltophilia W81 mutant with overproduction of an extracellular serine protease	Biological control of *Pythium ultimum*	54
S. maltophilia 18	*Fusarium graminearum*; wheat	155
S. maltophilia RAY132	Sulphur-oxidizing PGPR; canola	19
S. maltophilia PD3533	*Ralstonia solanacearum* race 3 biovar 2; potato	59
S. maltophilia R551-3	Endophytic strain isolated from poplar	32

*In a series of papers, the potential of *S. maltophilia* to control plant pathogens was described[56,61]. Later, a taxonomic study published by Sullivan *et al.* showed that this strain belongs to *Lysbacter enzymogenes*[156]. PGPR, plant growth promoting rhizobacteria.

are primarily known for the active transport of iron–siderophore complexes in Gram-negative bacteria. In *Xanthomonas campestris*, different subsets of TBDRs mediate iron uptake and the use of plant carbohydrates[75]. There are major differences, however, in the complement of genes encoding TBDRs; the *S. maltophilia* R551-3 genome carries 82 such genes compared with 65 in the *S. maltophilia* K279a genome. Many of the genes that are present in *S. maltophilia* R551-3 but absent from *S. maltophilia* K279a are linked to genes encoding proteins that are involved in iron transport and siderophore uptake. Such an over-representation of TBDRs is found in only a limited number of organisms, but is common in *Xanthomonas* spp. and in aquatic bacteria that scavenge complex carbohydrates[75]. Although both *S. maltophilia* R551-3 and K279a produce the siderophore enterobactin, this additional capacity for iron uptake suggests that iron competition with other organisms for endophytic (or rhizospheric) growth is important.

Bioactive natural products. Many plant-associated bacteria are well known for their diverse range of secondary metabolic products, including antibiotics, anticancer compounds, VOCs and antifungal, antiviral, insecticidal and immunosuppressant agents. *S. maltophilia* strains also produce bioactive compounds, including antibiotics and enzymes[76,77]. Several proteases produced by *Stenotrophomonas* spp. are so much more effective than those currently in use in industry that it is thought these proteases could 'revolutionize' washing agents[78]. A selection of these compounds has been highlighted in BOX 1. Although a wide range of biologically active compounds has been isolated from *Stenotrophomonas* spp., these organisms still remain an untapped source of novel natural products.

Biotope
The natural environment of a microorganism.

VOCs. The VOCs that are produced by *Stenotrophomonas* spp. can also negatively influence fungal growth and serve as inter- and intra-organismic communication signals[64,65]. Many different VOCs that are produced by *S. maltophilia* and *S. rhizophila* inhibit mycelial growth of the soil-borne pathogen *Rhizoctonia solani* by more than 90%[63]. Two of these VOCs have been characterized as β-phenylethanol and dodecanal. The precise mode of action of these secondary metabolites on the target organism is not known. By contrast, VOCs such as acetone, 2-methyl-1-butanol, heptanal and octanal, which are produced by *Trichoderma* spp., are known to reduce fungal growth by inhibiting protein synthesis[78].

Antimicrobial resistance

Many strains of *S. maltophilia* are also well known for their multiple antibiotic resistance phenotypes[7], which is consistent with the elevated antibiotic and bactericidal selection pressure that is found in their biotopes[79]. Multiple antibiotic resistance could help *S. maltophilia* to compete in the rhizosphere[3,79,80], which supports intense microbiological activity and competition in comparison to the nutrient-limited bulk soil. Comparative genomic analysis and experimental testing of the clinical and endophytic *S. maltophilia* isolates K279a and R551-3 showed that many of the genes that encode antimicrobial drug resistance and resistance-nodulation-division (RND) family transporters (tripartite efflux pumps that are involved in antibiotic resistance) are conserved (Supplementary information S4 (table)). In addition, the *S. maltophilia* R551-3 genome carries two additional RND operons (Stemr_2065-67 and Stemr_951-52) that are putatively involved in antibiotic efflux, a macrolide ATP-binding cassette-type transporter (Stemr_2509-10) and three putative major facilitator superfamily antibiotic transporters (Stemr_3598, Stemr_3605 and Stemr_3603, the last of which is putatively involved in chloramphenicol transport). The presence of these genes indicates that the endophytic and clinical strains have a similar level of antibiotic resistance, with possibly an even broader resistance spectrum for the endophytic strain *S. maltophilia* R551-3. In both strains, most antibiotic resistance genes are not associated with mobile genetic elements, such as phages or transposons, which makes it unlikely that *S. maltophilia* K279a acquired its antibiotic resistance genes in the clinical environment.

Adaptation and metabolic versatility

Stenotrophomonas spp. can efficiently colonize such different biotopes as plants, humans and marine environments. Comparative studies of the recently determined genome sequence of the endophytic *S. maltophilia* strain R551-3 with that of the clinical isolate *S. maltophilia* K279a have provided insight into functions that could be associated with adaptation to these different niches. Approximately 85% of the 4,175 *S. maltophilia* R551-3 genes are homologous to genes from *S. maltophilia* K279a, and have the same organization in both strains (FIG. 4). This indicates that the ancestral *S. maltophilia* core genome had to be well equipped to allow survival, colonization and competition for resources in such a

Box 1 | ***Stenotrophomonas* species as a source of useful compounds and activities**

Stenotrophomonas spp. have promising applications in bioremediation and phytoremediation[44] as a result of their ability to metabolize many of the compounds that are present in the rhizosphere, including xenobiotics. A selection of the xenobiotic compounds that *Stenotrophomonas* spp. can degrade is provided in the table. Strains of *Stenotrophomonas maltophilia* could be exploited in the bioremediation of polluted soils owing to their intrinsic resistance to heavy metals. *Stenotrophomonas* spp. are also capable of biocatalysis, including the conversion of linoleic acid to 10-hydroxy-12(Z)-octadecenoic acid.

Useful compound or activity	Refs
Degradation of xenobiotic compounds	
Biodegradation of *p*-nitrophenol, 4-chlorophenol and 4-nitroaniline	139
N-demethylation of the insecticide acetamiprid	140
Biodegradation of nonylphenol	141
Degradation of polypropylene glycols	142
Decolourization of synthetic dyes	67
Degradation of keratin	143
Degradation of herbicides 4-(2,4-dichlorophenoxy) butyric acid and 4-(4-chloro-2-methylphenoxy) butyric acid	144
Heavy metal tolerance and remediation	
Accumulation of intracellular uranium	145
Tolerance of heavy metals	52
Removal of Au(III) from contaminated waste water	146
Cr(VI) resistance	147
Biocatalysis and synthesis of novel compounds	
Conversion of linoleic acid to 10-hydroxy-12(Z)-octadecenoic acid	148
7α-OH epimerization of bile acids	149
Hydroxysteroid dehydrogenase	150
Cholylglycine hydrolase	150
Aminopeptidase activity against 4-hydroxyproline-containing peptides	151
Synthesis of glucosylglycerol	39
Saccharification of alginate	152
Synthesis of terephthalic acid	153
Production of the glycosidase inhibitor valienamine from validomycin A	154
Biocontrol and antimicrobial activity	
Production of antifungal xanthobaccins and the macrocyclic lactam antibiotic maltophilin	23,61

wide range of biotopes. Divergence in the gene complement of the two organisms might reflect adaptation to specific niches, and in the following sections we highlight some of these differences.

The *S. maltophilia* R551-3 genome contains 27 regions that are absent from *S. maltophilia* K279a; the size of these regions ranges from 1.7 kb to 61.5 kb (Supplementary information S2,S3 (tables)). Six of these regions represent putative genomic islands, as characterized by different codon usage from the rest of the genome, location next to a tRNA gene and/or the presence of a flanking integrase gene. By contrast, the genome of *S. maltophilia* K279a contains 19 regions that are absent from *S. maltophilia* R551-3 (Supplementary information S2,S3 (tables)), five of which are putative genomic islands[80]. These islands are often inserted at the same positions in both the *S. maltophilia* R551-3 and K279a genomes, which points to the existence of insertion hotspots in the core genome of this species (FIG. 5). In addition to genomic islands, the *S. maltophilia* R551-3 genome carries 14 complete insertion sequence (IS) elements: five intact copies of the IS*481* family, three intact copies of the IS*3* (also known as IS*150*) family (identical to IS*Psy9* from K279a) and six intact copies of the IS*110* family. Two additional truncated transposases of the IS*110* family were also identified. In addition, two phages were found, one of which (Stemr_910-36) also occurs in *S. maltophilia* K279a.

Filamentous haemagglutinin proteins are adhesins that are secreted by the type V protein secretion pathway and are involved in cell–cell aggregation. These filamentous haemagglutinins have also been shown to mediate contact between the phytopathogen *Xylella fastidiosa* and plant cells[81] and are important virulence factors that are involved in the adhesion of *Bordetella pertussis* to mammalian host cells[82]. *S. maltophilia* R551-3

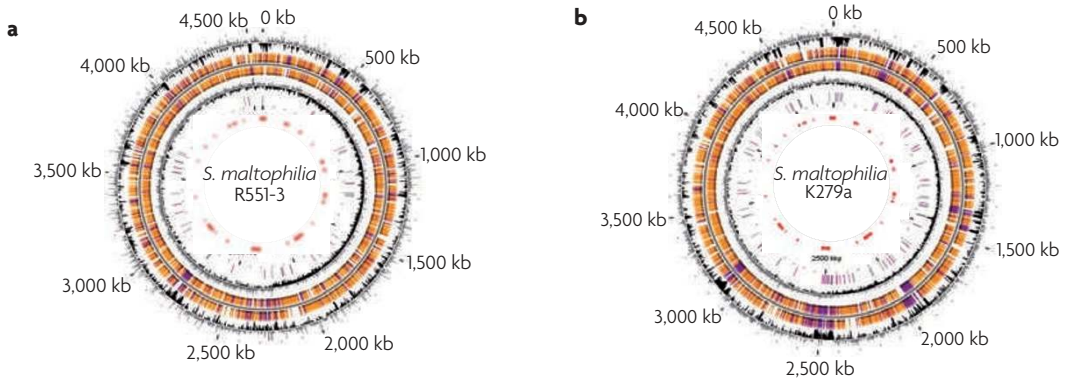

Figure 4 | **Genome maps of *Stenotrophomonas maltophilia* R551-3 and K279a.** Genome maps of the poplar endophyte *S. maltophilia* R551-3 (**a**) and of the opportunistic pathogen *S. maltophilia* K279a (**b**) are shown. From the outside in, the circles represent coordinates in kilobase pairs (kbp),%GC content, predicted open reading frames (ORFs) in the clockwise and anticlockwise orientations, GC skew ((G–C and G+C) in a 1,000-bp window), transposable elements (pink) and pseudogenes (grey), and the putative *S. maltophilia* K279a genomic islands (red).

encodes three filamentous haemagglutinins (Stemr_0113, Stemr_2248 and Stemr_2356). One of these (Stemr_0113) has a low level of amino acid sequence similarity (only 53% identity) with its *S. maltophilia* K279a homologue (*shlA*, which encodes Smlt1390) compared with the average similarity of proteins that are shared by the two strains. The *S. maltophilia* K279a haemagglutinin is located with five haemagglutinin open reading frame fragments. Another region that is specific to *S. maltophilia* K279a and is located on a putative complex transposon carries genes that encode an adhesin and a type IV pilus as well as a peptidase (Supplementary information S2 (table)). All these differences between *S. maltophilia* K279a and *S. maltophilia* R551-3 could be related to niche adaptation or host preference.

A key component of the bacterial outer membrane is LPS, and changes in LPS structure have been correlated with changes in resistance to various antimicrobial agents. Many studies have examined the LPS in *S. maltophilia* in an effort to assess its contribution to antimicrobial resistance in this organism[83,84] and as a basis for serotyping. As outlined above, mutations in *manA*, *rmlA* and *rmlC* affect LPS structure in *S. maltophilia* WR-C[35]. Adjacent to these genes in the sequenced genomes is a locus that is also probably involved in LPS biosynthesis and that shows considerable variability between the two *S. maltophilia* strains (Supplementary information S5 (figure)). This locus is flanked by the genes encoding cystathionine gamma lyase (*metB*) at one end and an electron transport flavoprotein (*etfA*) at the other. An equivalently located, highly variable LPS locus has been described in a range of xanthomonads that infect rice, citrus and crucifers[85] and was probably acquired by horizontal gene transfer[85]. Differences in the complement and nature of the genes in this locus are indicative of alterations in the structure of LPS, particularly the O antigen moiety. Serotyping of heat-stable O antigens from *S. maltophilia* has revealed a considerable level of variation between isolates, with 31 defined serotypes. The structure of the O antigen polysaccharides has been described for a number of these serotypes. Most of the polymers have branched repeating units, often with lateral pentosyl substitutions[86].

Variation in LPS biosynthetic gene clusters between strains is common in bacterial pathogens of animals, for which it might have a role in evading the host immune system. The role of differences in O antigen or LPS structure between related plant pathogenic or plant-associated bacteria is less certain, although involvement in host-range selection and specificity has been proposed[87]. Serotype analysis of a range of *S. maltophilia* strains, however, shows no clear delineation between clinical and environmental isolates. Furthermore, other roles for variations in O antigen structure, such as promoting insensitivity to phage infection, should not be overlooked.

The endophytic strain *S. maltophilia* R551-3, which has no direct plant growth promoting effects on its poplar host, does not carry genes for the plant growth promotion mechanisms that have been described for other endophytes, such as metabolism of the plant signal molecules γ-amino butyric acid and phenyl acetic acid, degradation of the ethylene precursor 1-aminocyclopropane-1-carboxylic acid and acetoin production. In addition, only low levels of IAA are produced by *S. maltophilia* R551-3 (REF. 32).

Although *S. maltophilia* is related to plant pathogenic *Xanthomonas* spp., it is not a phytopathogen and accordingly neither the *S. maltophilia* K279a nor R551-3 genomes encode genes that are known to contribute to *Xanthomonas* virulence, including those encoding the type III secretion system and genes encoding certain plant cell wall degrading enzymes, such as pectinases. These sequences also do not seem to encode the virulence factor type VI secretion system. In addition, neither genome carries the zonula occludens toxin (*zot*) gene that was identified in several clinical isolates of *S. maltophilia*[88]. This gene is similar to the *zot* gene in *Vibrio cholerae*, which encodes the major virulence factor enterotoxin[88]. However, genes that are involved in phytopathogenesis, including those encoding enzymes such as cellulase (glycosyl hydrolase family 5) and those encoding type I, type II (*Sec*), type IV, type V and the twin arginine transporter (TAT) secretion systems, are present. Functional genomic analysis will allow an

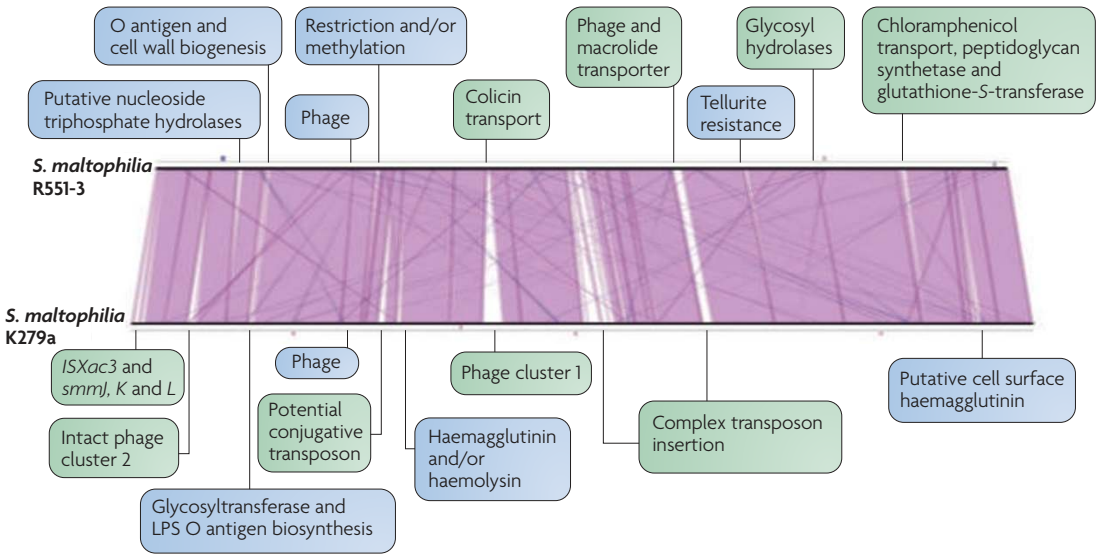

Figure 5 | **Comparison of gene content and organization in the genomes of *Stenotrophomonas maltophilia* R551-3 and K279a.** The genomes were compared using LinePlot from MaGe (see Further information). Syntenic regions between *S. maltophilia* R551-3 and K279a are displayed in purple, and the location and putative functions of selected genes within regions that are specific to each strain are indicated. The green boxes represent putative genomic islands whereas the blue boxes represent virulence genes. LPS, lipopolysaccharide.

investigation of the factors that are important for the association of *Stenotrophomonas* spp. with plants.

S. maltophilia: an opportunistic pathogen

S. maltophilia is the only species of *Stenotrophomonas* that is known to cause human disease[5], but there is considerable phylogenetic and phenotypic variability among *S. maltophilia* isolates, including those from patients in a single hospital[89–91]. This is probably the result of the many environmental niches of this bacterium; most infections are likely to reflect contact with separate environmental sources. Indeed, there are few instances of outbreaks of *S. maltophilia*, and those that occur are caused by a single contaminated source, such as a water source[92–95]. Despite this, there is evidence that certain phylogenetic groups are better able to cause infection than others[96].

S. maltophilia is almost exclusively a hospital-acquired pathogen and has been associated with bacteraemic infections and pneumonia, both with a high rate of mortality[97], in immunocompromised patients. This reflects a requirement for three major risk factors for infection: severe debilitation and/or neutropenia; the presence of indwelling devices such as ventilator tubes and/or intravenous catheters for prolonged periods; and multiple and/or prolonged courses of broad-spectrum antimicrobial drugs[98–100]. There are also examples of soft tissue, ocular, wound and burn infections, and endocarditis[18].

The bacteraemia isolate *S. maltophilia* K279a carries several genes that encode factors that could allow this strain to adhere to surfaces and form biofilms, which are both key factors in the colonization of indwelling devices. Studies have shown that *S. maltophilia* isolates have cytotoxic effects *in vitro* against HEp-2, Vero and HeLa cell lines after 24 hours[101], and *S. maltophilia* K279a killed almost all of the N2 *Caenorhabditis elegans* in the assay within 24 hours[102]. However, as one might expect of a true opportunist, *S. maltophilia* has no type III secretion system[80].

A recent study by Waters and colleagues[103] tried to address the lack of documentation of the potential of *S. maltophilia* for virulence by investigating the immunostimulatory properties of 24 *S. maltophilia* clinical respiratory and non-respiratory isolates (from blood, skin and soft tissue). In this study, which involved a neonatal mouse model of pneumonia and macrophage cell lines, they determined the rates of pneumonia, bacteraemia and mortality, as well as the inflammatory response that is elicited by *S. maltophilia* infection. They demonstrated that the respiratory and non-respiratory *S. maltophilia* isolates were highly immunostimulatory but weakly invasive, which indicates that these isolates could contribute to airway inflammation.

Whether *S. maltophilia* clinical isolates are colonizers or true pathogens is still controversial in some cases. This is particularly the case for pneumonia, because it is rare to culture pure *S. maltophilia* from the lungs, and severely debilitated patients are often colonized asymptomatically[104,105]. Nonetheless, a recent study showed that 4.5% of nosocomial pneumonia in patients in intensive care units and 6% of ventilator-associated pneumonias are caused by *S. maltophilia*[106]. The attributable mortality for *S. maltophilia* pneumonia (as far as this can be accurately quantified in patients with multiple and complex pathologies) is estimated at 20–30%[107]. As many as 25% of adult patients with cystic fibrosis carry *S. maltophilia* in their lungs at any one time, although these numbers are highly variable[108]. Also, there is no evidence of any reduction in lung function associated

with *S. maltophilia* colonization[109]. Although the rates are variable, approximately 1% of all nosocomial bacteraemias are caused by *S. maltophilia* and the attributed mortality has been estimated at approximately 25%[110]. These bacteraemias are usually caused by an indwelling device, and the prognosis is usually good following the removal of the device[111–113].

The primary reason for the increase in *S. maltophilia* infections is the intrinsic resistance of this species to many front-line antimicrobials, such as β-lactams, including carbapenems[114], aminoglycosides (except gentamicin)[48,80,115,116], macrolides, tetracycline, chloramphenicol and older quinolones[80,117–119]. Furthermore, *S. maltophilia* isolates can rapidly develop resistance to newer fluoroquinolones, gentamicin and minocycline through mutation; the underlying mechanisms are not certain, but are likely to be the result of the overproduction of intrinsic efflux pumps[89]. Typically, empiric therapy for *S. maltophilia* is trimethoprim–sulphamethoxazole (TMP–SMX), to which >95% of isolates are sensitive[120,121]. However, resistance is increasing as a result of the spread of acquired mobile resistance determinants[122,123] and, in many patients, TMP–SMX therapy is contra-indicated[124]. Alternatives include ticarcillin–clavulanate, respiratory quinolones such as gatifloxacin and moxifloxacin, minocycline and possibly tigecycline[120,125]. For how long these drugs would remain clinically efficacious if they were used as front-line therapy is uncertain, however, as resistant mutants arise spontaneously at high rates *in vitro*[96] (V. C. Gould and M.B.A., unpublished observations).

The *de novo* mobilization of antibiotic resistance genes from environmental bacteria or opportunistic pathogens has contributed greatly to the increase in antibiotic resistance in more common and important pathogens. Examples include the mobilization of the *SHV* and *CTX-M* β-lactamase genes from *Klebsiella pneumoniae* and *Kluyvera* spp., respectively, on composite transposons that are likely to have formed since the clinical use of antibiotics began[126,127]. One potential consequence of the increased colonization of patients by *S. maltophilia* is the mobilization of its L1 metallo-β-lactamase gene onto a plasmid that can then confer broad-spectrum β-lactam resistance, including to the last-line carbapenems, in *P. aeruginosa* and even the Enterobacteriaceae. Another possibility is the mobilization of a potential quinolone resistance determinant, *qnr*, that was identified in the *S. maltophilia* K279a[128] and R551-3 genome sequences (Supplementary information S4 (table)). Resistance plasmid and transposon carriage has been demonstrated in *S. maltophilia*, as has sharing of these elements with *E. coli in vitro*[123,129–131], suggesting that it might be only a matter of time before L1 mobilization occurs, which would be a hugely significant event.

Polymicrobial infections and interspecies signalling. There is an increasing appreciation of the polymicrobial nature of human infections and of the potentially important role for interspecies interactions in bacterial virulence and the response to therapy. *S. maltophilia* can be found together with the opportunistic pathogen *P. aeruginosa* in diverse niches, including the lungs of patients with cystic fibrosis, where *S. maltophilia* can protect antibiotic-sensitive strains of *P. aeruginosa* by degrading antibiotics[132]. Interspecies signalling between these organisms can also influence *P. aeruginosa*. *S. maltophilia* possesses a cell–cell signalling system that is mediated by a diffusible signal factor (DSF) that was first identified in the related plant pathogen *X. campestris*[102,133]. In *S. maltophilia* strain WR-C the DSF can be one of eight structurally related fatty acids that include *cis*-11-methyl-2-dodecenoic acid, the DSF signal from *X. campestris*[133,134]. Genome analyses revealed that *S. maltophilia* does not synthesize *N*-acyl homoserine lactones (*N*-AHLs) or autoinducer 2 (AI2), which are signal molecules that are commonly found in other Gram-negative organisms, and *N*-AHLs have not been detected in *S. maltophilia* cultures[135,136]. In the clinical isolate *S. maltophilia* K279a, DSF signalling controls several functions, including the production of an extracellular protease, aggregative behaviour and virulence in a nematode model[102]. Although *P. aeruginosa* does not synthesize DSF, it can respond to the signal that is produced by *S. maltophilia* by altering biofilm architecture and increasing tolerance to the cationic antimicrobial peptides polymyxin B and colistin[137,138]. This response of *P. aeruginosa* to DSF requires PA1396, a sensor kinase with an input domain that is related to the sensory input domain of RpfC, which is responsible for DSF perception in xanthomonads. Homologues of PA1396 occur in other pseudomonads, some of which are plant pathogenic or plant associated, as well as in unrelated bacteria, including the poplar endophyte *Enterobacter* sp. 638. These observations indicate that modulation of bacterial behaviour through DSF-mediated interspecies signalling with *S. maltophilia* is a phenomenon that could also occur in a non-pathogenic context in rhizospheric or endophytic communities.

Implications for biotechnological uses. The application of rhizospheric and endophytic *S. maltophilia* strains to control plant pathogens[59] or promote plant health should be carefully considered. Not only do these strains present a risk as reservoirs for antibiotic resistance genes, but they also have potential as opportunistic pathogens. It is known that clinical isolates of *S. maltophilia* and other opportunistic pathogens can actively multiply in the rhizosphere[49]. This has led to suggestions that the rhizosphere is an environmental reservoir for such opportunists. Furthermore, the mechanisms responsible for the colonization of plants and for the antagonistic activity of *S. maltophilia* strains against plant pathogens are similar to those that are responsible for the colonization of human tissues and for pathogenicity[79]. Such considerations should perhaps be translated into appropriate measures, such as banning plants from hospitals.

Concluding remarks

A fuller understanding of the versatility, adaptation and potential uses of this fascinating group of organisms presents both considerable challenges and opportunities for the future. Determination of the genome sequences of the clinical and endophytic *S. maltophilia* strains forms the basis for functional genomic analyses

Riboswitch
A conformational switch in RNA molecules that is induced by small metabolites and leads to a switch in gene regulatory function.

to test the contribution of specific functions to the tenacity of these bacteria in colonization, their broad resistance to antibiotics and their ability to enter into close endophytic associations with plants. These studies might also be expected to reveal alternative targets for antimicrobial action that could include interference with quorum sensing or cell–cell signalling, interference with the action of riboswitches and inhibition of adherence to surfaces and biofilm formation. Given the ubiquitous nature of *Stenotrophomonas* spp., the impact of interactions with other organisms in polymicrobial communities, which may be associated with infections or endophytic colonization, merits attention. Further insights into the role of *Stenotrophomonas* spp. in the nitrogen cycle should emerge from analysis of the genome of *Stenotrophomonas* sp. SKA14, a nitrogen-fixing bacterium that was isolated from the Baltic Sea. The sequencing of other *Stenotrophomonas* spp., such as *S. rhizophila*, that have potential uses in promoting plant growth, biocontrol or bioremediation but are not pathogenic are also warranted. Finally, *Stenotrophomonas* spp. should continue to be a source of useful or novel enzymatic capabilities, reflecting their metabolic versatility.

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DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
etfA | *metB*

Entrez Genome Project: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj
Bordetella pertussis | *Caenorhabditis elegans* | *Escherichia coli* | *Klebsiella pneumoniae* | *Medicago sativa* | *Pseudomonas aeruginosa* | *Rhizoctonia solani* | *Shewanella denitrificans* | *Solanum tuberosum* | *Stenotrophomonas maltophilia* K279a | *Stenotrophomonas maltophilia* R551-3 | *Triticum astivum* | *Vibrio cholerae* | *Xanthomonas axonopodis* | *Xanthomonas campestris* | *Xylella fastidiosa* | *Zea mays*

UniProtKB: http://www.uniprot.org
CupA | PA1396 | SME1 | Smlt1390 | Smlt2757 | Smlt2759 | Zot

FURTHER INFORMATION

MaGe: http://www.genoscope.cns.fr/agc/mage
***Stenotrophomonas maltophilia* K279a genome:**
http://www.sanger.ac.uk/Projects/S_maltophilia
***Stenotrophomonas maltophilia* 5513 genome:**
http://genome.jgi-psf.org/finished_microbes/stema/stema.home.html

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