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Taxonomy, Physiology, and Natural Products of *Actinobacteria*

Essaid Ait Barka,[a] Parul Vatsa,[a] Lisa Sanchez,[a] Nathalie Gaveau-Vaillant,[a] Cedric Jacquard,[a] Hans-Peter Klenk,[b] Christophe Clément,[a] Yder Ouhdouch,[c] Gilles P. van Wezel[d]

Laboratoire de Stress, Défenses et Reproduction des Plantes, Unité de Recherche Vignes et Vins de Champagne, UFR Sciences, UPRES EA 4707, Université de Reims Champagne-Ardenne, Reims, France[a]; School of Biology, Newcastle University, Newcastle upon Tyne, United Kingdom[b]; Faculté de Sciences Semlalia, Université Cadi Ayyad, Laboratoire de Biologie et de Biotechnologie des Microorganismes, Marrakesh, Morocco[c]; Molecular Biotechnology, Institute of Biology, Sylvius Laboratories, Leiden University, Leiden, The Netherlands[d]

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Published 25 November 2015

Citation Barka EA, Vatsa P, Sanchez L, Gaveau-Vaillant N, Jacquard C, Klenk H-P, Clément C, Ouhdouch Y, van Wezel GP. 2016. Taxonomy, physiology, and natural products of *Actinobacteria*. Microbiol Mol Biol Rev 80:1–43. doi:10.1128/MMBR.00019-15.

Address correspondence to Essaid Ait Barka, ea.barka@univ-reims.fr, or Gilles P. van Wezel, g.wezel@biology.leidenuniv.nl.

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SUMMARY

Actinobacteria are Gram-positive bacteria with high G+C DNA content that constitute one of the largest bacterial phyla, and they are ubiquitously distributed in both aquatic and terrestrial ecosystems. Many *Actinobacteria* have a mycelial lifestyle and undergo complex morphological differentiation. They also have an extensive secondary metabolism and produce about two-thirds of all naturally derived antibiotics in current clinical use, as well as many anticancer, anthelmintic, and antifungal compounds. Consequently, these bacteria are of major importance for biotechnology, medicine, and agriculture. *Actinobacteria* play diverse roles in their associations with various higher organisms, since their members have adopted different lifestyles, and the phylum includes pathogens (notably, species of *Corynebacterium*, *Mycobacterium*, *Nocardia*, *Propionibacterium*, and *Tropheryma*), soil inhabitants (e.g., *Micromonospora* and *Streptomyces* species), plant commensals (e.g., *Frankia* spp.), and gastrointestinal commensals (*Bifidobacterium* spp.). *Actinobacteria* also play an important role as symbionts and as pathogens in plant-associated microbial communities. This review presents an update on the biology of this important bacterial phylum.

INTRODUCTION

The phylum *Actinobacteria* is one of the largest taxonomic units among the major lineages currently recognized within the *Bacteria* domain (1). The actinobacterial genomes sequenced to date belong to organisms relevant to human and veterinary medicine, biotechnology, and ecology, and their observed genomic heterogeneity is assumed to reflect their biodiversity (2). The majority of the *Actinobacteria* are free-living organisms that are widely distributed in both terrestrial and aquatic (including marine) ecosystems (3). *Actinobacteria* are Gram-positive filamentous bacteria with a high guanine-plus-cytosine (G+C) content in their genomes. They grow by a combination of tip extension and branching of the hyphae. This is what gave them their name, which derives from the Greek words for ray (aktis or aktin) and fungi (mukēs). Traditionally, actinomycetes were considered transitional forms between fungi and bacteria. Indeed, like filamentous fungi, many *Actinobacteria* produce a mycelium, and many of these mycelial actinomycetes reproduce by sporulation. However, the comparison to fungi is only superficial: like all bacteria, actinomycetes' cells are thin with a chromosome that is organized in a prokaryotic nucleoid and a peptidoglycan cell wall; furthermore, the cells are susceptible to antibacterial agents (Fig. 1). Physiologically and ecologically, most *Actinobacteria* are aerobic, but there are exceptions. Further, they can be heterotrophic or chemoautotrophic, but most are chemoheterotrophic and able to use a wide variety of nutritional sources, including various complex polysaccharides (4, 5). *Actinobacteria* may be inhabitants of soil or aquatic environments (e.g., *Streptomyces*, *Micromonospora*, *Rhodococcus*, and *Salinispora* species), plant symbionts (e.g., *Frankia* spp.), plant or animal pathogens (e.g., *Corynebacterium*, *Mycobacterium*, or *Nocardia* species), or gastrointestinal commensals (e.g., *Bifidobacterium* spp.).

BIOLOGY OF *ACTINOBACTERIA*

Most of the *Actinobacteria* (the streptomycetes in particular) are saprophytic, soil-dwelling organisms that spend the majority of their life cycles as semidormant spores, especially under nutrient-limited conditions (6). However, the phylum has adapted to a wide range of ecological environments: actinomycetes are also present in soils, fresh and salt water, and the air. They are more abundant in soils than other media, especially in alkaline soils and soils rich in organic matter, where they constitute an important part of the microbial population. *Actinobacteria* can be found both on the soil surface and at depths of more than 2 m below ground (7).

The population density of *Actinobacteria* depends on their habitat and the prevailing climate conditions. They are typically present at densities on the order of 10^6 to 10^9 cells per gram of soil (7); soil populations are dominated by the genus *Streptomyces*, which accounts for over 95% of the *Actinomycetales* strains isolated from soil (8). Other factors, such as temperature, pH, and soil moisture, also influence the growth of *Actinobacteria*. Like other soil bacteria, *Actinobacteria* are mostly mesophilic, with optimal growth at temperatures between 25 and 30°C. However, thermophilic *Actinobacteria* can grow at temperatures ranging from 50 to 60°C (9). Vegetative growth of *Actinobacteria* in the soil is favored by low humidity, especially when the spores are submerged in water. In dry soils where the moisture tension is greater,

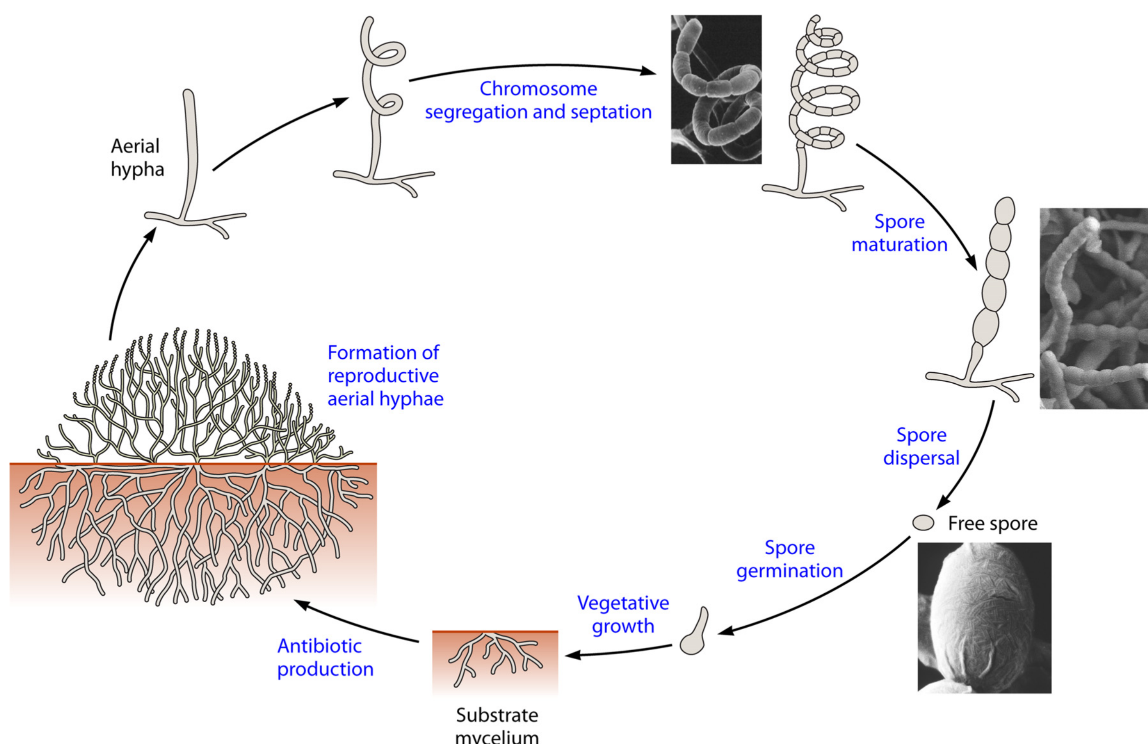

FIG 1 Schematic representation of the life cycle of sporulating actinomycetes.

growth is very limited and may be halted. Most *Actinobacteria* grow in soils with a neutral pH. They grow best at a pH between 6 and 9, with maximum growth around neutrality. However, a few strains of *Streptomyces* have been isolated from acidic soils (pH 3.5) (10). The first study on the effect of climate on the distribution of *Actinobacteria* was done by Hiltner and Strömer (11), who showed that these bacteria account for 20% of the microbial flora of the soil in spring and more than 30% in the autumn because of the large amounts of crop residues available at this time of year. However, during the winter, frost reduces their relative abundance to only 13%.

Taxonomy of *Actinobacteria*

Actinobacteria represent one of the largest taxonomic units among the 18 major lineages currently recognized within the *Bacteria* domain, including 5 subclasses, 6 orders, and 14 suborders (1). The genera of this phylum exhibit enormous diversity in terms of their morphology, physiology, and metabolic capabilities. The taxonomy of *Actinobacteria* has evolved significantly over time with the accumulation of knowledge. The order *Actinomycetales*, established by Buchanan in 1917 (12), belongs to this group of prokaryotic organisms.

The phylum *Actinobacteria* is delineated on the basis of its branching position in 16S rRNA gene trees. However, rRNA sequences do not discriminate well between closely related species or even genera, which can create ambiguity. For instance, the taxonomic status of the genus *Kitasatospora* (13) within the family *Streptomycetaceae* has been disputed for many years (1, 14, 15), although a recent detailed genetic analysis provided strong evidence that it should be regarded as a separate genus (16). A similar close relationship exists between *Micromonospora*, *Verrucosispora*, and *Salinispora*. Additional genetic markers have therefore been used to discriminate between closely related genera, including *rpoB* and, most recently, *ssgB*, which is particularly useful for discriminating between closely related genera (17). Moreover, the massive recent increase in the availability of genome sequence information has provided detailed insights into genome evolution and made it possible to identify genes specific to organisms at the level of genera and family (18).

An updated taxonomy of the phylum *Actinobacteria* that is based on 16S rRNA trees was recently reported (1). That update eliminated the taxonomic ranks of subclasses and suborders, elevating the former subclasses and suborders to the ranks of classes and orders, respectively (19). The phylum is thus divided into six classes: *Actinobacteria*, *Acidimicrobiia*, *Coriobacteriia*, *Nitriliruptoria*, *Rubrobacteria*, and *Thermoleophilia*.

The class *Actinobacteria* contains 16 orders, including both of the previously proposed orders, *Actinomycetales* and *Bifidobacteriales* (20). The order *Actinomycetales* is now restricted to the members of the family *Actinomycetaceae*, and the other suborders that were previously part of this order are now designated distinct orders (19). Consequently, 43 of the 53 families within the phylum *Actinobacteria* are assigned to a single class, *Actinobacteria*, whereas the other five classes together contain only 10 families (21).

Morphological classification. The main characteristics used to delineate the taxonomy of *Actinobacteria* at the genus and species levels are microscopic morphology and chemotaxonomy. The latter of these characteristics primarily relates to the composition of the cell wall and the whole-cell sugar distribution, although phospholipid composition and menaquinone type may also be considered for fine-tuning purposes (22).

Mycelial fragmentation can be regarded as a special form of vegetative reproduction. However, the *Actinobacteria* with primarily mycelial lifestyles usually reproduce by forming asexual spores. *Actinobacteria* exhibit a wide variety of morphologies, differing mainly with respect to the presence or absence of a substrate mycelium or aerial mycelium, the color of the mycelium, the production of diffusible melanoid pigments, and the structure and appearance of their spores (Fig. 1).

(i) Mycelial morphology. Except for *Sporichthya* sp., which produces aerial hyphae that are initiated upright on the surface of the medium by holdfasts, *Actinobacteria* form a substrate mycelium in both submerged and solid-grown cultures. However, on solid surfaces, many differentiate to form aerial hyphae, whose main purpose is to produce reproductive spores (23, 24). The substrate mycelium develops from outgrowth of a germinating spore. The branching substrate mycelium is often monopodial, but in some rare cases, *Actinobacteria*, such as *Thermoactinomyces*, exhibit dichotomous branching (25). On the other hand, members of the *Micromonosporaceae* family produce an extensive substrate mycelium with an absent or rudimentary aerial mycelium.

Actinobacteria exhibit a wide variety of morphologies, including coccoid (*Micrococcus*) and rod-coccoid (*Arthrobacter*), as well as fragmenting hyphal forms (*Nocardia* spp.) and also forms with permanent and highly differentiated branched mycelia (e.g., *Streptomyces* spp., *Frankia*) (26). Rhodococci form elongated filaments on the substrate and do not produce a true mycelium (27), while corynebacteria do not produce mycelia at all. However, as in other *Actinobacteria*, the filaments grow at the apex instead of by lateral wall extension (28, 29). *Actinobacteria* belonging to the genus *Oerskovia* are characterized by the formation of branched substrate hyphae that break up into flagellated motile elements (30). Further, mycobacteria and rhodococci do not usually form aerial hyphae, although some exceptions exist (31).

(ii) Spore chain morphology. Spores are extremely important in the taxonomy of *Actinobacteria* (32). The initial steps of sporulation in several oligosporic *Actinobacteria* can be regarded as budding processes, because they satisfy the main criteria used to define budding in other bacteria (Fig. 2). Spores may be formed on the substrate and/or the aerial mycelium as single cells or in chains of different lengths. In other cases, spores may be harbored in special vesicles (sporangia) and endowed with flagella.

Thus, in the genera *Micromonospora*, *Micropolyspora*, and *Thermoactinomycètes*, spore formation occurs directly on the substrate mycelium (33), whereas in *Streptomyces* the spores grow out from the aerial mycelium. The *Actinoplanes* and *Actinosynnema* groups are characterized by motile spores, while *Thermoactinomyces* has unique heat-resistant endospores (33). Some other *Actinobacteria* genera have sclerotia (*Chainia*), synnemas (*Actinosynnema*), vesicles that contain spores (*Frankia*), or vesicles that are devoid of spores (*Intrasporangium*). Other genera, such as *Actinoplanes*, *Ampulariella*, *Planomonospora*, *Planobispora*, *Dactylosporangium*, and *Streptosporangium*, are classified based on their sporangial morphology. Figure 2 illustrates the different types of spores that can be found in actinomycetal genera. Finally, the morphology of the spores themselves can also be used to characterize species: they may have smooth, warty, spiny, hairy, or rugose surfaces (34).

(iii) Spore chain length. The number of spores per spore chain varies widely from genus to genus. The genera *Micromonospora*, *Salinispora*, *Thermomonospora*, *Saccharomonospora*, and *Promicromonospora* produce isolated spores, while *Microbispora* produces spores in longitudinal pairs. Members of the genera *Actinomadura*, *Saccharopolyspora*, *Sporicthya*, and some *Nocardia* spp. have short spore chains, while members of the genera *Streptomyces*, *Nocardioides*, *Kitasatospora*, *Streptoverticillium*, and some *Nocardia* spp. produce very long chains of up to 100 spores. In contrast, *Frankia* species produce sporangia, which are essentially bags of spores. Streptomycetes' spore chains can be classified as being straight to flexuous (Rectus-Flexibilis), open loops (Relinaculam-Apertum), open or closed spirals (spira), or verticillate (35).

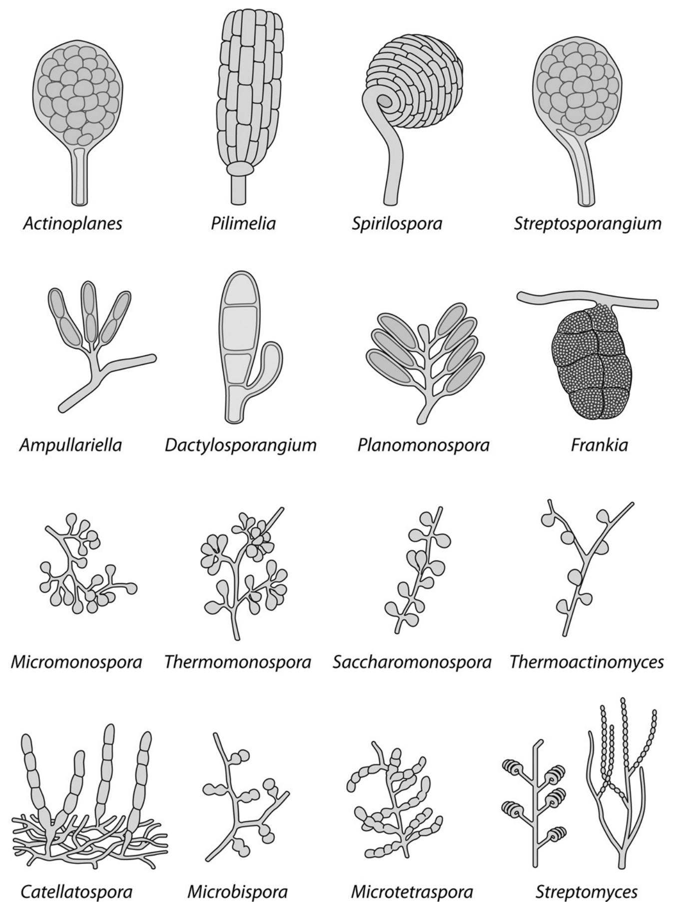

FIG 2 Schematic drawings of the different types of spore chains produced by actinomycetes.

(iv) Melanoid pigments. Melanins are polymers with diverse molecular structures that typically appear black or brown and are formed by the oxidative polymerization of phenolic and indolic compounds. They are produced by a broad range of organisms, ranging from bacteria to humans. *Actinobacteria* have long been known to produce pigments, which may be red, yellow, orange, pink, brownish, distinct brown, greenish brown, blue, or black, depending on the strain, the medium used, and the age of the culture (4).

Generally referred to as melanins, or melanoid pigments, these brown-black metabolic polymers are important not only because of their usefulness in taxonomic studies but also because of their similarity to soil humic substances (36, 37). Melanins are not essential for the organisms' growth and development, but they play a crucial role in improving their survival and competitiveness.

TABLE 1 Different types of cell wall components in *Actinomycetes*[a]

Cell wall type	Major parietal constituent(s)	Genera
I	LL-DAP, glycine, no sugar	*Arachnia*, *Nocardioides*, *Pimelobacter*, *Streptomyces*
II	*meso*-DAP, glycine, arabinose, xylose	*Actinomyces*, *Actinoplanes*, *Ampulariella*, *Catellatosporia*, *Dactylosporangium*, *Glycomyces*, *Micromonospora*, *Pilimelia*
III	*meso*-DAP, madurose (3-*O*-methyl-D-galactose)	*Actinocorallia*, *Actinomadura*, *Dermatophylus*, *Frankia*, *Geodermatophilus*, *Kitasatospora*, *Maduromycetes*, *Microbispora*, *Microtetraspora*, *Nonomuraea*, *Planobispora*, *Planomonospora*, *Planotetraspora*, some *Frankia* spp., *Spirillosporia*, *Streptosporangium*, *Thermoactinomyces*, *Thermomonospora*
IV	*meso*-DAP, arabinose, galactose	*Micropolyspora*, *Nocardioforms*
V	Deprived of DAP; possesses lysine and ornithine	*Actinomyces*
VI	Deprived of DAP; variable presence of aspartic acid, galactose	*Arcanobacterium*, *Actinomyces*, *Microbacterium*, *Oerskovia*, *Promicromonospora*
VII	Deprived of DAP; diaminobutyric acid, glycine, with lysine variable	*Agromyces*, *Clavibacter*
VIII	Deprived of DAP; ornithine	*Aureobacterium*, *Curtobacterium*, *Cellulomonas*

[a] Information summarized in this table was obtained from references 14, 45, 61, and 602.

Chemotaxonomic classification. Chemotaxonomy is the use of the distribution of chemical components to group organisms according to the similarities of their cellular chemistries (38, 39). The most commonly used chemical components in such systematics are cell wall amino acids, lipids, proteins, menaquinones, muramic acid types, sugars, and the base composition of DNA (40, 41). Chemotaxonomic classification and identification can also be performed on the basis of information derived from whole-organism chemical fingerprinting techniques. Below, we discuss chemotaxonomic markers that have been reported to be of particular value for the classification and identification of actinomycetes (1).

Analysis of the cell wall composition of *Actinobacteria* is taxonomically valuable because it differs between suborders (42). In particular, information on the chemical architecture of the peptidoglycan in the cell wall is valuable for classifying actinomycetes because it facilitates discrimination between groups of *Actinobacteria* above the genus level. Multiple discriminatory characteristics relating to the structure and composition of their peptidoglycans have been identified (43), including the identity of the amino acid in position 3 of the tetrapeptide side chain, the presence or absence of glycine in interpeptide bridges, and the peptidoglycan's sugar content (43). The presence or absence of specific optical isomers of the chiral nonproteinogenic amino acid 2,6-diaminopimelic acid (DAP) is another chemotaxonomically important characteristic of the cell walls of Gram-positive bacteria: the peptidoglycan of *Actinobacteria* may contain either LL- or DL-(*meso*)-DAP, depending on the genus. By considering DAP isomerism and the presence/absence of other amino acids and (amino)sugars, Lechevalier and Lechevalier (44) identified nine distinct actinobacterial cell wall chemotypes (Table 1). However, it is important to realize that while DAP analysis and other chemotaxonomic methods are extremely important in the taxonomy of *Actinobacteria*, diverse groups share the same DAP profile. For example, the genera *Streptomyces*, *Streptoverticillium*, *Arachnia*, and *Nocardioides* share the same chemotype (chemotype I), even though their different morphologies indicate that they belong to different families. Therefore, when assessing the phenotypic diversity of *Actinobacteria*, DAP profiling should be used in combination with other phenotypic or genotypic criteria (45). To this end, a system for classifying *Actinobacteria* based on both morphological and chemical characteristics has been proposed (4).

Cellular fatty acid patterns are also very useful chemotaxonomic indicators for the identification of specific *Actinobacteria* genera (46). Bacterial fatty acids range in chain length from two (C_2) to over 90 (C_{90}) carbon atoms, but only those in the range of C_{10} to C_{24} are of particular taxonomic value (47). Three major types of fatty acid profiles have been identified in *Actinobacteria* (46).

Several types of isoprenoid quinones have been characterized in bacteria (48), of which menaquinones are most commonly found in actinomycete cell envelopes (46–49). Menaquinone analysis has provided valuable information for the classification of *Actinomadura*, *Microtetraspora*, and *Streptomyces* strains (46, 50–52). In addition, cyclic menaquinones are characteristic of members of the genus *Nocardia* (53, 54), while fully saturated cyclic menaquinones have been reported for *Pyrobaculum organotrophum* (54).

Different types of phospholipids are discontinuously distributed in actinomycetes' cytoplasmic membranes, providing useful information for the classification and identification of actinomycete genera (41, 55). *Actinobacteria* have been classified into five phospholipid groups based on semiquantitative analyses of major phospholipid markers found in whole-organism extracts (56–58). This classification system was used in the identification of *Aeromicrobium* (59) and *Dietzia* (60). Importantly, it has been reported that members of the same *Actinobacteria* genus have the same phospholipid type.

Finally, sugar composition analysis is also important in chemotaxonomy. At the suprageneric level, neutral sugars (the major constituents of actinomycete cell envelopes) are useful taxonomic markers (Table 2). On the basis of the discontinuous distribution of major diagnostic sugars, *Actinomycetes* can be divided into five groups. Group A comprises those species whose cell walls contain arabinose and galactose; group B cell walls contain madurose (3-*O*-methyl-D-galactose); group C consists of those with no diagnostic sugars; group D cell walls contain arabinose and xylose; group E cell walls contain galactose and rhamnose (22, 61). In addition, the presence of 3′-*O*-methyl-rhamnose in *Catellatospora* (62) and of tyvelose in *Agro-*

TABLE 2 Taxonomic markers used as characteristics to differentiate the genera of *Actinomycetes*

Amino acid present	Sugar(s)	Morphological characteristics	Genus
No diaminopimelic acid	Xylose, madurose	Only substrate mycelium, breaks into motile elements	*Oerskovia*
		Sterile aerial mycelium, breaks into nonmotile elements	*Promicromonospora*
		Sporangia with motile spores	*Actinoplanes*
		Short chains of conidia on aerial mycelium	*Actinomadura*
L-Diaminopimelic acid	Xylose, madurose	Both aerial and substrate mycelia that break up into rods and coccoid elements	*Nocardioides*
		Only substrate mycelium, bearing terminal or subterminal vesicles	*Intrasporangium*
		Aerial mycelium with long chains of spores	*Streptomyces*, *Kitasatospora*
		Sclerotia	*Streptomyces*
		Very short chains of large conidia on the vegetative and aerial mycelia	*Streptomyces*
		Whorls of small chains of spores	*Streptoverticillium*
		No aerial mycelium, sporangia on the vegetative mycelium	*Kineosporia*
meso-Diaminopimelic acid	Xylose, arabinose	Conidia isolated on the vegetative mycelium	*Micromonospora*
		No sporangia, short chains of conidia	*Cattellatospora*
		Chains of conidia on the aerial mycelium	*Glycomyces*
		Dactyloid oligosporic sporangia, motile spores	*Dactylosporangium*
		Sporangia with spherical and motile spores formed on the surfaced of colonies	*Actinoplanes*
		Sporangia with rod-shaped spores, motility via polar flagella	*Ampullariella*
		Sporangia with lateral flagellated spores	*Pilimelia*
		Multilocular sporangia, spores are nonmotile	*Frankia*
	Madurose	Short chains of conidia on the aerial mycelium	*Actinomadura*
		Chains of conidia with spores	*Microbispora*
		Chains of conidia with 2 to 6 spores	*Microtetraspora*
		Sporangia with 2 motile spores	*Planobispora*
		Sporangia with 1 motile spore	*Planomonospora*
		Mycelium with spherical sporangia containing many rod-shaped, motile spores	*Spirillospora*
	Fructose	Multilocular sporangia	*Frankia*
		Sporangia with motile spores	*Actinoplanes*
	Rhamnose, galactose	Both substrate and aerial mycelia that break into nonmotile elements	*Saccharothrix*
	Rhamnose, galactose, mannose	Same as *Streptomyces*	*Streptoalloteichus*
	Galactose	Same as *Streptomyces*	*Kitasatospora*
	Arabinose, galactose	Presence of nocardiomycolic acid (NMA) in whole cells; both substrate and aerial mycelia fragment into rods and coccoid elements	*Nocardia*
		Presence of NMA; rods and extensively branched substrate mycelium that fragments into irregular rods and cocci	*Rhodococcus*
		Presence of NMA; straight to slightly curved rods occur singly, in pairs, or in masses; cells are nonmotile, non-spore forming, and do not produce aerial hyphae	*Tsukamurella*
		Presence of NMA; paired spores borne in longitudinal pairs on vegetative hyphae; aerial mycelium is sparse	*Actinobispora*
		No NMA, spores are long, cylindrical on aerial mycelium, formed by budding	*Pseudonocardia*
		No NMA; long chains of conidia on aerial mycelium	*Saccharomonospora*
		No NMA; aerial mycelium bearing long chains of conidia; halophilic	*Actinopolyspora*
		No NMA; substrate mycelium tends to break into nonmotile elements; aerial hyphae may form and may also segment	*Amycolata*, *Amycolatopsis*
		No NMA; aerial mycelium bearing curled hyphae embedded in amorphous matrix	*Kibdelosporangium*
		No NMA; both aerial and substrate mycelia bearing long chains of motile spores	*Aktinokineospora*
		No NMA; aerial mycelium tends to fragment into rods and cocci, short chains of spores	*Pseudoamycolata*
		Spores formed are not heat resistant	*Thermomonospora*
		Long chains of spores on aerial mycelium	*Nocardiopsis*
		Columnar hyphal structures called synnemata bearing chains of conidia capable of forming flagella	*Actinosynnema*
		Multilocular sporangia containing motile spores	*Geodermatophilus*

myces (63) has been valuable for the classification of some actinomycete taxa.

Molecular Classification

More recently, the morphological and chemical classification of actinomycetes have been challenged by molecular taxonomic data, much of which were obtained thanks to the rapid advancement of genome sequencing. Notably, some organisms that were inappropriately placed in certain taxonomic groups have recently been reclassified on the basis of molecular analyses (20). A recent example is the final definition of *Kitasatospora* as a separate genus within the *Streptomycetaceae* (17); genome sequencing resolved a long-running debate about this group's relationship with the genus *Streptomyces* and conclusively demonstrated that it is in fact a separate genus (15, 16, 64, 65).

At present, a new species cannot be claimed without genetic analysis based on sequencing the 16S rRNA gene and DNA-DNA hybridization, and even genome sequencing is becoming routine. Molecular and chemical composition criteria have been used to group the order *Actinomycetales* into 14 suborders: *Actinomycineae*, *Actinopolysporineae*, *Catenulisporineae*, *Corynebacterineae*, *Frankineae*, *Glycomycineae*, *Jiangellineae*, *Kineosporineae*, *Micrococcineae*, *Micromonosporineae*, *Propionibacterineae*, *Pseudonocardineae*, *Streptomycineae*, and *Streptosporangineae* (66). Moreover, sequencing of 16S rRNA genes has led to the recognition of 39 families and 130 genera (Fig. 3). All groups previously assigned to the taxonomic rank of "order" were recovered as being strictly monophyletic based on these molecular and chemical criteria, but some paraphyletic groups were found within the rank "suborder." This might be because the classification was mainly based on 16S rRNA gene trees, which were generated without bootstrap support and may thus include misleading results. The features of some of these genera are summarized below.

The genus *Tropheryma*. The most-studied member of the genus *Tropheryma* is *T. whipplei*, the causative agent of Whipple's disease, which is characterized by intestinal malabsorption leading to cachexia and death. *T. whipplei* isolates are typically found in human intracellular niches, such as inside intestinal macrophages and circulating monocytes (67, 68). It has a condensed genome of only 925,938 bp, with a G+C content of only 46% (69, 70), whereas other actinomycete genomes have much larger genomes (up to 10 MBp) and higher G+C contents. *T. whipplei* has a tropism for myeloid cells, particularly macrophages, although it can be found in various cell types. Further, genome sequencing revealed a lack of key biosynthetic pathways and a lower capacity for energy metabolism. Its small genome and lack of metabolic capabilities suggest that *T. whipplei* has a host-restricted lifestyle (69). Recent findings have shown that *T. whipplei* survives phagocyte killing and replicates in macrophages by interfering with innate immune activation (71).

The genus *Propionibacterium*. The genus *Propionibacterium* includes various species belonging to the human cutaneous propionibacteria, including *P. acnes*, *P. avidum*, *P. granulosum*, *P. innocuum*, and *P. propionibacterium*. *Propionibacterium acnes* is a non-spore-forming, anaerobic, pleomorphic rod whose end products of fermentation include propionic acid. The bacterium is omnipresent on human skin, predominantly within sebaceous follicles, where it is generally a harmless commensal. Nonetheless, *P. acnes* may be an opportunistic pathogen (72). Indeed, the bacterium has been isolated from sites of infection and inflammation in patients suffering from acne and other diverse conditions, including corneal ulcers, synovitis, hyperostosis, endocarditis, pulmonary angitis, and endophthalmitis (73, 74). Recently, Campisano et al. (75) reported a unique example of horizontal interkingdom transfer of *P. acnes* to the domesticated grapevine, *Vitis vinifera* L.

The genus *Micromonospora*. *Micromonospora* species are widely distributed in nature, living in different environments. They have long been known as a significant source of secondary metabolites for medicine, and it was recently demonstrated that *Micromonospora* species may also influence plant growth and development (76); *Micromonospora* strains have been identified as natural endophytes of legume nodules, although the precise nature and mechanism of their effects on plant development and productivity are currently unclear. While the genus exhibits considerable physiological and biochemical diversity, *Micromonospora* constitutes a well-defined group in terms of morphology, phylogeny, and chemotaxonomy. Its colonies can be a variety of colors, including white, orange, rose, or brown. However, species of the genus *Micromonospora* are not always easy to differentiate on the basis of morphology alone. Consequently, phylogenies and species identifications are now more commonly derived by analyzing the sequence of the 16S rRNA gene or *gyrB* (the gene encoding DNA topoisomerase). The genus *Micromonospora* consists primarily of soil actinobacteria, which account for 32 of its species, according to the latest version of Bergey's manual (77), although 50 soil actinobacteria in this genus have been validly described as of the time of writing. Most of these species were isolated from alkaline or neutral soils and to a lesser extent from aquatic environments. The spore population of *M. echinospora* is known to be heterogeneous with respect to its heat response characteristics, suggesting that routine heat activation could be utilized to eliminate the natural variability that exists within populations of this species and its relatives (78). Further, analysis of the genome of *M. lupini* Lupac 08 revealed a diverse array of genes that may help the bacterium to survive in the soil or in plant tissues. However, despite having many genes that encode putative plant material-degrading enzymes, this bacterium is not regarded as a plant pathogen (79). In addition, genome comparisons showed that *M. lupini* Lupac 08 is metabolically closely related to *Frankia* sp. strains ACN14a, CcI3, and EAN1pec. These results suggest that the *Micromonospora* genus has undergone a previously unidentified process of adaptation from a purely terrestrial to a facultative endophytic lifestyle.

The genus has also been reported to produce a large number of antibiotics (80) and is second only to *Streptomyces* in this respect, synthesizing up to 500 different molecules with various properties (77). *Micromonospora* species can produce hydrolytic enzymes, which allows them to play an active role in the degradation of organic matter in their natural habitats. Marine *Micromonospora* species have recently been reviewed with respect to their broad distribution and their potential use as probiotics (76, 81). Like other endophytic actinobacteria, *Micromonospora* can suppress a number of pathogens both *in vitro* and *in planta* by activating key genes in the systemic acquired resistance (SAR) or jasmonate/ethylene (JA/ET) pathways (76). Unfortunately, there have been few genomic studies on *Micromonospora* species, and there is a lack of tools for their genetic analysis despite their acknowledged capacity for secondary metabolite production (76).

The genus *Salinispora*. *Salinispora* belongs to the *Micromono-*

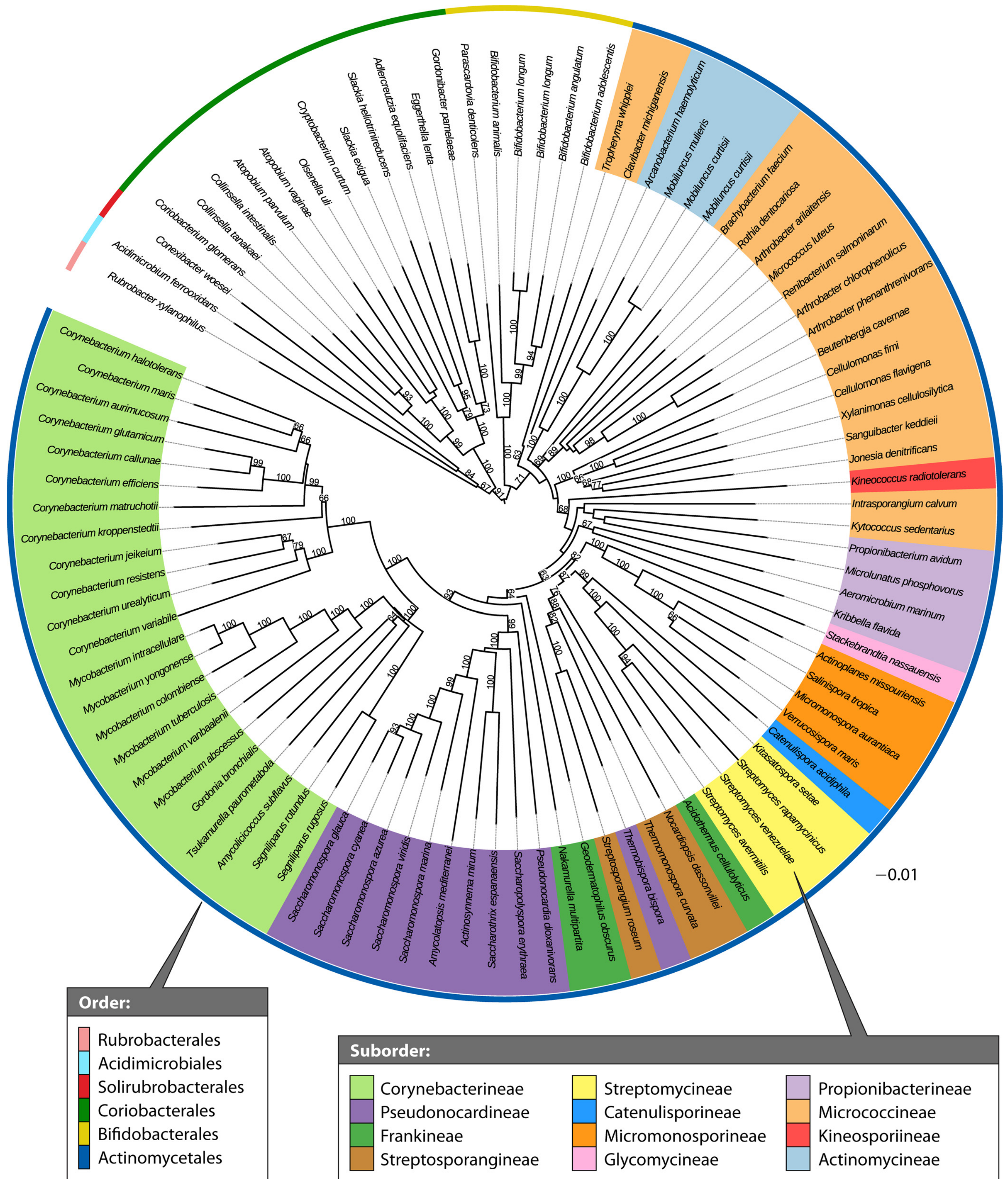

FIG 3 A genome-based phylogenetic tree based on 97 genome sequences of the phylum *Actinobacteria*. Type strain genome projects were selected as previously described (676), provided that they yielded at most 25 contigs. Phylogenetic reconstruction, including the assessment of branch support, was done using amino acid sequences according to the methods described by Meier-Kolthoff et al. (677, 678). The tree was visualized by using ITOL (679). Branch support values below 60% are not shown, but the tree generally reveals high support throughout.

sporaceae and is the first *Actinobacteria* genus known to require seawater for growth (82). The genus is widely distributed in tropical and subtropical marine sediments (83) and includes three distinct but closely related clades corresponding to the species *S. arenicola*, *S. pacifica*, and *S. tropica*. Like their terrestrial actinomycete counterparts, *Salinispora* spp. produce numerous secondary metabolites with diverse potential pharmaceutical applications. For instance, salinosporamide A, isolated from *S. tropica*, is currently in phase 1 clinical trials in patients with multiple myeloma, lymphomas, leukemia, and solid tumors (84).

Although the three currently known species of *Salinispora* cooccur at six widely separated and distinct locations (82), only strains of *S. tropica* isolated from the Caribbean produce the potent anticancer compound salinosporamide A (85). In addition to its production of various secondary metabolites, this genus has attracted major interest for the novel phenomenon of species-specific secondary metabolite production (86, 87). Although it is clear that many of the genes for secondary metabolite production in the *Salinispora* genome were acquired via horizontal gene transfer, the ecological and evolutionary significance of these mechanisms remain unclear (86).

The genus *Mycobacterium*. The relatively simple morphology of mycobacteria partly explains why it is sometimes overlooked when considering criteria for classifying actinomycetes (88, 89). With the genera *Corynebacterium* and *Nocardia*, *Mycobacterium* forms a monophyletic taxon within the *Actinobacteria*, the so-called CMN group (90). This group shares an unusual waxy cell envelope that contains mycolic acids, meaning these bacteria are unusual in being acid fast and alcohol fast. The mycobacterial cell wall contains various polysaccharide polymers, including arabinogalactan, lipomannan, lipoarabinomannan, and phosphatidylinositol mannosides (91, 92). Representatives of the genus *Mycobacterium* have been the subjects of three major 16S rRNA sequencing studies (93–95). Mycobacteria are generally free-living saprophytes (96), and they are the causative agents of a broad spectrum of human diseases. Mycobacterial diseases are very often associated with immunocompromised patients, especially those with AIDS. In addition, *M. bovis* and *M. tuberculosis*, isolated initially from infected animals, are most likely obligate parasites of humans (97). Both species can survive within macrophages and cause pulmonary disease, although organs other than lungs may be affected. *M. leprae*, which causes leprosy, lives in Schwann cells and macrophages; infection with this species results in a chronic granulomatous disease of the skin and peripheral nerves (98). Interestingly, the pathogenic *M. ulcerans*, which is the third most common causative agent of mycobacterial disease, has also been isolated as a soil inhabitant in symbiosis with roots of certain plants living in tropical rain forests and similar environments (99, 100). *Mycobacterium marinum* was initially identified as a causative organism of tuberculosis in fish in 1926 (101) and was subsequently shown to also cause skin disease in humans (102). *M. marinum* is a nontuberculosis mycobacterium that is a causative agent of human skin infections acquired through aquatic sources. Most cases of *M. marinum* infection are reported to have occurred after exposure to contaminated aquarium water or contact with fish and shellfish (103).

The genus *Nocardia*. The genus *Nocardia* is a ubiquitous group of environmental bacteria that is most widely known as the causative agent of opportunistic infection in immunocompromised hosts. It forms a distinct clade that is associated with the genus *Rhodococcus*. Both the *Nocardia* and *Rhodococcus* genera belong to the family *Nocardiaceae*, which is a suborder of the "aerobic actinomycetes." *Nocardia* species are ubiquitous soilborne aerobic actinomycetes, with more than 80 different species identified, of which at least 33 are pathogenic (104). *Nocardia* infections are mainly induced through inhalation or percutaneous inoculation from environmental sources (105), but nosocomial transmission has also been reported. The pathogen can spread to the brain, kidneys, joints, bones, soft tissues, and eyes, causing disseminated nocardiosis in humans and animals (106). Although *Nocardia* species are rare, they now account for 1 to 2% of all reported brain abscesses. However, the mortality rate for brain abscesses associated with *Nocardia* infection is substantially higher (31%) than that for brain abscesses in general (<10%) (107).

Moreover, *Nocardia* species produce industrially important bioactive molecules, such as antibiotics and enzymes (108, 109). Within the *Nocardia* clade, two sublines distinguishable by nucleotide differences in helix 37-1 are recognized; one consists of *Nocardia asteroides* and allied taxa, while the second consists of *Nocardia otitidiscaviarum* and related species. *N. asteroides*, the causal agent for most clinical human nocardial infections, was reorganized into multiple species on the basis of drug susceptibility patterns: *Nocardia abscessus*, the *Nocardia brevicatena-Nocardia paucivorans* complex, the *Nocardia nova* complex, the *Nocardia transvalensis* complex, *Nocardia farcinica*, and *N. asteroides* (104). Recently, *Nocardia cyriacigeorgica* was differentiated from *N. asteroides* (110).

In the last 2 decades, *Nocardia* infections have become regarded as an emerging disease among humans and domestic animals worldwide because of improved methods for pathogen isolation and molecular identification and a growing immunocompromised population (111). *Nocardia* species are recognized as opportunistic pathogens (112) and are known to compromise immune function. Moreover, they have been associated with organ and bone marrow transplants (113), long-term steroid use, connective tissue diseases, human immunodeficiency virus (HIV) infections, chronic obstructive pulmonary disease, alcoholism, cirrhosis, systemic vasculitis, ulcerative colitis, and renal failure (114).

In companion animals, *Nocardia* infections are usually reported as coinfections with immunosuppressive infectious diseases such as distemper in dogs and leukemia and immunodeficiency in cats (115).

The genus *Corynebacterium*. The genus *Corynebacterium* was initially defined in 1896 to accommodate mainly pathogenic species exhibiting morphological similarity to the diphtheroid bacillus (116). Therefore, the genus comprised, for several decades, an extremely diverse collection of morphologically similar Gram-positive microorganisms, including nonpathogenic soil bacteria (117). Following chemotaxonomic studies and 16S rRNA sequence analysis, there are currently almost 70 recognized *Corynebacterium* species. Some well-known representatives include *C. glutamicum*, which (like the thermostable *C. efficiens*) is widely used in industry for the production of amino acids such as L-glutamic acid and L-lysine for human and animal nutrition, respectively (118). Several genome sequences of *Corynebacterium* species have been reported, including those of *C. ulcerans* (119), *C. kutscheri* (120), *C. kroppenstedtii* (121), and *C. argentoratense* (122), providing important new insights into the genomic architecture of the genus. A prophage, CGP3, that integrates into the

genome of *C. glutamicum* and encodes an actin-like protein, AlpC, was recently described (123). CGP3 appears to be inactive in terms of cell lysis and virion production and is therefore referred to as a cryptic prophage, which likely became trapped in the genome in the course of evolution (123). This suggests that bacterial phages use an actin-based transport system similar to that found in vertebrate viruses, such as the herpesvirus. Among the known pathogenic members of *Corynebacterium* are *C. diphtheria*, which is a notorious strictly human-adapted species and the causative agent of the acute, communicable disease diphtheria, which is characterized by local growth of the bacterium in the pharynx along with the formation of an inflammatory pseudomembrane (124). The virulence factor in diphtheria is an exotoxin that targets host protein synthesis (125). Another important *Corynebacterium* pathogen is *C. ulcerans*, which is increasingly acknowledged as an emerging pathogen in various countries; infections with this species can mimic diphtheria because it harbors lysogenic-β-corynephages that carry the the diphtheria toxin (DT) gene, which is responsible for most of the systemic symptoms of diphtheria (126). *C. ulcerans* also induces clinical symptoms in the lower respiratory tract, including pneumonia (127) and pulmonary granulomatous nodules (128). However, its pathogenicity does not necessarily depend on the production of DT (129). A final important pathogen in this genus is *C. jeikeium*, which was initially isolated from human blood cultures and is associated with bacterial endocarditis contracted following cardiac surgery (130). It was subsequently shown to be a natural inhabitant of human skin and has been implicated in a variety of nosocomial infections (131).

The genus *Gordonia*. Initially proposed by Tsukamura (132), this genus has been isolated from the sputum of patients with pulmonary disease and also from soil samples. There are currently 29 validly described species in this genus (1). Bacteria of this genus are aerobic and catalase positive, forming rods and cocci. The gordonae are widely distributed and are common in soil, but some strains have been linked with foams found in activated sludge at sewage treatment plants. Three species originally assigned to *Rhodococcus*, namely, *R. bronchialis* (132), *R. rubropertinctus* (133), and *R. terrae* (132), have more recently been reaffiliated to the genus *Gordona* as *Gordona bronchialis* (132), *Gordona rubropertincta* (133), and *Gordona terrae* (132). The original spelling *Gordona* (*sic*) was corrected to *Gordonia* by Stackebrandt et al. (134).

The genus *Rhodococcus*. The genus *Rhodococcus* is a heterogeneous group of microorganisms whose members are more closely related to those of the genus *Nocardia* than to those of the genus *Mycobacterium. Rhodococcus* species include symbionts (*Rhodococcus rhodnii*) and pathogens to animals (e.g., *R. equi*), plants (*Rhodococcus fascians*), and humans (e.g., *R. equi*, *R. rhodochrous*, and *R. erythropolis*) (135). *Rhodococcus equi* is the *Rhodococcus* species that is most likely to act as a pulmonary pathogen in young horses and HIV-infected humans (136).

The *Rhodococcus* genus has had a long and confused taxonomic pedigree (137, 138). However, many of the early uncertainties have been resolved satisfactorily through the application of chemotaxonomic and phylogenetic character analyses. In the last edition of *Bergey's Manual of Systematic Bacteriology*, rhodococci were assigned to two aggregate groups based primarily on chemical and serological properties (21). Key diagnostic characteristics for rhodococci are the presence of tuberculostearic acid, mycolic acids with lengths of between 34 and 64 carbon atoms, and with the major menaquinone type being dihydrogenated menaquinones that possess eight isoprenoid units but which lack the cyclic element that is the characteristic motif of the *Nocardia* genus (135).

Rhodococci are aerobic, Gram-positive, catalase-positive, partially acid-fast, nonmotile actinomycetes that can grow as rods but also as extensively branched substrate hyphae. Some strains produce sparse, aerial hyphae that may be branched or form aerial synnemata, which consist of unbranched filaments that coalesce and project upwards (53). Rhodococci are very important organisms with remarkably catabolic versatility, because they carry genes encoding enzymes that can degrade an impressive array of xenobiotic and organic compounds (139). In addition to their bioremediation potential, they produce metabolites of industrial potential, such as carotenoids, biosurfactants, and bioflocculation agents (140). Some species, such as *Rhodococcus rhodochrous*, also synthesize commercially valuable products, such as acrylamide (135).

The nomenclature of *Rhodococcus equi* remains controversial. In a commentary on the nomenclature of this equine pathogen, Goodfellow et al. (141) noted that the taxon is regrettably left without a valid name, because *Rhodococcus* itself is an illegitimate name and, according to the nomenclature code, should not be used. "*Prescottella equi*" was suggested as a new name for the taxon that would provide nomenclatural stability; consequently, clinicians and scientists working on this taxon should adopt the name "*P. equi*."

The genus *Leifsonia*. Evtushenko et al. (142) introduced the genus *Leifsonia* to accommodate Gram-positive, non-spore-forming, irregular rod- or filament-shaped, motile, mesophilic, catalase-positive bacteria containing DL-2,4-diaminobutyric acid in their peptidoglycan layer. Currently, the genus harbors 12 species and two subspecies, with *Leifsonia aquatica* as the type species. Members of the genus *Leifsonia* have been isolated from different ecological niches, including plants (*L. poae* and *L. xyli*), soil (*L. naganoensis* and *L. shinshuensis*), distilled water (e.g., *L. aquatica*), Himalayan glaciers, and Antarctic ponds (*L. rubra* and *L. aurea*) (142–146).

Leifsonia xyli comprises two subspecies: *L. xyli* subsp. *cynodontis*, a pathogen that causes stunting in Bermuda grass (*Cynodon dactylon*), and *L. xyli* subsp. *xyli* (142). Information on the biology and pathogenicity of *L. xyli* subsp. *xyli* is limited. Like the gammaproteobacterium *Xylella fastidiosa*, *L. xyli* subsp. *xyli* belongs to a unique group of xylem-limited and fastidious bacterial pathogens and is the causative agent of ratoon stunting disease, the main sugarcane disease worldwide (147).

The genus *Bifidobacterium*. Bifidobacteria, first isolated by Tissier (148), are the only family of bacteria in the order *Bifidobacteriales*. The *Bifidobacteriaceae* family contains the type genus *Bifidobacterium* (149), and members of the family *Bifidobacteriaceae* have different shapes, including curved, short, and bifurcated Y shapes. They were initially classified as *Bacillus bifidus communis*. The cells have no capsule and they are non-spore-forming, nonmotile, and nonfilamentous bacteria. The genus encompasses bacteria with health-promoting or probiotic properties, such as antimicrobial activity against pathogens that is mediated through the process of competitive exclusion (150), and also bile salt hydrolase activity, immune modulation, and the ability to adhere to mucus or the intestinal epithelium (151). For commercial exploitation, bifidobacterial strains are typically se-

lected for fast growth, antibacterial activity, good adhesion properties, and utilization of prebiotic substrates (151). Among the many probiotic features that have been attributed to bifidobacteria are (i) the induction of immunoglobulin production, (ii) improvement of a food's nutritional value by assimilation of substrates not metabolized by the host, (iii) anticarcinogenic activity, and (iv) folic acid synthesis (152–154). Some bifidobacteria produce antimicrobials (155) and notably, also bacteriocins (156, 157).

The genus *Gardnerella*. Classification for the genus *Gardnerella* is controversial: the genus has often been described as Gram variable but has a Gram-positive wall type (158). *Gardnerella vaginalis* is a facultative anaerobic bacterium and the only species of this genus belonging to the *Bifidobacteriaceae* family (159). *G. vaginalis* is strongly associated with bacterial vaginosis, a disease characterized by malodorous vaginal discharge, but it also occurs frequently in the vaginal microbiota of healthy individuals (160). *G. vaginalis*-associated vaginosis is a risk factor for poor obstetric and gynecologic outcomes, as well as the acquisition of some sexually transmitted diseases. In addition, clinical studies have demonstrated a relationship between *G. vaginalis* and preterm delivery (161). The issue of *G. vaginalis* commensalism is still ambiguous, as the vaginal bacterial community is dynamic and tends to change over the menstrual cycle, leading to a transient dominance of *G. vaginalis* even in healthy women (162).

The genus *Streptomyces*. The various mycelial genera of *Actinobacteria* harbor some of the most complex known bacteria (163), such as *Streptomyces*, *Thermobifida*, and *Frankia*. Of the three genera, *Streptomyces* has received particular attention for three main reasons. First, streptomycetes are abundant and important in the soil, where they play major roles in the cycling of carbon trapped in insoluble organic debris, particularly from plants and fungi. This action is enabled by the production of diverse hydrolytic exoenzymes. Second, the genus exhibits a fairly wide phylogenetic spread (164). Third, streptomycetes are among Nature's most competent chemists and produce a stunning multitude and diversity of bioactive secondary metabolites; consequently, they are of great interest in medicine and industry (165). Streptomycetes are the only morphologically complex *Actinobacteria* whose development has been considered in detail. For more details on this genus, which serves as a model system for bacterial antibiotic production, see the section on "Physiology and Antibiotic Production of *Streptomyces*," below.

The genus *Frankia*. *Frankia* is the only nitrogen-fixing actinobacterium and can be distinguished by its ability to enter into symbiotic associations with diverse woody angiosperms known collectively as actinorhizal plants. The most notable plant genera in this group are *Alnus*, *Casuarina*, and *Elaeaginus*, and their symbiosis with *Frankia* enables them to grow well in nitrogen-poor soils (166, 167). Like *Streptomyces*, the DNA of *Frankia* has a particularly high G+C content of 72 to 73% (2). *Frankia* can form three different cell types, growing as mycelia or as multilocular sporangia. Under nitrogen-limited and aerobic conditions, *Frankia* develops so-called vesicles at the tips of hyphae or at the ends of short side hyphae (168). For a long time, *Frankia* spp. were believed to be the only bacteria within the *Actinobacteria* able to fix atmospheric nitrogen. However, Gtari et al. (169) recently reviewed the sparse physiological and biochemical studies conducted on *Actinobacteria* over the last 50 years and concluded that nitrogen fixation within this group is unlikely to be restricted to frankiae.

The genus *Thermobifida*. The genus *Thermobifida*, established by Zhang et al. (170), was originally assigned to the highly heterogeneous genus *Thermomonospora*. A phylogenetic analysis based on 16S rRNA sequences prompted the reclassification of *Thermobifida alba* and *Thermobifida fusca*, which were previously classified as *Thermomonospora* species (33, 137). Later, *Thermobifida cellulolytica* was added to this genus (171). More recently, *Thermobifida halotolerans* sp. nov. was proposed as representative of a novel species of *Thermobifida* (172). Members of the genus *Thermobifida* are Gram-positive, non-acid-fast, chemo-organotrophic aerobic organisms that form an extensively branched substrate mycelium. *Thermobifida* species are moderately thermophilic, growing optimally at 55°C, and act as major degraders of plant cell walls in heated organic materials, such as compost heaps, rotting hay, manure piles, or mushroom growth medium.

PHYSIOLOGY AND ANTIBIOTIC PRODUCTION OF *STREPTOMYCES*

The *Streptomyces* Life Cycle

Streptomycetes play key roles in soil ecology because of their ability to scavenge nutrients and, in particular, to hydrolyze a wide range of polysaccharides (cellulose, chitin, xylan, and agar) and other natural macromolecules (173). The life cycle of the multicellular mycelial *Streptomyces* starts with the germination of a spore that grows out to form vegetative hyphae, after which a process of hyphal growth and branching results in an intricately branched vegetative mycelium (174). A prominent feature of the vegetative hyphae of *Streptomyces* is that they grow by tip extension (28). This in contrast to unicellular bacteria, like *Bacillus subtilis* and *Escherichia coli*, where cell elongation is achieved by incorporation of new cell wall material in the lateral wall (175). Exponential growth of the vegetative hyphae is achieved by a combination of tip growth and branching. The fact that cell division during vegetative growth does not lead to cell fission but rather to cross-walls that separate the hyphae into connected compartments (176) makes streptomycetes a rare example of a multicellular bacterium, with each compartment containing multiple copies of the chromosome (177, 178). The spacing of the vegetative cross-walls varies significantly, both between different *Streptomyces* species and within individual species between different growth conditions and mycelial ages.

Under adverse conditions, such as nutrient depletion, the vegetative mycelium differentiates to form erected sporogenic structures called aerial hyphae. This is also the moment in the life cycle when most antibiotics are produced (179, 180). *Streptomyces* and other filamentous microorganisms are sessile; when nutrient depletion occurs, the vegetative or substrate mycelium is autolytically degraded by a programmed cell death (PCD)-like mechanism to acquire the building blocks needed to erect a second mass of (aerial) mycelium (181–183). PCD results in the accumulation of amino acids, aminosugars, nucleotides, and lipids around the lysing substrate mycelium (184–186), which inevitably attract motile competing microbes in the habitat; it is logical to assume that antibiotics are produced at this time to protect the pool of nutrients. One well-studied system revolves around the PCD-responsive nutrient sensory regulator DasR, which controls early development and antibiotic production and responds to the accu-

mulation of cell wall-derived *N*-acetylglucosamine (186, 187). The role of DasR as a regulator of antibiotic production is discussed in more detail in the section on controlling antibiotic production. A cascade of extracellular proteases and protease inhibitors also plays a well-established role in PCD and development in streptomycetes, as reviewed elsewhere (173, 188).

Two rounds of PCD occur during the *Streptomyces* life cycle (189). After spore germination, a compartmentalized mycelium grows out and then undergoes a first round of PCD that affects the material formed during early vegetative growth. This is then followed by a second round of PCD that is initiated during the onset of development (189). At this stage, the vegetative or substrate hyphae are lysed so as to provide nutrients for the next round of biomass formation, i.e., the growth of the aerial mycelium. The aerial hyphae give the colonies their characteristic fluffy appearance and eventually differentiate to form chains of unigenomic spores (23). Genes that are required for the formation of aerial hyphae are referred to as *bld* genes, in reference to the bald ("hairless") phenotype of mutants lacking the fluffy aerial hyphae (190), while mutants whose development is blocked at a stage prior to sporulation are called *whi* (white), due to their failure to produce the gray spore pigment (174, 191).

Genes that are required for aerial growth or for sporulation were originally identified by screening for mutants after random mutagenesis by using UV irradiation or treatment with chemical mutagens, or by transposon-mediated mutagenesis, resulting in a collection of *bld* and *whi* mutants that were subsequently classified on the basis of their morphology (174, 190–195). Several new classes of developmental genes have been identified on the basis of physiological criteria, such as the acceleration of aerial mycelium formation in *S. lividans* (*ram* genes, for rapid aerial mycelium [196]), complementation of mutants of *S. griseus* with disturbed sporulation (*ssgA*-like genes, for sporulation of *Streptomyces griseus* [197]), or disruptions in sugar metabolism (186, 198, 199).

Most *bld* and *whi* genes that have been identified to date have a (predicted) regulatory function at the transcriptional or translational level, with many encoding predicted transcription factors. Some of the best-studied examples are *bldD*, a highly pleiotropic transcription factor that controls hundreds of development-related genes (200–202), the RNA polymerase σ factors *bldN* (203) and *whiG* (204, 205), which control early events during sporulation (although *bldN* is also strongly transcribed during aerial growth), and *whiH*, which controls the onset of sporulation-specific cell division (206, 207). There is also extensive control at the translational level. A wonderful example is *bldA*, which specifies a tRNA molecule responsible for the translation of the rare leucine codon UUA (208, 209). Deletion of *bldA* has a pleiotropic effect on gene expression in streptomycetes (210, 211). A major target of *bldA*-mediated translational control is *bldH* (*adpA*), which encodes an important global regulator of development and antibiotic production (212–215). Transcription of *adpA* is activated in response to the γ-butyrolactone A-factor in *S. griseus* and to the related molecule SCB1 in *S. coelicolor* (216–220). An interesting feedback loop exists whereby the translation of the *adpA* mRNA depends on BldA (221, 222), while AdpA in turn controls *bldA* transcription (223).

Recently, it was elegantly shown by the group of Mark Buttner that the activity of BldD, which represses many developmental genes during vegetative growth, is controlled posttranslationally by the signaling molecule cyclic-di-GMP (CDG) (224). Binding of tetrameric CDG to BldD brings together the DNA binding domains of the BldD dimer, thus enabling the protein to bind to its target sites (224). An example of metabolic control is presented by the pleiotropic nutrient sensory regulator DasR, which is essential for development and pleiotropically represses antibiotic production (see below). DNA binding by DasR is controlled by the binding of GlcNAc-related metabolites as ligands (186, 225). An overview of key developmental events and regulatory networks in streptomycetes is presented in Fig. 4. An extensive overview of the very complex and intriguing regulatory networks that control the onset of sporulation is beyond the scope of this review; we refer the reader to the excellent previously published reviews of this field for further information (23, 173, 188, 226, 227).

Environmental Control of Aerial Hypha Formation

In addition to being defective in aerial hypha formation, early developmental (*bld*) mutants also exhibit disrupted antibiotic production. This underlines the connection between development and secondary metabolism (see below). Most *bld* mutants fail to produce antibiotics, although some, in particular *bldF*, are antibiotic overproducers. By definition, all of the nonessential genes that are required for aerial hypha formation are *bld* genes. Extracellular complementation experiments where *bld* mutants were grown in close proximity to one another without physical contact suggested the existence of a hierarchical relationship between at least some of the *bld* genes (228–231). Aerial hypha formation could be restored from one *bld* mutant to another, which is consistent with the idea of a signaling cascade that generates a signal that ultimately leads to the onset of development. However, these experiments were almost exclusively performed on a single reference medium, namely, nutrient-rich R2YE agar plates with glucose, and many *bld* mutants have a conditional bald phenotype—in other words, they are able to produce at least some aerial hyphae and spores on minimal media with nonrepressive carbon sources, such as mannitol (192, 198, 227). A logical assumption is that this is the result of carbon catabolite repression (CCR), whereby favorable carbon sources such as glucose signal the presence of abundant food, thus favoring growth over development and antibiotic production (232, 233).

In streptomycetes, CCR largely depends on the glycolytic enzyme glucose kinase, and deletion of the *glkA* gene encoding glucose kinase therefore abolishes CCR (232, 234, 235). Suggestively, deleting *glkA* in *bldA* mutants of *S. coelicolor* restores their ability to sporulate on glucose-containing media (236). Conversely, mutants that lack the *bldB* gene (which encodes a small 99-amino-acid [aa] protein) are defective in CCR, although the mode of action of BldB is as yet unclear (192, 237). It should be noted that Glk-independent pathways of CCR that affect development and antibiotic production also exist, adding further complexity to the picture (238). Other *bld* genes relevant to sugar metabolism are *ptsH*, *ptsI*, and *crr*, which encode the global components HPr, enzyme I (EI), and enzyme IIA ($EIIA^{Crr}$), respectively, of the phospohoenolpyruvate (PEP)-dependent phosphotransferase system (PTS), which transports sugars such as *N*-acetylglucosamine and fructose in *S. coelicolor* (239, 240). Other examples are *dasABC*, which encodes a chitobiose sugar transporter (199, 241), and the pleiotropic sugar regulators *atrA* (242) and *dasR* (186, 187). Perhaps surprisingly, the nonsporulating phenotype of the *das* and *pts* transport mutants is independent of the carbon source and thus probably also of the transport activity (186, 199, 241).

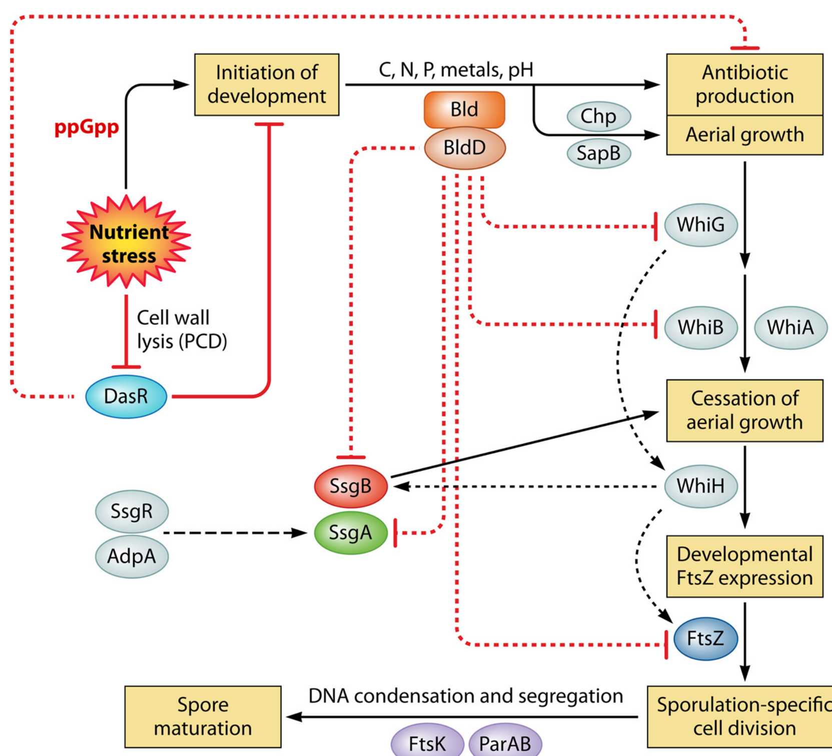

FIG 4 Major events during development of *Streptomyces*. Nutrient stress is a major trigger of development, leading to the accumulation of ppGpp, resulting in cessation of early growth and repression of the nutrient sensory DasR protein by cell wall-derived metabolites following PCD of the substrate mycelium. Bld proteins and environmental signals control the procession toward aerial growth and antibiotic production. The developmental master regulator BldD (when bound to tetrameric cyclic-di-GMP) represses the transcription of genes for many key developmental regulatory proteins, including WhiB, WhiG, SsgA, and SsgB, as well as FtsZ. Chaplins and SapB provide a supportive hydrophobic layer to allow aerial hyphae to become erect and break through the moist soil surface. White proteins control aerial growth, whereby WhiAB and SsgB likely play a role in growth cessation. Eventually, FtsZ accumulates and localizes to septum sites in an SsgAB-dependent manner. Ladders of FtsZ are formed, which subsequently delimit the spore compartments. Chromosome condensation and segregation are followed by septum closure and spore maturation. The onset of antibiotic production typically correlates temporally to the transition from vegetative to aerial growth. Solid black arrows represent major transitions in development. Dark dotted lines indicate transcriptional control (arrows for activation, ovals for repression).

These examples highlight the important and complex connections between carbon utilization and development in streptomycetes.

Metals also play a key role in the onset of development. *Streptomyces lividans* requires a large amount of copper for proper aerial growth (243). This defect can be rescued by enhanced expression of the *ram* cluster (196), which ultimately leads to the production of the surfactant SapB (see the next section). Recently, Sébastien Rigali and colleagues showed that development can be restored to *bldJ* and *bldK* mutants by supplementing R2YE agar with iron (244). The *bldK* gene cluster encodes an oligopeptide transporter (228, 245), while the function of *bldJ* is unknown (228). Interestingly, mass spectrometric analysis revealed that all of the *bld* mutants that were tested showed either severely reduced (for *bldA*, *bldJ*, and *ptsH* mutants) or enhanced (for *bldF*, *bldK*, *crr*, and *ptsI* mutants) production of the iron-binding siderophore desferrioxamine (244). The same paper also mentioned unpublished data suggesting that deregulated desferrioxamine production occurs in *bldB*, *bldC*, *bldD*, *dasA*, and *adpA* mutants when grown on R2YE agar plates and may thus be a more general feature of many *bld* mutants (244). Further complications arise from the fact that both *bldJ* mutants and mutants lacking the *citA* gene for citrate synthase (which also fail to develop on R2YE under "standard" conditions), do successfully develop on R2YE when the medium is strongly buffered (246). Besides shedding more light on the nature of *bld* mutations, these experiments also show that environmental factors, such as metal availability, pH, and carbon and nitrogen sources, have profound effects on the onset of development, and so the composition of the medium should be considered very carefully when planning experiments to study development in streptomycetes.

Facilitating Aerial Growth: the Roles of Chaplins, Rodlins, and SapB

Aerial hyphae differ substantially from vegetative hyphae. One major difference is that aerial hyphae of wild-type cells typically do not branch extensively, are nearly twice as wide as vegetative hyphae, and undergo rapid growth. The aerial hyphae are also surrounded by a sheath that later becomes part of the spore coat (247–251). This sheath is hydrophobic on the air-facing side, allowing the aerial hyphae to break through the moist soil-air surface with the assistance of the turgor pressure generated by the hyphae (252, 253), similarly to what has been proposed for fungi (254). Chaplins are potent surfactants, reducing the surface tension from 72 to 24 mJ m^{-2} (247, 255). An important function of the sheath may also be to create a channel along the outer hyphal wall that can facilitate nutrient transport, as proposed by Keith

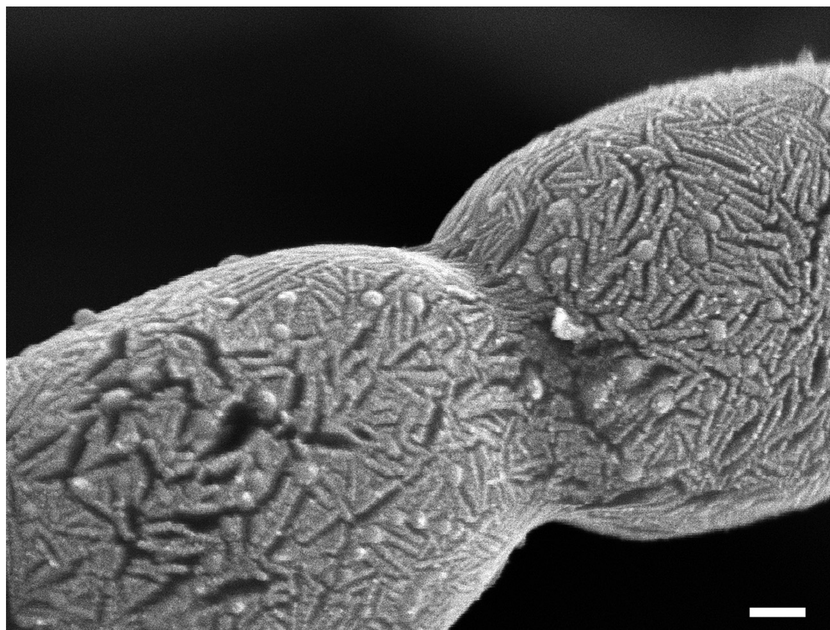

FIG 5 Scanning electron micrograph of the surface layer of mature spores, revealing a distinctive rodlet layer. This layer consists of hydrophobic chaplin (Chp) and rodlin (Rdl) proteins. Bar, 100 nm.

Chater (173, 256). This argument suggests that nutrients and other metabolites might diffuse from the vegetative hyphae in the basal part of the colony up to the growing tips of the aerial hyphae (173, 256), which would be an attractive alternative to transport through hyphae and could potentially resolve the longstanding debate about how nutrients are transported efficiently across long distances over the cross-walls (188).

The sheath consists of a number of hydrophobic proteins, in particular chaplins and rodlins (230, 247, 249, 257–260). Together, these proteins form the so-called rodlet layer, which decorates the spores with a seemingly random pattern of small lines running in all directions; high-resolution electron microscopy shows that these lines consist of small protein assemblies (Fig. 5). Typical rodlet layer formation depends on the rodlin proteins RdlA and RdlB; deletion of the *rdl* genes instead results in decoration with fine lines consisting of the chaplins (248). *S. coelicolor* contains eight chaplins, three large ones (ChpABC) with two chaplin domains and a sortase domain and five smaller chaplins (ChpDEFGH) bearing a single chaplin domain (247, 249). The chaplins assemble on the hyphal surface into an amphipathic protein layer that consists of amyloid-like fibrils. Of the chaplins, the vegetatively expressed ChpC, ChpE, and ChpH proteins are sufficient for sporulation (261). ChpE and ChpH are secreted into the surrounding medium to reduce the surface tension so as to enable the hyphae to grow into the air (247, 255).

Closer analysis of the ChpH protein showed that it has two amyloidogenic domains at its N and C termini, which are both required for aerial hypha formation, while only the C-terminal domain is required for assembly of the rodlet ultrastructure (262). In addition to the chaplins, there are two rodlin proteins that also contribute to the development of the sheath's rodlet ultrastructure and the spore surface (258). Suggestively, most of the genes for the chaplins and the two rodlin genes lie in close proximity on the genome (263). However, the rodlins are not required for sporulation, even though they are needed for the sheath's development into paired rodlet structures (258). It is clear that these hydrophobic structural proteins play key roles in the aerial development of streptomycetes, but the precise role of each of the individual components remains to be resolved.

In addition to ChpE and ChpH, the onset of aerial growth requires the extracellular accumulation of yet another hydrophobic surfactant, SapB (230, 264). SapB-type proteins are widespread in streptomycetes; well-studied examples include AmfS in *S. griseus* and SapT in *S. tendae* (265, 266). In *S. coelicolor*, SapB is encoded by the *ramS* gene in the *ramCSAB* gene cluster (196, 267), which is controlled by the orphan response regulatory gene *ramR* (268–270). In turn, at least in *S. griseus*, transcription of the *amf* operon, and thus of *amfS*, depends on AdpA and therefore ultimately also on BldA (215). RamS is produced as a 42-aa propeptide that is subsequently modified and exported in a way very similar to that for lantibiotics, although the way the propeptide is processed is yet unknown. During modification by RamC, four dehydroalanine residues and two lanthionine bridges are introduced (271). Thus, a highly modified 21-aa molecule of 2,027 Da is produced (271), with all the structural and genetic features of type II lantibiotics (259, 272). Despite the exciting insights that have been obtained into the biological role of SapB so far, the precise mechanism by which it controls the developmental growth of streptomycetes awaits further elucidation, as do the transcriptional and posttranscriptional control mechanisms underlying its biosynthesis (273).

As a final comment on this topic, it is important to note that even the extracellular addition of the fungal hydrophobin SC3 (obtained from the basidiomycete *Schizophyllum commune*) restores aerial growth to several *bld* mutants of *S. coelicolor* that are deficient in the production of chaplins and/or SapB (264, 265).

This again underlines the importance of the extracellular accumulation of a hydrophobic layer for the early stages of aerial growth.

From Aerial Hyphae to Spores: Sporulation-Specific Cell Division and the Cytoskeleton

Like vegetative hyphae, aerial hyphae grow by tip extension. Once sufficient aerial biomass is generated, a signal is transmitted that results in growth cessation, followed by the onset of sporulation. The signal for growth cessation is not yet known but likely relates to the Whi regulatory proteins WhiA and WhiB, as well as the cell division activator SsgB. Mutations of *whiA* and *whiB* produce identical phenotypes, with hypercoiling and very long aerial hyphae that fail to initiate cell division (23, 174, 274), while *ssgB* mutations produce a large colony phenotype, forming an extremely large aerial biomass (275).

The landmark event in the onset of sporulation is the initiation of sporulation-specific cell division, which is notable because the process of cell division is completely different between vegetative and aerial hyphae. Wonderful movies of septum formation during early growth of the hyphae of *S. coelicolor* show how irregular the placement of septa is in vegetative hyphae, with cross-walls dividing the vegetative hyphae into multigenomic compartments (276). In contrast, during sporulation-specific cell division in aerial hyphae, many septa are formed almost simultaneously and in a highly symmetrical fashion, followed by the formation of spore compartments and cell fission, resulting in chains of spores that each contain a single copy of the chromosome (reviewed in references 277 and 278). Most bacteria divide by binary fission, whereby a single mother cell symmetrically divides into identical daughter cells. This process involves the formation of a cytokinetic ring structure, of which the scaffold is formed by the polymerization of thousands of copies of the tubulin homolog FtsZ at division sites (279–283). However, in streptomycetes, the long aerial hyphae differentiate into chains of spores after a uniquely coordinated cell division event. Distinctive ladders of FtsZ are thereby produced that consist of up to 100 septa, and this eventually leads to the production of chains of haploid spores (284–286). Sufficient accumulation of FtsZ is required to support sporulation, and developmental *ftsZ* transcription is largely dependent on the "early" *whi* regulatory genes *whiA*, *whiB*, *whiG*, *whiH*, *whiI*, and *whiJ* (287). Consistent with the notion that the control of *ftsZ* transcription may be a key event, at least in *S. coelicolor*, the nonsporulating phenotype of many of these early *whi* mutants could be overruled by constitutive expression of *ftsZ* during development (288). This also suggests that no other genes that are required for sporulation completely depend on these *whi* genes, at least not when FtsZ is overexpressed.

A unique feature of *Streptomyces* biology is that cell division is not required for growth and *ftsZ* null mutants are viable (289). While the *ftsZ* mutant also fails to make cross-walls, most of the other cell division mutants are only defective in sporulation-specific cell division (278, 290–293). This illustrates a major difference between vegetative and aerial cell division.

While sporulation-specific cell division is mechanistically very similar to that in bacteria that divide by binary fission, the way septum site localization is controlled is completely different, involving actinomycete-specific proteins (177, 277, 278). In unicellular bacteria, the positioning and timing of the formation of a septum involves the action of negative-control systems such as Min, which prevents Z-ring assembly at the cell poles (294, 295), and nucleoid occlusion, which prevents DNA damage by blocking Z-ring formation over nonsegregated chromosomes (296). The Z-ring is tethered to the membrane by dedicated anchoring proteins, such as FtsA and ZipA in *Escherichia coli* (297, 298). All of these systems are absent in streptomycetes. It is therefore unclear how streptomycetes avoid DNA damage in the multinucleoid hyphae. Elegant work on DNA partitioning revealed the important role of the ParAB proteins in DNA segregation during growth and development (299–301). FtsK helps to avoid "guillotining" of the DNA by pumping chromosomes into the spore compartments prior to septum closure, and *ftsK* mutants frequently generate spores with incomplete chromosomes (302–304). Other proteins that should be considered are SmeA and SffA, which play key roles in DNA translocation during sporulation (302), and also the DNA-packaging proteins HupS (305), sIHF (306, 307), Smc (308), and Dps (309).

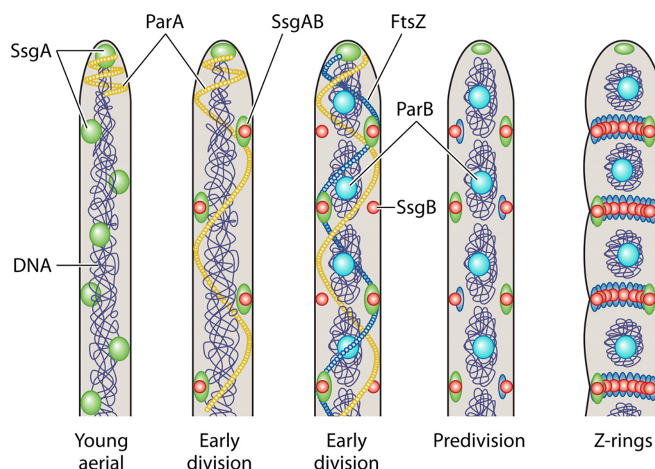

FIG 6 Model for the control of sporulation-specific cell division in *Streptomyces*. When sporulation starts, SsgA localizes dynamically in young aerial hyphae, while SsgB and FtsZ are still diffuse at this stge. At this point, ParA is constrained to the hyphal tip. During early cell division, SsgA and SsgB colocalize temporarily at either side of the aerial hyphae, with ParA extending downward as filaments along the aerial hypha. ParB complexes are then formed over the uncondensed chromosomes, while FtsZ assembles in spiral-like filaments. Subsequently, FtsZ and SsgB colocalize and stay together until FtsZ disperses, whereby SsgB recruits FtsZ and stimulate its polymerization into protofilaments. The way the SsgB-FtsZ complex is tethered to the membrane in the absence of a membrane domain in either protein is unclear, but a likely role is played by the SepG protein (SCO2078 in *S. coelicolor*) encoded by a gene upstream of *divIVA* (L. Zhang, J. Willemse, D. Claessen, and G. P. van Wezel, unpublished data). Z-rings are then formed at the sporulation stage, followed by chromosome condensation and segregation and the production of sporulation septa. SsgA eventually marks the future germination sites. The figure was adapted from references 277 and 316.

In terms of septum site localization, a key role is played by the SsgA-like proteins (SALPs), which only occur in sporulating actinobacteria (310, 311). SsgA activates sporulation-specific cell division (312, 313), and both *ssgA* and *ssgB* are required for sporulation (275, 314, 315). The symmetrical spacing of the many Z-rings is achieved by SsgB, which directly recruits FtsZ and also stimulates its polymerization (316). SsgB localizes to future division sites prior to and independent of FtsZ (316). Thus, cell division is positively controlled in streptomycetes (Fig. 6). The next obvious question is how SsgB itself is localized, especially given that it lacks a membrane domain. Another important cell division protein that controls sporulation-specific cell division in *Strepto-*

myces is CrgA, which affects sporulation-specific cell division by influencing Z-ring assembly (317). In contrast to the SALPs, CrgA also occurs in nonsporulating actinomycetes, and it interacts with FtsZ, FtsI, and FtsQ in *Mycobacteria* (318). The phenotypes of *crgA* null mutants and overexpressing strains suggest that CrgA affects both cell division and the cytoskeleton, although its precise mode of action is still unknown.

Streptomycetes probably have a much more elaborate cytoskeleton than most other bacteria, which may be explained by their hyphal rather than planktonic growth (319). Besides the tubulin homolog FtsZ and the actin-like proteins MreB and Mbl (320, 321), a large number of proteins with coiled-coil structural elements occur in these bacteria, and evidence is accumulating regarding their important role in growth, cell shape, and morphogenesis (319, 322–324). The protein FilP forms intermediate filament-like structures that contribute to mechanical stress resistance (322). In addition, the Scy protein, encoded by a gene immediately adjacent to *filP*, apparently functions as a "molecular assembler" and sequesters DivIVA (323). DivIVA is essential for growth in streptomycetes and localizes to tips to drive apical growth, although the molecular mechanism of this process is still unclear (325, 326). In this way, Scy establishes growth nuclei for apical growth and branching. It also interacts with the chromosome-partitioning protein ParA (327) and the intermediate filament-like protein FilP, which in turn interacts with DivIVA. The apical assembly that drives tip growth was termed the tip organizing complex (TIPOC) by Gabriella Kelemen and colleagues (323, 328, 329). SsgA (330) and the polysaccharide synthase CslA (323, 328, 329) are other proteins that are part of this TIPOC. Clearly, we can only see the tip of the iceberg at present, and future discoveries will undoubtedly shed new light on these processes.

STREPTOMYCETES AS ANTIBIOTIC FACTORIES

Actinomycetes produce approximately two-thirds of all known antibiotics, the majority of which are produced by streptomycetes. Consequently, these microorganisms are very important in the fight against emerging multidrug-resistant pathogens (331–333). *Streptomyces coelicolor* is a model system for studying (the control of) antibiotic production. Scientists have marveled for decades at the ability of single streptomycetes species to produce a plethora of different antibiotic compounds. For example, those produced by *S. coelicolor* include actinorhodin (Act [334]), undecylprodigiosin (Red [335]), calcium-dependent antibiotic (CDA [336]), and methylenomycin (Mmy [337]), the latter of which is carried on a plasmid. However, when the genome sequence of *S. coelicolor* was published (263), it became apparent that this species' true potential as a producer of natural products had actually been underestimated: over 20 biosynthetic gene clusters for secondary metabolites were identified (338), including one that appears to be for the production of a cryptic polyketide antibiotic (Cpk [339]). It rapidly became apparent that such "concealment" of antibiotic-producing capabilities is the norm rather than the exception, with some streptomycetes harboring more than 50 different secondary metabolite gene clusters (340–343). It therefore appears that the potential of these organisms for novel drug production is much greater than originally anticipated. This has prompted extensive research in applied genomics into so-called cryptic, silent, or sleeping antibiotics (reviewed in references 344 to 347) and methods for activating their biosynthesis (348–352).

Correlation between Growth and Antibiotic Production

Programmed cell death and the DasR system. The production of antibiotics (and other secondary metabolites) is temporally correlated to the onset of development in the *Streptomyces* life cycle (179, 180). This correlation may exist because of the need to defend the colony when it is undergoing PCD. Evidence supporting such a direct link between PCD and antibiotic production was provided by the observation that cell wall-derived *N*-acetylglucosamine (GlcNAc) acts as a signal for the onset of development and as a global elicitor molecule for antibiotic production (186, 187). In competitive soil habitats, the timing of development is crucial. However, it is not clear how colonies know when to initiate this process, which has such major consequences for the colony. As long as sufficient nutrients are available, growth should prevail over development, while during starvation, sporulation and subsequent spore dispersal are essential for the survival of the progeny. The signals that trigger such events should be unmistakable, and GlcNAc may serve this purpose well. In nature, GlcNAc can be obtained from hydrolysis of the abundant natural polymer chitin by the chitinolytic system, or from hydrolysis of microorganism cell walls. For bacteria, GlcNAc is a favorable C and N source and a major constituent of the cell wall peptidoglycan. Some 13 chitinases and chitosanases have been identified in *S. coelicolor* (353–355).

Interestingly, under poor nutritional conditions, supplementing with GlcNAc accelerates both the onset of development and antibiotic production, suggesting that under these conditions GlcNAc signals nutrient stress, resulting in accelerated development. Conversely, in rich media, higher concentrations of GlcNAc block development and antibiotic production, thus inducing a response typical of vegetative growth (187). The different growth conditions of minimal and rich media likely resemble conditions of feast or famine in the natural environment (i.e., the soil), with GlcNAc acting as an important signaling molecule that would typically be derived from chitin in nutrient-rich soil during feast periods or from the *Streptomyces* cell walls during PCD (famine), respectively. The secret of this dual signaling role appears to lie in the nature of the sugar transporters. Monomeric GlcNAc enters the cell via the NagE2 permease (356), which is part of the PEP-dependent phosphotransferase system (PTS) (357, 358), while chitobiose (dimeric GlcNAc), which is the subunit of chitin, enters via the ABC transporters DasABC or NgcEFG (241, 353, 359). Subsequently, internalized GlcNAc is converted by the enzymes NagA and NagB to glucosamine-6-phosphate (GlcN-6-P) (360), a central metabolite that can then enter glycolysis (as fructose-6P) or the pathway toward peptidoglycan synthesis.

GlcNAc-derived GlcN-6-P acts as an allosteric effector of the GntR family regulator DasR (186), a global regulator that controls the GlcNAc regulon (186, 360, 361), and also the production of antibiotics (187) and siderophores (362). GlcNAc-dependent nutritional signaling is most likely mediated through changes in the intracellular level of GlcN-6-P, which binds as a ligand to the GntR family regulator DasR, leading to derepression of DasR-mediated control of antibiotic production (187). As shown by genome-wide transcription and ChIP-on-chip analysis, all pathway-specific activator genes for antibiotic biosynthetic gene clusters are controlled by DasR (363). Thus, antibiotic biosynthesis and secretion is induced by adding GlcNAc to minimal medium with a poor carbon source. As mentioned above, these conditions activated

the *cpk* gene cluster (187), which encodes genes that for the cryptic polyketide Cpk and was more recently established as coelimycin P1 (364). This suggests that similar conditions could be used to activate other cryptic antibiotic gene clusters which are expressed poorly (or not at all) under normal growth conditions.

It was recently shown that "hostile" interactions between streptomycetes such as antibiosis and suppression of production by competitors primarily occur under nutrient-limiting conditions; conversely, under nutrient-rich conditions, social interactions are favored (365). These observations suggest that antibiotics are indeed used as weapons in nature. This concept is in contrast with studies suggesting that antibiotics act as signals for intercellular communication (366–368). The latter hypothesis is based on the rationale that the secreted antibiotics may not reach sufficiently high concentrations to cause appreciable growth inhibition and the observation that subinhibitory concentrations of antibiotics induce responses such as biofilm formation (369) or virulence (370) that may benefit the target cells (371). In terms of concentrations in the soil, the same argument can be made for GlcNAc, which only activates antibiotic production at millimolar concentrations on agar plates. Presumably, small molecules reach higher local concentrations, for instance, in close proximity to a producing colony or, in the case of natural products, by binding to dead plant or animal material. In this context, it is worth remembering that cellulose is a preferred column material for the purification of natural products. Information on the interactions between microbes is not just of ecological and evolutionary importance, since it could also be useful in drug discovery efforts. Indeed, data on the interactions between microbes could provide key clues concerning the activation of cryptic biosynthetic pathways (372–376).

Stringent control. As discussed, nutrient deprivation and the resulting growth cessation are the primary triggers for the onset of antibiotic production. Starvation results in the depletion of amino acids and hence uncharged tRNAs, which then occupy the ribosomal A-site. This in turn induces the production of the small molecules guanosine tetraphosphate and pentaphosphate (377). However, (p)ppGpp, or "magic spot," as it was originally known, is produced in response to basically all processes that relate to changes in nutrient availability and might affect growth, adaptation, secondary metabolism, survival, persistence, cell division, motility, biofilm formation, development, competence, and virulence (378). The synthesis of (p)ppGpp from GTP and ATP can be carried out by either RelA, which is ribosome associated and activated by the binding of uncharged tRNAs to the ribosome, or by SpoT, which produces (p)ppGpp in response to nutrient starvation (378). The ribosomal protein L11, encoded by *rplI* (*relC*), activates RelA and thus ppGpp synthesis (379). Deletion of the *relA* gene suppresses antibiotic production, underlining the important role of the stringent response in controlling antibiotic production (380). Indeed, under nitrogen-limiting conditions ppGpp causes a dramatic switch in the physiology of streptomycetes, activating the expression of genes involved in morphological and chemical differentiation, including the production of CDA and actinorhodin, and at the same time repressing genes involved in normal growth (381). The exact mechanism by which ppGpp acts upon such a wide range of genes remains to be elucidated. However, the response to fatty acid starvation involves the direct binding of the unacylated ("uncharged") fatty acid acyl carrier protein (ACP) to SpoT (382), and it has been suggested (180) that perhaps the ACPs of polyketide synthases help to control the stringent response in a similar fashion, providing a possible explanation of the relationship between the stringent response and secondary metabolism.

Morphological control. A complex relationship exists between morphology and antibiotic production. Streptomycetes display a great many different morphologies in submerged cultures, ranging from fragmented growth to dense clumps, and this can have a major influence on their production levels (24). For example, in *Saccharopolyspora erythraea*, erythromycin production is favored by clumps with a minimum size of around 90 μm in diameter (383). The connection between mycelial morphology and production is further exemplified by avermectin production by *S. avermitilis*, which is favored by small dense pellets (384), and by *S. coelicolor*, in which forced fragmentation by overexpression of the cell division activator protein SsgA abolishes actinorhodin production. However, it is dangerous to generalize, as the same strain shows a 20- to 50-fold increase in undecylprodigiosin production in a fermentor (310, 313, 315), and chloramphenicol production by *Streptomyces venezuelae* is not hampered by the extremely fragmented growth of the producing organism (385, 386). It was previously suggested that antibiotics that are produced during exponential growth may benefit from fragmented growth, while those produced during the transition or stationary phases are produced much more efficiently by clumps (236).

More insights into the genetic factors that control mycelial growth should allow scientists to significantly improve the yield of natural product formation by actinomycetes. A novel set of genes was recently discovered in *Streptomyces* that control pellet growth, called *mat*, for mycelial aggregation (387). The genes were discovered 30 years ago via reverse engineering of a strain of *S. lividans* that was selected for fragmented growth in a chemostat (388). Deletion of the *mat* genes (SCO2962 and SCO2963 in *S. coelicolor*) prevented pellet formation and increased both growth rate and enzyme production in *S. lividans* (387). The *mat* genes are probably responsible for the production of a secreted polysaccharide, which presumably glues the hyphae together and thus promotes pellet aggregation.

In silico models have been developed to better understand mycelial growth (389–391), although many were primarily based on physiological and nutritional parameters. Helped by the strong increase in computing power in the modern era, new models were developed recently (392, 393). In particular, a three-dimensional model was developed that includes parameters such as hyphal growth, branching, fragmentation, cross-wall formation, and collision detection, as well as oxygen diffusion (392). For the rational design of actinomycetes as production hosts, it is imperative that we better understand how morphology correlates with production. For example, when and especially where are natural products (and enzymes) secreted? Secretion at apical sites would imply that fragmented growth is favorable because it increases the number of hyphal tips per length unit, as opposed to when production primarily takes place inside mycelial clumps. Interestingly, production of enzymes through the twin arginine translocation (Tat) exporter occurs closely behind the hyphal tips in *S. coelicolor* (16, 394); in line with this concept, Tat substrates are secreted more efficiently in fragmenting strains of *S. coelicolor and S. lividans* (313). An extensive review of the industrial implications of the correlation between growth and natural product formation is be-

yond the scope of this review, so we refer the interested reader elsewhere (24, 395–398).

From global control to the activation of specific gene clusters. The global regulatory networks ultimately relay information toward the individual biosynthetic gene clusters, acting at the level of pathway-specific control. Transcription of antibiotic biosynthetic gene clusters typically depends on a pathway-specific activator gene inside the cluster. Many of these are controlled in a growth phase-dependent manner, with the SARP family regulators (399) being the best-known examples. Particularly well-known members of this family are ActII-ORF4 and RedD, which activate the production of the pigmented antibiotics actinorhodin and undecylprodigiosin, respectively, in *S. coelicolor*, and StrR for production of the aminoglycoside streptomycin in *S. griseus* (400–402). As exemplified by the actinorhodin biosynthetic activator gene *actII*-ORF4, transcription of which is controlled by over 15 different regulatory proteins, the timing and accumulation of a pathway-specific activator may be very complex (236, 395). However, once activated, there appears to be little additional control downstream, as long as the necessary precursors are present. Indeed, when *redD*, the pathway-specific activator gene for production of prodiginines in *S. coelicolor*, is placed under the control of another regulatory element, the result is that control of prodiginin production becomes dictated by the regulatory network controlling that element (275, 314, 315). In other words, placing *redD* under the control of the promoter for the global nitrogen regulator (*glnR*) or the sporulation-specific sigma factor (*sigF*) ensures that production is controlled by nitrogen or produced in aerial hyphae, respectively. This implies that there may be few genetic limitations regarding the production of natural products in time and space once an appropriate activator is expressed. From a production point of view this is an advantage, because restrictions due to growth phase-related control mechanisms can be dealt with by changing the regulatory element. This is particularly important for heterologous expression of biosynthetic gene clusters that are being uncovered at a high rate in actinomycetes in the era of genome sequencing. In particular, the combination of synthetic biology approaches with expression in optimized heterologous *Streptomyces* production platforms is a promising development (403–408).

ACTINOBACTERIA AS SOURCES OF NATURAL PRODUCTS

Actinobacteria as Sources of Antibiotics

Actinobacteria are of great importance in the field of biotechnology, as producers of a plethora of bioactive secondary metabolites with extensive industrial, medical, and agricultural applications (Table 3 provides examples and coresonding references). In particular, *Actinobacteria* produce the majority of the naturally occurring antibiotics. The first antibiotics discovered in *Actinobacteria* were actinomycin from a culture of *Streptomyces antibioticus* in 1940 (409), streptothricin from *Streptomyces lavendulae* in 1942 (410), and streptomycin from *Streptomyces griseus* in 1944 (411), all of which were discovered by Waksman and colleagues. Streptomycetes have been the major source of clinical antibiotics and are responsible for over 80% of all antibiotics of actinobacterial origin (333). That actinomycin, streptomycin, and streptothricin were the first to be found is not surprising, as these molecules occur at much higher frequencies than many other antibiotics. For example, streptothricin is found in some 10% of all streptomycetes isolated randomly from soil and streptomycin is found in 1% and actinomycin in 0.1%, while conversely, erythromycin and vancomycin are found in around 10^{-5} soil isolates, and daptomycin is found only at a frequency of around 10^{-7} (412). Major classes of clinical antibiotics produced by actinomycetes are the following: aminoglycosides (neomycin, kanamycin, streptomycin (413–415), angucyclines (auricin; also, antitumor agents like landomycin and moromycin (416), ansamycins (rifamycin, geldanamycin) (417), anthracyclines (primarily antitumor agents, e.g., daunorubicin) (418, 419), β-lactams (cephamycins) (420) and also the important β-lactamase inhibitor clavulanic acid (421, 422), chloramphenicol (423), glutarimides (cycloheximide) (424), glycopeptides (vancomycin, teichoplanin) (425, 426), lipopeptides (daptomycin) (427), lantibiotics (mersacidin, actagardine) (272), macrolides (clarythromycin, erythromycin, tylosin, clarithromycin) (428, 429), oxazolidinones (cycloserine) (430), streptogramins (streptogramin) (431), and tetracyclines (432). The producing capacity of individual actinomycetes can also vary enormously. Some *Streptomyces* species produce a single antibiotic, while others produce a range of different compounds and compound classes.

Besides antibiotics, *Actinobacteria* also produce a wide variety of other secondary metabolites with activity as herbicides (54), antifungals, antitumor or immunosuppressant drugs, and anthelmintic agents (433). Examples are given below.

Actinobacteria as Sources of Insecticides

Macrotetrolides are active against mites, insects (434–436), coccidia (437), and helminths (438), and they also show immunosuppressive effects (439). They are produced by a variety of *Streptomyces* species (for a review, see Jizba et al. [434]). However, with regard to the composition of the macrotetrolide complex, only *S. aureus* S-3466 (440), which produces a mixture of tetranactin (the most active member of the compound group) with dinactin and trinactin (435, 441), has been utilized for commercial purposes (442). Tetranactin, a cyclic antibiotic produced by *Streptomyces aureus* with a molecular structure related to cyclosporine, is used as emulsion against carmine mites of fruits and tea. A true success story in terms of anthelmintics is ivermectin (443), which is a dehydro derivative of avermectin produced by *Streptomyces avermitilis*. After its appearance in the late 1970s, ivermectin was the world's first endectocide, which at the time was a completely novel class of antiparasitic agents, with strong and broad-spectrum activity against both internal and external nematodes and arthropods. Recently, the Nobel Prize for Physiology or Medicine 2015 was awarded to Satoshi Omura and William C. Campbell for their discovery of avermectin, jointly with Youyou Tu for the discovery of the antimalarial drug artemisinin.

Actinobacteria as Sources of Bioherbicide and Bioinsecticide Agents

Mildiomycin, an antifungal metabolite isolated from cultures of *Streptoverticillium rimofaciens* Niida, is strongly active against several powdery mildews on various crops (444) and inhibits fungal protein biosynthesis (445). The primary sites of action of these antibiotics are at locations where chitin synthesis occurs in the cell wall, there is cation leakage from mitochondria, inositol biosynthesis is occurring, or sites of protein and DNA synthesis. The compounds mentioned above are a few examples of agroactive compounds isolated from *Actinobacteria*. Validamycin A was

TABLE 3 Examples of bioactive molecules produced by *Actinobacteria* genera and their activities

Type of compound and producing species	Bioactive agent(s)	Source or reference
Antibacterial agent producers		
Verrucosispora spp.	Abyssomycin	603
Streptomyces anulatus	Actinomycins	409
Streptomyces canus	Amphomycin	604
Micromonospora spp.	Anthracyclin	605
Streptomyces cattley	Antibiotics and fluorometabolites	606
Streptomyces canus	Aspartocins	607
Streptomyces avermitilis	Avermectin	608
Streptomyces venezuelae	Chloramphenicol	609
Micromonospora spp.	Clostomicins	609
Streptomyces griseus	Cycloheximide	620
Streptomyces orchidaceus	Cycloserine	610
Streptomyces roseosporus	Daptomycin	611
Saccharopolyspora erythraea	Erythromycin (Ilotycin)	612
Micromonospora purpurea	Gentamicin	613
Streptomyces hygroscopicus	Hygromycin	614
Streptomyces kanamyceticus	Kanamycin	615
Streptomyces kitasoensis	Leucomycin	616
Streptomyces lincolnensis	Lincomycin	617
Marinispora spp.	Marinomycin	618
Streptomyces fradiae	Neomycins	619
Micromonospora spp.	Netamicin	80
Streptomyces niveus	Novobiocin	620
Streptomyces antibioticus	Oleandomycin	621
Streptomyces rimosus	Oxytetracycline	622
Streptomyces spp.	Pristinamycin	623
Streptomyces lindensis	Retamycin	624
Streptomyces mediterranei	Rifamycin	625
Nocardia lurida	Ristocetin	621
Streptomyces ambofaciens	Spiramycin	626
Streptomyces virginiae	Staphylomycin	627
Streptomyces endus	Stendomycin	628
Streptomyces lydicus	Streptolydigin	629
Streptomyces griseus	Streptomycin	411
Streptomyces lavendulae	Streptothricin	410
Streptomyces aureofaciens	Tetracycline	630
Micromonospora spp.	Thiocoraline	631
Amycolatopsis orientalis	Vancomycin	632
Antifungal agent producers		
Streptomyces anulatus	Actinomycins	603
Streptomyces nodosus	Amphotericin B	633
Streptomyces griseochromogenes	Blasticidin	634
Streptomyces griseus	Candicidin	635
Streptomyces spp.	Carboxamycin	636
Streptomyces venezuelae	Chloramphenicol	637
Streptomyces padanus	Fungichromin	638
Streptomyces galbus	Galbonolides	675
Streptomyces violaceusniger YCED-9	Guanidylfungin	564
Streptomyces venezuelae	Jadomycin	639
Streptomyces kasugaensis	Kasugamycin	452
Streptomyces spp.	Kitamycin	640
Streptomyces natalensis	Natamycin	641
Streptomyces tendae	Nikkomycin	642
Streptomyces diastatochromogenes	Oligomycin	643
Streptomyces humidus	Phenylacetate	644
Streptomyces cacaoi	Polyoxin B	453
Streptomyces canus	Resistomycin	645
Streptomyces lavendulae	Streptothricin	410
Streptomyces canus	Tetracenomycin	645
Nocardia transvalensis	Transvalencin	646
Streptomyces hygroscopicus	Validamycin	647

(Continued on following page)

TABLE 3 (Continued)

Type of compound and producing species	Bioactive agent(s)	Source or reference
Bioherbicide/biopesticide producers		
Actinomadura spp.	2,4-Dihydro-4-(β-D-ribofuranosyl)-1, 2, 4 (3H)-triazol-3-one (herbicide)	648
Streptomyces hygroscopicus	Herbimycin	649
Streptomyces avermitilis	Ivermectin (derivative of avermectin)	650
Streptomyces prasinus	Prasinons	651
Saccharopolyspora spinosa	Spinosad (neurotoxic insecticides)	652
Antiparasitic agent producers		
Streptomyces avermitilis	Avermectins	608
Streptomyces coelicolor	Prodiginine	653
Streptomyces bottropensis	Trioxacarcin	654
Antiviral agent producers		
Streptomyces antibioticus	9-β-D-Arabinofuranosyladénine	655
Streptomyces hygroscopicus	Hygromycin	614
Streptomyces spp.	Panosialins	656
Hypercholesterolemia agent producer		
Streptomyces hygroscopicus	Rapamycin	674
Antitumor agent producers		
Micromonospora spp.	Anthraquinones	657
Nocardia asteroides	Asterobactine	658
Streptomyces spp.	Borrelidine	659
Micromonospora spp.	Diazepinomicin	660
Actinomadura spp.	IB-00208	661
Micromonospora spp.	LL-E33288 complex	76
Micromonospora spp.	Lomaiviticins	76
Micromonospora spp.	Lupinacidins	657
Thermoactinomyces spp.	Mechercharmycin	662
Marinospora spp.	Marinomycin	618
Salinispora tropica	Salinosporamide	621
Streptomyces peucetius	Doxorubicin (adriamycin)	664
Streptomyces peucetius	Daunorubicin (daunomycin)	665
Micromonospora spp.	Tetrocarcin	76
Micromonospora spp.	Thiocoraline	666
Immunostimulatory agent producers		
Nocardia rubra	Rubratin	667
Streptomyces olivoreticuli	Bestatin	668
Kitasatospora kifunense	FR-900494	669
Immunosuppressive agent producers		
Nocardia brasiliensis	Brasilicardin	670
Streptomyces filipinensis	Hygromycin	671
Streptomyces filipinensis	Pentalenolactone	671
Therapeutic enzyme (antitumor) producers		
Streptomyces spp.	L-Asparaginase	672
Streptomyces olivochromogenes	L-Glutaminase	673

commercialized by Takeda for the control of pathogens in rice and other plants and as a tool for damping off diseases in vegetable seedlings. On the other hand, some secreted metabolites are cytotoxic and can include chemical structures such as macrolides, α-pyrones, lactones, indoles, terpenes, and quinones (446). For instance, resistomycin, a quinone-related antibiotic, has a unique structure and exhibits bactericidal and vasoconstrictive activity based on the inhibition of RNA and protein synthesis (447, 448).

The genome sequences of important *Actinobacteria* species reported to date indicate that as much as 90% of the chemical potential of these organisms remains undiscovered and that the biosynthetic machinery encoded by many of these genetic loci may be activatable under laboratory conditions (449). The predictive models of Watve et al. (450) suggested that over 150,000 bioactive metabolites from members of the genus *Streptomyces* alone within this order are still waiting to be discovered (328, 451). Molecular techniques such as combinatorial biosynthesis may lead to the discovery of drugs that cannot be found naturally and of biosynthetic components that can be interchanged and modified to produce bioactive products with unique properties.

Actinobacteria as Sources of Antifungal Agents

Kasugamycin is a bactericidal and fungicidal metabolite secreted by *Streptomyces kasugaensis* (452) that acts as an inhibitor of protein biosynthesis in microorganisms but not in mammals. The systemically active kasugamycin was marketed to control rice blast (*Pyricularia oryzae cavara*) and bacterial *Pseudomonas* diseases in several crops. In 1965, Isono et al. (453) isolated the first members of a new class of natural fungicides, polyoxins B and D, from metabolites of *Streptomyces cacaoi* var. asoensis. These substances act by interfering with fungal cell wall synthesis by inhibiting chitin synthase (454). Polyoxin B is applied against a number of fungal pathogens in fruits, vegetables, and ornamentals, while polyoxin D is used to control the causative agent of rice sheath blight, *Rhizoctonia solani* (455).

In 1968, the validamycin family was detected by researchers at Takeda Chemical Industries in a greenhouse assay for the treatment of sheath blight disease in rice plants caused by the fungus *Rhizoctonia solani*. Validamycin A, the major and most active component of the complex, was isolated from *Streptomyces hygroscopicus* var. limoneus. Within the fungal cell, validamycin is converted to validoxylamine A, a particularly strong inhibitor of trehalose that suppresses the breakdown of intracellular trehalose (456). Trehalose is well known as a storage carbohydrate, and trehalase plays an essential role in the transport of glucose in insects and fungi (457). This mode of action gives validamycin A a favorable biological selectivity, since vertebrates do not depend on the hydrolysis of the disaccharide trehalose for their metabolism (457).

INTERACTIONS BETWEEN *ACTINOBACTERIA* AND OTHER ORGANISMS

Interactions between *Actinobacteria* and Invertebrates

Insect-bacterium symbioses are widespread in the environment (458), and antibiotic-producing bacterial symbionts are often recruited to protect the host and/or their resources (459, 460). Many insects (e.g., ants, termites, gall midges, and beetles) have developed a specific association with their microbial communities. These interactions are diverse, ranging from antagonism and commensalism to mutualism, and from obligate to facultative (461).

Interaction with ants. Microbial communities of many groups of insects have been widely studied (462), and particularly complex associations have been documented between gut bacteria and insects (463, 464). Attine ants have evolved a mutualism with *Actinobacteria* that produce antibiotics that the ants use as weedkillers to keep their fungal gardens free of other microbes (460, 465). For instance, the ants (genera *Atta* and *Acromyrmex*) cut leaves and then masticate them into a fine biomass that is fed to the symbiotic fungus (*Leucoagaricus gongylophorus*) which, in turn, provides lipid- and carbohydrate-rich hyphae known as gongylidia that will be used by the ants (466).

The ants rely on a similar mutualistic association with members of the *Actinobacteria* (genus *Pseudonocardia*) that produce antibiotics that help suppress *Escovopsis*, which has a devastating effect on the fungus gardens of leaf-cutting ants in the absence of the bacterium (467–470), by significantly reducing the colony fitness or even inducing colony death (471). Other *Actinobacteria* genera may play a similar role (472, 473). The presence and maintenance of *Streptomyces* bacteria seems to be of prime importance, as the bacteria appear to be the primary defense against *Escovopsis*, which ants possess (467, 474).

Interactions with beetles. Multiple bacterial genera of the *Gammaproteobacteria* and *Actinobacteria* classes were found in the larvae, pupae, and adult guts of the bark beetle *Dendroctonus rhizophagus*. The class of *Actinobacteria* was represented by *Ponticoccus gilvus* and *Kocuria marina*, both of which can degrade carboxymethylcellulose *in vitro*. Neither *Actinobacteria* species has ever been reported in other bark beetles, suggesting that these bacteria could be involved in the degradation of cellulosic substrates such as pine bark and phloem, enabling them to serve as a carbon source (475). This postulate is supported by the presence of cellulose-degrading bacteria in the gut of insects that feed on woody tree tissues, such as wood-boring beetles, including *Saperda vestita* and *Agrilus planipennis* (476, 477).

Interactions with protozoans. *Mycobacterium ulcerans* is responsible for a necrotizing cutaneous infection called Buruli ulcer, which has been reported in more than 30 countries worldwide, mainly in tropical and subtropical climates. However, *M. ulcerans* can probably not live freely due to its natural fragility, slow-growth development, and inability to withstand exposure to direct sunlight. Further, *M. ulcerans* is sensitive to several antibiotics, such as streptomycin and rifampin. *M. ulcerans* therefore rarely occurs as a free-living microorganism, even though *Streptomyces griseus* and *Amycolatopsis rifamycinica*, producers of streptomycin and rifampin, thrive under such conditions (478, 479).

To survive, *Mycobacterium* has adapted to a more protected niche by utilizing free-living amoebae (FLA) as carriers. In their protozoan hosts, "hidden" mycobacteria might find easier opportunities to infect vertebrate end hosts, multiplying within protozoans to escape immune reactions (480). This ability to persist within amoebae has been widely documented (481–483). The internalization of infectious agents inside other parasites represents an evolutionary strategy for survival that may sometimes enhance pathogenesis or transmissibility (480).

Interactions between *Actinobacteria* and Vertebrates

Actinobacteria, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, and *Proteobacteria* dominate the gut microbiota, demonstrating a similar overall composition at the phylum level in various gastrointestinal tract locations, including human gastric fluid, intraoral niches (484, 485), throat (486), distal esophagus (487), stomach mucosa (486), and feces (488). Further, *Actinobacteria* are prominent among the identified microbiota of the oral cavity but are significantly less abundant in the lower gastrointestinal and genital tracts.

Children with diabetes reportedly exhibit substantially lower numbers of *Actinobacteria* and *Firmicutes* compared to healthy children. Further, within the *Actinobacteria*, the number of *Bifidobacterium* was significantly lower in children with diabetes (489).

Metagenomic studies of mucosal and fecal samples retrieved from healthy subjects demonstrated the presence of six dominant phylogenetic phyla, including *Actinobacteria* (490). The role of bifidobacteria in gut ecology illustrates the importance of *Actinomyces* and other *Actinobacteria* (491). The phyla *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, and *Proteobacteria* constitute more than 99% of all gut microbiota in dogs and cats. Compared with the case in humans, which harbor 10^{18} bacterial cells, *Bifidobacteria* is less abundant in cats and dogs (492, 493).

Although the aerobic *Actinobacteria* are infrequently encountered in clinical practice, they are important potential causes of serious human and animal infections. These bacteria have emerged as unusual but important potential human pathogens that cause significant disease, affecting not only immunocompetent hosts but also severely immunocompromised patients. McNeil and Brown (494) reviewed the data on medically important aerobic *Actinobacteria* and epidemic diseases that these organisms cause in animals and humans. For instance, the genus *Nocardia* comprises several species that are known to be unusual causes of a wide spectrum of clinical diseases in both humans and animals, infecting cattle, horses, dogs, and swine (494). While the majority of nocardial infections have been attributed to *Nocardia asteroides*, other pathogenic *Nocardia* species that have been reported include *N. brasiliensis*, *N. otitidiscaviarum*, and *N. transvalensis*. In a taxonomic revision of the *N. asteroides* taxon, two new species, *N. farcinica* and *Nocardia nova*, were separated (495).

Reports of human infection with *Rhodococcus* spp. have been rare (494). The disease they cause can have a variable clinical presentation depending upon the host's underlying immune status and possibly upon the site of inoculation and the virulence of the infecting microorganism. Consequently, in severely immunocompromised patients, primary pulmonary *Rhodococcus equi* infections (pneumonia and lung abscesses) have been reported most frequently (494).

Only a few invasive humans infections, such as mycetoma caused by *Streptomyces* spp., have been documented to date (496). They can, however, be caused by *S. somaliensis* and *S. sudanensis* (497, 498). The majority of invasive *Streptomyces* infections are associated with bacteremia and lung infections, namely, pneumonia, abscess, and pneumonitis (499). Streptomycetes are infrequent pathogens, although *S. somaliensis* and *S. sudanensis* can cause infections.

As for *Rhodococcus*, most of the infected patients had some underlying immunosuppressive condition, such as HIV infection, cancer, systemic lupus erythematosus (SLE), Crohn's disease, etc. Moreover, *S. pelletieri*, *S. griseus*, *S. lanatus*, and *S. albus* have been isolated from various patients with lung pathology (496, 500–502). Other opportunistic pathogenic *Actinobacteria* include *Amycolata autotrophica*, *A. orientalis*, *Micromonospora* spp., *N. dassonvillei*, and *Oerskovia* spp. (494).

Interactions between *Actinobacteria* and Plants

As stated previously, actinomycetes are abundantly present in soils and represent a high proportion of the microbial flora of the rhizosphere (503). *Actinobacteria* thus unsurprisingly play diverse roles in plant-associated microbial communities. Some genera are viewed predominantly as soil saprophytes with crucial roles in nutrient cycling, while others are endophytes, beneficial symbionts, or even pathogens of plants.

Plant-*Actinobacteria* deleterious interactions. (i) *Actinobacteria* as plant pathogens. The successful infection of a plant host is a complex multistep process, requiring the pathogen to sense the presence of a suitable host, penetrate and colonize the plant tissue, and survive in the presence of host defense mechanisms. In comparison to other bacteria, actinomycetes play a relatively minor role in plant diseases. However, they represent major pathogens of certain crops in particular areas, and under special conditions affect the quality and the quantity of agricultural products. This may result in huge agricultural losses, especially of potatoes but also of other root crops, such as beet, carrot, parsnip, radish, sweet potato, and turnip (504, 505).

Recent progress in molecular genetics and the understanding of the genomics of plant pathogenicity has been made for the *Actinobacterial* genera *Clavibacter*, *Streptomyces*, *Leifsonia*, and *Rhodococcus*. Further, plant-pathogenic *Actinobacteria* in the genera *Streptomyces* and *Rhodococcus* have very wide host ranges, including economically important crops and model plants. For instance, in the genus *Streptomyces*, plant pathogenicity is rare, with only a dozen or so species possessing this trait of the more than 900 species described. Nevertheless, such species have a significant impact on agricultural economies throughout the world due to their ability to cause important crop diseases, such as potato common scab, which is characterized by lesions that form on the potato tuber surface. The most well-known phytopathogenic *Actinobacteria* are *Streptomyces scabiei*, *S. acidiscabies*, and *S. turgidiscabies*, which induce devastating scab diseases on a broad spectrum of plants. *Streptomyces scabiei*, the most ancient of these pathogens, is found worldwide, whereas *S. turgidiscabies* and *S. acidiscabies* are emergent pathogens that were first described in Japan and the northeastern United States, respectively (506–508).

S. scabiei and *S. turgidiscabies* both cause "common" scab in potatoes (*Solanum tuberosum*); the disease is characterized by gray spores borne in spiral chains and that produce melanin (509). Another disease, the "acid scab," is associated with *S. acidiscabies* (510). The typical and acid scab strains differ with respect to pigmentation, spore chain morphology, raffinose utilization, and tolerance of low pH. In addition, *S. acidiscabies* differs from *S. scabiei* in phenotype and ecology by having flexuous spore chains, a growth medium-dependent spore mass color ranging from white to salmon-pink, a red or yellow pH-sensitive diffusible pigment, and no melanin.

Russet scab is commonly restricted to nature of the potato's skin and affects the quality of the crop. This disease caused by soilborne streptomycetes different from *S. scabies* has been reported in Europe and the United States since the beginning of the century (511). The disease is divided into two types. The first type is American russet scab, caused by the genus *Streptomyces* and species different from *S. scabiei* (which forms a pigmented mycelium, flexuous spore chains, and no melanin) and from *S. acidiscabies* (mass spore color, inability to grow at pH 4.5). The second type is European russet (or netted) scab, which is apparently distinct from the American variant (512) with respect to cultivar susceptibility, root attack, and optimum soil temperature.

No specific taxonomic investigations have been carried out on *S. ipomoeae*, the causal agent of the sweet potato soil rot disease characterized by dwarfed plants with little or no growth and minor discolored leaves, with many plants dying before the end of the season. The organism apparently persists for long periods, even in the absence of the host plant.

In the 1980s, *Actinobacteria* were reported to plug the xylem vessels of silver, sugar, and Norway maples, leading to early decay and dieback of the tree branches (513, 514). A variety of streptomycetes of different species (*S. parvus*, *S. sparsogenes*, *Streptomyces* sp.) were isolated from the plugs. The isolates were capable of growing within the tree vessels and *in vitro* in the presence of several phenols. Although sugar maples in the northeastern United States are routinely tapped to collect maple sap for conversion to maple syrup, the mode of penetration of the *Actinobacteria* into the host is not known. Similarly, a lignocellulose-degrading

streptomycete (*S. flavovirens*) was found to decompose the intact cell walls of the phloem of Douglas firs, and hyphae were found in the cavities deriving from the destruction of the walls of the parenchyma and sclereids (515).

Rhodococcus fascians was first isolated and identified in 1930 as the causal agent of sweet pea fasciations (516). Since then, the symptoms caused by *R. fascians* in diverse plant species have been described (reviewed by Goethals et al. [517]). The bacterium infects both monocot and dicot hosts, many of which are economically important (518). Extensive epiphytic growth precedes intercellular invasion through stomata. *R. fascians* causes various effects in its hosts, including leaf deformation and formation of witches' broom, fasciations, and leafy galls (517, 519). The symptoms are caused by the hyperinduction of shoots through activation of dormant axillary meristems and *de novo* meristem formation, probably as the result of elaborate manipulation of host hormone balances and pathogen-derived auxins and cytokinins (520, 521). In contrast to *Streptomyces* and *Rhodococcus*, plant-pathogenic species in the *Actinobacteria* genera *Clavibacter* and *Leifsonia* are host specific at the species or subspecies level.

Clavibacter michiganensis is another aerobic nonsporulating Gram-positive plant-pathogenic member of the *Actinobacteria* and is currently the only known species within the genus *Clavibacter*. *C. michiganensis* is composed of a number of host-specific subspecies, all of which colonize the xylem. Currently, *C. michiganensis* is represented by five subspecies: *C. michiganensis* subsp. *insidiosus*, *C. michiganensis* subsp. *michiganensis*, *C. michiganensis* subsp. *nebraskensis*, *C. michiganensis* subsp. *sepedonicus*, and *C. michiganensis* subsp. *tesselarius*.

C. michiganensis subsp. *michiganensis* provokes bacterial canker formation in tomatoes, a serious emerging disease of tomatoes wherever tomato plants are grown. This disease has caused substantial economic losses worldwide (522). Another important plant pathogen is *C. michiganesis* subsp. *sepedonicus*, which causes a disease in potatoes known as ring rot, due to the way it rots the vascular tissue inside potato tubers. *C. michiganensis* subsp. *nebraskensis* causes wilt and blight in maize. *C. michiganensis* subsp. *tesselarius* induces leaf freckles and leaf spots in wheat. Wilting and stunting in alfalfa (*Medicago sativa*) are induced by *C. michiganensis* subsp. *insidiosus* (523). The severity of these diseases and the difficulty of controlling the spread of the corresponding pathogens has resulted in the pathogens being classified as quarantine organisms under the European Union Plant Health Legislation, as well as the laws of many other countries.

The genus *Leifsonia* includes xylem-limited, fastidious, bacterial pathogens. The best-known of these pathogens is *L. xyli* subsp. *xyli*, the causative agent of a systemic disease called ratoon stunting of sugarcane. Plant growth inhibition, the hallmark of this disease, may be due to a putative fatty acid desaturase that modifies the carotenoid biosynthesis pathway to produce abscisic acid, a growth inhibitor (524).

(ii) Traits of pathogenicity. The mechanisms by which a pathogen can induce the development of lesions on the host are still not well known, although recent advances in this field have provided some ideas. An important feature in the interaction of a pathogen and its host is the establishment of an equilibrium that allows both partners to survive in nature. If no resistant or tolerant plant cultivars are available, pathogen infection will inevitably lead to disease outbreaks. Despite the economic importance of plant-pathogenic *Streptomyces* species, very little is known about the molecular mechanisms used by these organisms to sense the presence of a suitable plant host, colonize the host's tissues, and resist its defense mechanisms.

The virulence factors of *C. michiganensis* subsp. *michiganensis* seem to be extracellular enzymes, particularly proteases. Dreier et al. (525) reported the participation of three proteases (Pat-1, ChpC, and ChpG) in the pathogen's initial interactions with the host plant, but their exact target remains unknown. Several potential virulence genes are clustered in the *chp-tomA* region of the bacterial genome, which may be a pathogenicity island and crucial for successful colonization. It was recently shown that the virulence of *Clavibacter michiganensis* subsp. *michiganensis* toward tomato plants can be modulated by three different mechanisms: loss of plasmids accompanied by the loss of the pathogenicity factors celA and pat-1, resulting in reduced virulence or even nonvirulence in a plasmid-free derivative; transfer of plasmids to plasmid-free *C. michiganensis* subsp. *michiganensis* derivatives, which restores full virulence; and loss of the pathogenicity island due to stress-activated *recA*-dependent recombination events, which leads to a low-titer colonizer that may carry the plasmids and the pathogenicity factors necessary for effective colonization but which can be considered a nonvirulent endophyte (526).

Ammonium assimilation and nitrogen control in *M. tuberculosis* have been studied intensively, with a particular focus on glutamine synthetase I (GSI), an enzyme whose extracellular release was identified as a potentially important determinant of pathogenicity (527).

Phytotoxin production is commonly involved in the pathogenicity of *Streptomyces*. Some early work on potato scab disease demonstrated that darkening of tuber cells during pathogen colonization was a response to the action of a toxin or enzyme secreted by the scab organism. A key virulence determinant in scab-causing streptomycetes is a family of phytotoxic secondary metabolites called thaxtomins, of which thaxtomin A is the most abundant (528). Thaxtomin production is usually positively correlated with pathogenicity. Further, thaxtomin induces a variety of phenotypic changes in the plant host, including cell hypertrophy, root and shoot stunting, tissue necrosis, alterations in plant Ca^{2+} and H^{+} ion influxes, inhibition of cellulose synthesis, programmed cell death, and production of the antimicrobial plant phytoalexin scopoletin (529–533). In addition, thaxtomin helps *S. scabiei*, *S. turgidiscabies*, and *S. acidiscabies* penetrate plant cell walls by inhibiting cellulose biosynthesis (reviewed by Loria et al. [505]), which presumably enables the bacterium to secrete proteins onto the host cell membrane. An additional virulence determinant that has been described in plant-pathogenic streptomycetes is a secreted necrogenic protein called Nec1. Thaxtomin and Nec1 were the first virulence determinants to be identified and are thought to contribute to tissue penetration and suppression of plant defense responses, respectively. Thaxtomins are cyclic dipeptides (2,5-diketopiperazines) derived from L-phenylalanine and L-tryptophan, and they contain a 4-nitroindole moiety that is essential for their phytotoxicity (528). The production of thaxtomin A was positively correlated with disease severity (534). Mutants of *S. scabiei* and *S. acidiscabies* that were deficient in thaxtomin A biosynthesis did not cause symptoms on potato tubers, establishing the thaxtomins as important pathogenicity determinants (535, 536). Eleven family members have been isolated and characterized and are distinguished by the presence or absence of *N*-methyl and/or hydroxyl groups. Thaxtomin A, the predomi-

nant family member produced by *S. scabiei*, *S. turgidiscabies*, and *S. acidiscabies*, is required for scab disease development (536–538). The *S. scabiei* coronafacic acid-like biosynthetic cluster contributes to host-pathogen interactions, as demonstrated recently by Bignell et al. (504). In addition, an extracellular esterase from *S. scabiei* has been characterized, sequenced, and identified as a potential virulence factor whose activity may be regulated by the availability of zinc (539).

Several bacterial and fungal genomes have been reported to encode proteins with distant homology to plant expansins (540). These proteins are required for virulence, have C-terminal expansin-like domains, and are found in many plant-associated microorganisms, including the phytopathogenic *Actinobacteria* organisms *Clavibacter michiganensis* subsp. *sepedonicus* (526, 541). The *S. scabiei* expansin-like proteins exhibit 66% homology with each other at the amino acid level and are also closely related to putative expansin-like proteins from two nonpathogenic *Streptomyces* species. It is tempting to speculate that SCAB44951 might be important for plant-microbe interactions, because it can mimic specific plant PR-1 proteins and thus manipulate plant defense responses during infection. Interestingly, the PR-1-type protein identified in *S. scabiei* is part of the pathogenome and is conserved in *S. ipomoeae*, further supporting a potential role for this protein in Streptomyces-plant interactions.

Propionibacterium acnes produces abundant porphyrins, which might contribute to skin damage (542). The interaction of porphyrins with oxygen is thought to contribute to keratinocyte damage and consequently to have implications regarding the pathogenesis of progressive macular hypomelanosis (543).

Concanamycins are produced by several *Streptomyces* species, including *S. diastatochromogenes* (544), *S. neyagawaensis* (545), *S. graminofaciens* (546), and *S. scabiei* (547, 548). For instance, concanamycins A and B, produced by *S. scabiei*, exhibit phytotoxic activity (549) and have been proposed (but not proven) to be virulence determinants in that organism. It should be noted that the other concanamycin family members are not produced in *S. acidiscabies* or *S. turgidiscabies* (548–550).

Plant-*Actinobacteria* beneficial interactions. *Actinobacteria* are microorganisms capable of colonizing the rhizosphere through their antagonistic and competitive characteristics concerning other soil microorganisms (503). Like other beneficial microorganisms, *Actinobacteria* can affect plant growth in two general ways, either directly or indirectly. Indirect promotion occurs when they prevent the harmful effects of one or more deleterious microorganisms. This is chiefly done through biocontrol or antagonism toward soil plant pathogens. Specifically, colonization or the biosynthesis of antibiotics (551) and other secondary metabolites can prevent pathogen invasion and establishment. Direct promotion of plant growth occurs when the plant is supplied with a compound that is synthesized by the bacteria, or when the latter otherwise facilitates plant uptake of soil nutrients. Possible contributions of this sort include nitrogen fixation, siderophore synthesis, phytohormone synthesis, and solubilization of minerals to make them available for plant uptake and use (552).

(i) *Actinobacteria* as biological control agents. The *Actinobacteria* are widely recognized for their potential in biocontrol (553–555) because they are important producers of bioactive compounds (556). Over the past 50 years, there have been many studies on the mechanisms by which *Actinobacteria* might inhibit pathogens in soil, including antibiosis, nutrient competition, production of degradative enzymes, nitrous oxide production, and quorum quenching (557–559). Their adaptability to different environments in the rhizosphere makes them a strong competitor. Some are known for their production of siderophores, which can chelate iron, depriving other organisms of this important micronutrient (560, 561). Siderophore production by *S. griseorubiginouse* is effective in the fight against *Fusarium* wilt of banana caused by *Fusarium oxysporum* f. sp. *cubenese* (561). *Actinobacteria* have also been reported to secrete enzymes that degrade the mycelial cell walls of fungal parasites, as described in several studies (556, 562–565). Several chitinolytic enzymes have been identified in some species of *Actinobacteria*, including *S. antibioticus* (566), *S. aureofaciens* (566), *S. lividens* (567), *S. plicatus* (568), *S. halsteii* AJ-7 (569), and *S. lydicus* WYEC108 (570). A biofungicide containing *Streptomyces lydicus* WYEC 108 was approved by AG (Natural Industries Inc., TX, USA) and registered in 2004 as Actinovate soluble (EPA registration number 73314-1). The product, which is completely water soluble, is a biofungicide that effectively protects against and controls many common foliar and soilborne diseases.

Actinobacteria are also widely known for their ability to produce antibiotics that allow them to inhibit plant pathogens (556, 571, 572). Trejo-Estrada et al. (564) have shown a correlation between the production of antibiotics in soil *Actinobacteria* and effectiveness in the fight against plant pathogens. For example, *Streptomyces violaceusniger* YCED9 produces three antifungal compounds, including nigrecine, geltanamycine, and guanidylfingine, that fight against plant pathogens (564). Similarly, several antibiotics produced by *Actinobacteria* are currently used in biological control (Table 3).

Millard (573) reported that green manures, or crops grown specifically for biomass to be incorporated into soil, could reduce the infection of potatoes by pathogenic *Streptomyces scabiei*. Later, in 1926, Sanford (574) noted that *Actinomyces scabiei* was "very sensitive to the secreted products of many molds and bacteria, some of which prevent its growth," and suggested that green manures favored the antagonistic bacteria that inhibited the pathogen. Subsequently, Millard and Taylor (575) showed that soil inoculation with a saprophytic (nonpathogenic) *Actinomycete* isolate could significantly reduce both disease (potato scab) and pathogen populations, concluding that the saprophytic inoculated strain outcompetes the pathogen in soil, thereby reducing plant disease.

Antibiotic-mediated inhibition of pathogens is generally the primary focus in efforts to suppress plant diseases. However, the diversity of secondary metabolites produced by *Streptomyces* and other species also offers great potential for suppressing fungal, bacterial, oomycete, and nematode pathogens.

(ii) *Actinobacteria* as plant growth-promoting rhizobacteria. In attempts to develop commercial biocontrol and plant growth-promoting products using rhizobacteria, it is important to recognize the specific challenges they present. To begin with, the interaction between plant growth-promoting rhizobacteria (PGPR) species and their plant symbionts appears to be specific, even within a crop or cultivar (552, 576). While a rhizobacterium screened for growth promotion may reveal positive effects on one crop, it may have no effect or even retard the growth of another (577, 578). Although rhizobacteria may present unique challenges to our attempts to harness their beneficial attributes, the prospects for improving agriculture by using PGPR for biocontrol seem to

be excellent. The first step toward exploiting PGPR species to enhance plant growth will be to better understand the systems that enable them to act as efficient plant growth enhancers.

Since the 1990s, several nitrogen-fixing *Actinobacteria* have been recognized and found to be associated with plants. *Corynebacterium* sp. AN1 isolated from the plant forest phyllosphere reduces acetylene and can be regarded as a substitute for nitrogenous fertilizer as a means of promoting maize growth (579). *Pseudonocardia dioxanivorans* CB1190 isolates, which can grow on 1,4-dioxane as their sole source of carbon and energy, have also been shown to fix dinitrogen (580). Despite the well-documented history of *Streptomyces* in biocontrol and preliminary evidence of their capacity to enhance plant growth (581), the potential of *Streptomyces* species as PGPR has not been widely studied. This is surprising because streptomycetes, which generally account for an abundant percentage of the soil microflora, are particularly effective colonizers of plant root systems and are able to endure unfavorable growth conditions by forming spores (582).

Merriman et al. (583) reported the use of *Streptomyces griseus* (Krainsky) Waksman and Henrici isolates to treat the seeds of barley, oat, wheat, and carrot, in order to increase their growth. The isolate was originally selected for the biological control of the pathogen *Rhizoctonia solani*. Though the *S. griseus* isolate did increase the average grain yield, dry foliage weight, tiller number, and advanced head emergence for both wheat and oat relative to controls, the differences were not statistically significant. However, the isolate was more successful as a seed treatment for carrots. Marketable yields were increased over controls by 17% and 15% in two separate field trials. In addition, both trials also provided an improved yield of large- and very-large-grade carrots relative to controls (583). Nearly 20 years later, El-Abyad et al. (584) described the use of three *Streptomyces* spp. in the control of bacterial, *Fusarium*, and *Verticillium* wilts, early blight, and bacterial canker of tomato. In addition, tomato growth was significantly improved by the use of the antagonistic *Streptomyces* spp. for a seed coating. An increased availability of growth regulators produced by the inoculum was the reason proposed for the improvement in tomato growth, although this has not yet been formally tested (584). While studies conducted by El-Abyad et al. (584) and Merriman et al. (583) reported plant growth enhancement to be a function of the magnitude of inoculation with *Streptomyces*, but the behavior of the inocula under gnotobiotic conditions and the possible mechanisms of streptomycete-mediated growth promotion should be investigated further.

(iii) *Actinobacteria* as symbionts. *Streptomyces* spp. constitute protective mutualistic symbioses in which the host feeds and protects the bacteria and in return the bacteria provide antibiotics to protect the host, or their resources, from pathogens (585). Other genera of *Actinobacteria*, namely, *Frankia* and *Micromonospora*, form mutualistic symbioses with higher organisms via nitrogen-fixing actinonodules in trees and shrubs (586, 587).

For a long time, diazotrophy in the *Actinobacteria* was thought to be limited to the genus *Frankia*. However, molecular studies have increased the number of known *nifH*-containing *Actinobacteria* beyond *Frankia* spp. (587–591). The discovery of these actinobacteria has stimulated further discussion and inquiries on the origin and emergence of diazotrophy among *Actinobacteria*. Nitrogen-fixing *Actinobacteria* in the genus *Frankia* live as soil saprophytes and as endophytic symbionts in over 200 plant species (592). The genus *Frankia* has a special significance as the nitrogen-fixing partner in a symbiosis with certain nonleguminous plants, most notably of the genera *Alnus*, *Casuarina*, and *Elaeaginus*, permitting these plants to grow well in nitrogen-poor soils. Some species of higher plants are symbiotic, forming endophytic associations with actinomycetes to achieve actinorhizal nitrogen fixation (168). The genus *Frankia* establishes a symbiotic relationship with many flowering plants. The best-known example is the alder (*Alnus*), where these *Actinobacteria* are found in the roots, in nodules where nitrogen gas is allowed to reach the nitrogenase (168).

(iv) *Actinobacteria* as endophytes. Endophytic *Actinobacteria* have been isolated from a wide variety of plants. The most frequently observed species belong to the genera *Microbispora*, *Nocardia*, *Micromonospora*, and *Streptomyces*, the most abundant (566, 593). Unlike pathogenic streptomycetes, endophytic species persist inside the plant host for long periods of time without causing observable disorder symptoms and lack known virulence determinants shared with phytopathogenic *Streptomyces* spp. (503). Endophytic streptomycetes may improve the growth of their plant host by producing auxins that promote root growth and development (594, 595). Moreover, endophytic colonization of *Pisum sativum* with the endophyte *S. lydicus* improves the frequency of root nodulation by *Rhizobium* spp., causing enhanced iron and molybdenum assimilation and vigorous plant growth (596).

(v) *Actinobacteria* as elicitors of plant defense. In addition to direct toxic effects on other microbes, nitrous oxide production by *Streptomyces* has been suggested to activate plant defenses, improving the plant's protection against pathogens (597). Recently, Mahmoudi et al. (559) reported that streptomycetes can degrade the signaling compounds that coordinate the expression of genes required for pathogenicity in *Pectobacterium carotovorum*, suggesting a further mechanism for disease suppression. In addition, the production of chitinases or plant growth-promoting compounds has been reported to contribute to disease suppression by some *Streptomyces* isolates (598–601).

CONCLUSIONS AND FUTURE PERSPECTIVES

In this review, we have provided a comprehensive overview of the current knowledge concerning the biology of the phylum *Actinobacteria* and applications of its members in medicine, agriculture, and industry. Distributed in both terrestrial and aquatic ecosystems, its members play a crucial role in the recycling of refractory biomaterials. The diversity of this phylum is large and includes many beneficial but also some pathogenic species. *Mycobacterium tuberculosis* is carried by 2 billion people in the world and is the causative agent of tuberculosis, killing several million people every year. There are also the scab-causing streptomycetes, which have a broad host range, infect plants, and are known for their ability to cause necrotic scab-like lesions on economically important root and tuber crops, such as potato. On the other hand, the *Actinobacteria* have numerous clear potential benefits for humans as sources of novel antibiotics, antifungals, anticancer agents, and other secondary metabolites that might be used in medicine or to improve plant growth and resistance to diseases. *Actinobacteria* are also very promising for biocontrol of pests and as plant growth promoters. With the rapid developments in the fields of genomics, synthetic biology, and ecology and the strong requirement for new antimicrobial compounds to combat antimicrobial resistance, the biology of the *Actinobacteria* is a highly dynamic research field and we expect to see many new advances in this field in the years to come.

ACKNOWLEDGMENTS

We are grateful to Dennis Claessen for discussions.

This work is supported by the research program "Assessing and reducing environmental risks from plant protection products" funded by the French Ministries in charge of Ecology and Agriculture.

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Essaid Ait Barka is a professor of Plant Physiology at the University of Reims. He studied Plant Biology at the Cady Ayad University in Marrakesh (1988) and got his Ph.D. from Reims University (1993), on the plant reaction to low temperatures stress. As a postdoc at Laval University (Canada) and Penn State University (USA), he worked as research professor at NSAC (Nova Scotia, Canada). He is interested in the interactions between plants and pathogenic/nonpathogenic microorganisms, and his current research is directed toward basic and applied aspects of using beneficial microorganisms as microbial inoculants to promote plant growth and provide biological resistance against plant biotic and abiotic stresses. His investigations aim to understand the molecular mechanisms of cross talk between plant defense signal transduction pathways and beneficial microorganisms. He has many partnerships with the private and public sectors and is coinventor of two patents in the field of biocontrol.

Christophe Clément is a Professor at the University of Reims, France. He received his Ph.D. in Plant Physiology from the University of Reims, France, in 1994. He obtained the head position of the lab in 2001. His research is focused on the physio-molecular analysis of plant responses to both biotic and abiotic stresses.

Gilles P. van Wezel is a Professor of Molecular Biotechnology, at the Institute of Biology at Leiden University. He studied biochemistry at the Free University in Amsterdam (1987) and performed his Ph.D. investigation in the group of Leendert Bosch in Leiden (1994) on the control of translational genes in *Streptomyces*. As a postdoc (EU Human Capital Mobility) in the laboratory of Mervyn Bibb at the John Innes Centre in Norwich (United Kingdom), he worked on the control of carbon metabolism in *Streptomyces*, and the link between sugar utilization and antibiotic production is still a major theme in his research. His current research focuses on the systems biology of growth, cell division, and antibiotic production of *Streptomyces*. A major application is the activation of silent biosynthetic gene clusters and elucidation of novel molecules with bioactivity against multidrug-resistant pathogens.