Biosynthesis and Intracellular Organization of Magnetosomes in Magnetotactic Bacteria

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Contents

Abstract Magnetotactic bacteria are ubiquitous aquatic microorganisms capable of orientation within the earth's magnetic field. They receive their stunning proficiency from magnetosomes, which are unique organelles used to synthesize nanometer-sized crystals of magnetic iron minerals. Most of these microorganisms cannot be cultivated under laboratory conditions, much less genetically engineered with only few exceptions. However, two *Magnetospirillum* species have emerged as model organisms to study magnetosome formation and magnetotaxis on genetic level, and within the past decade, much has been revealed about the process of magnetosome biogenesis. In this chapter, we summarize these new insights and place the molecular mechanisms of magnetosome formation in the context of the complex cell biology of *Magnetospirillum* spp. After giving an overview of magnetosome vesicle synthesis and biomineralization, we focus on recent findings in positioning and dynamics of the organelles and the biological implications of it, which emphasize that magnetotactic spirilla have evolved sophisticated mechanisms to construct, incorporate, and inherit a navigational device perfectly.

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1 Introduction

Magnetotactic bacteria (MTB) are defined by the biomineralization of dedicated intracellular structures, the magnetosomes, which consist of membrane-enclosed crystals of a magnetic iron mineral. Magnetosomes function as sensors for the earth's magnetic field, which is assumed to direct the swimming of bacterial cells along vertical redox gradients within sediments of natural waters (Blakemore et al. 1980; Bazylinski and Frankel 2004; Simmons et al. 2006). The ability to form magnetosomes with diverse shapes and alignments has been found in many phylogenetic groups of prokaryotes (Jogler et al. 2011; Lefèvre et al. 2014; Lin et al. 2017), and magnetotactic microorganisms are abundant and widespread in almost any aquatic habitat.

Magnetosomes are the best-studied examples of lipid-bounded bacterial organelles, and recent research has revealed that they represent one of the most complex structures found in prokaryotic cells (Uebe and Schüler 2016). Besides their function in magnetotactic navigation and motility, magnetosomes have emerged as an effective model for studying cell biology and formation of prokaryotic organelles. In addition, bacterial magnetosomes that can be isolated from disrupted cells represent magnetic nanoparticles with exceptionally well-defined characteristics such as high crystallinity, strong magnetization, and a uniform size distribution, which is owing to the precise control that is exerted during all stages of biomineralization (Faivre and Schüler 2008; Staniland and Rawlings 2016). In addition, the defined composition of the enveloping magnetosome membrane provides an excellent target for functionalization by chemical and genetic coupling of diverse functional moieties such as fluorophores, enzymes or ligands, and antibody fragments (Mickoleit and Schüler 2018; Vargas et al. 2018). Therefore, much of the interest in their biosynthesis has been motivated by their potential use in several biotechnical and biomedical settings. For example, the use of bacterial magnetosomes has been successfully tested in pilot applications such as magnetic imaging techniques like magnet resonance imaging (MRI) and magnetic particle imaging (MPI) (Kraupner et al. 2017) or magnetic hyperthermia (Hergt et al. 2008; Le Fèvre et al. 2017), in which they outperformed abiogenic magnetic nanoparticles generated by chemical synthesis.

Most of our knowledge about magnetosome structure and biosynthesis comes from studies of the two closely related Alphaproteobacteria *Magnetospirillum magneticum* (*Mmag*) and *Magnetospirillum gryphiswaldense* (*M. gryphiswaldense*), which in contrast to most other MTB can be cultivated and genetically manipulated reasonably well. Both species are microaerophiles that can also grow anaerobically by denitrification, they share many similarities with respect to their magnetosome biosynthesis and cell morphology, yet they also exhibit several notable differences in magnetosome structure and intracellular organization. While increasing knowledge is accumulating also from other cultured and uncultured MTB, in this chapter we will mostly focus on magnetosome structure, biosynthesis, and biological function in magnetospirilla.

2 Architecture and Biosynthesis of Magnetosomes

In both *Mmag* and *M. gryphiswaldense*, magnetosomes consist of single cubo-octahedral crystals of magnetite (Fe_3O_4) which in their mature state are about 45 nm in size (Fig. 1). Early studies in the related *M. magnetotacticum* indicated that each magnetite particle is enveloped by a membrane containing phospholipids

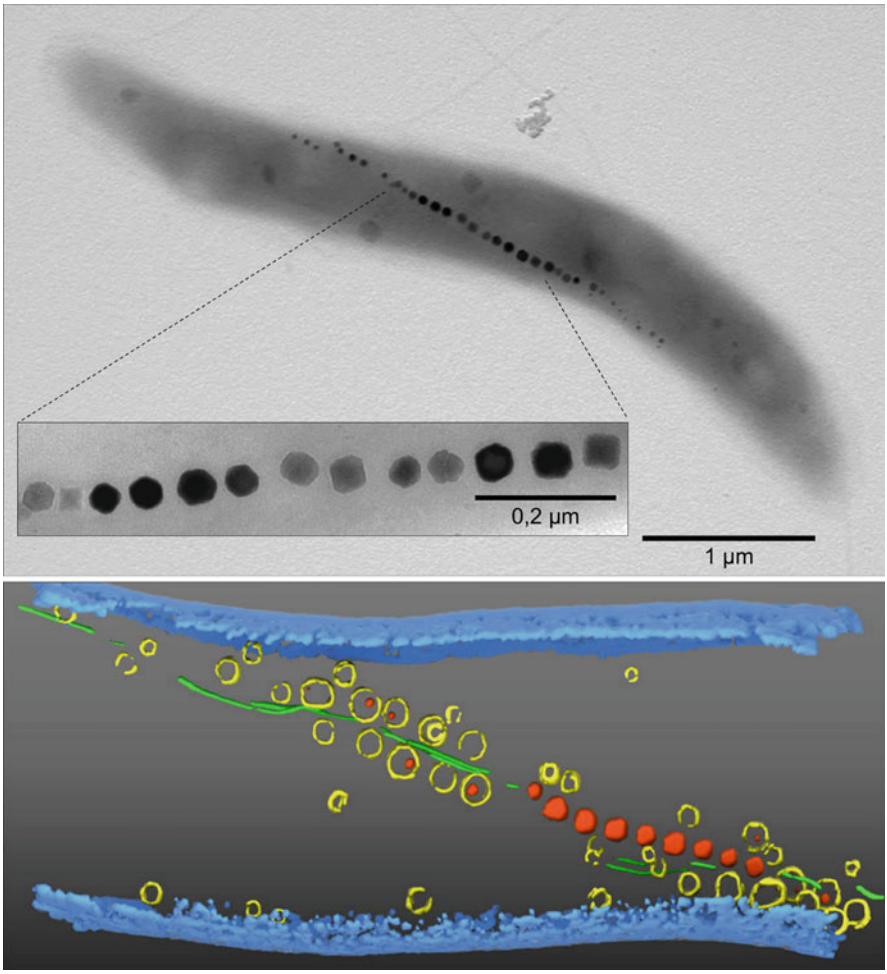

Fig. 1 Upper panel: Transmission electron micrograph of an *M. gryphiswaldense* wild-type cell. The magnetosomes are arranged in a straight chain within the curved bacterium. Inset: Magnification of the chain center highlighting the crystalline magnetite core of the magnetosomes. Lower panel: Rendered electron cryo-tomogaphy image of a section from an *M. gryphiswaldense* wt cell containing the magnetosome chain (mod. after (Scheffel et al. 2006)). The magnetite core of the magnetosomes is colored in red. The magnetosome vesicles (yellow) are cut and appear as open circles. The MamK filament is shown in green and the cellular membrane in blue

Table 1 Synopsis of genes known to control magnetosome biosynthesis in magnetotactic spirilla

Gene	Affected function upon deletion
mamA ("mms24"), mamB, mamQ/mamQ-like	Vesicle formation
mamC ("mms13"), mamD ("mms7")/mamD-like, mamE/limE/mamE-like, mamF/mamF-like, mamG, mamH, mamI, mamL/mamL-like, mamM, mamN, mamO/limO, mamP, mamR, mamS, mamT, mamX, mamZ, mms5, mms6, mms36, mms48, mmsF, mmxF, feoB1, feoB2, ftsZm, feR5, feR6, Amb411	Iron transport/magnetite biomineralization and crystal size control
mamJ/limJ/mamJ-like, mamK/mamK-like, mamY	Magnetosome chain formation, localization and dynamics
mamU, mamV, mamW, mms5	Uncertain
nap, nirS, nirN, norC, norB, fnr, cbb3, fur (not MAI-encoded)	Redox balance or iron homeostasis

All essential and most of the accessory genes cluster in a genomic island (magnetosome island, MAI). Few genes have been identified and named twice such as *mamA/mms24*. The "*-like*" genes are restricted to *Mmag* and have been identified as paralogs of the respective *mam*-genes in a second genomic "islet" of this organism. This redundancy is partially responsible for some differences in deletion mutant phenotypes of *M. gryphiswaldense* and *Mmag*. In other magnetotactic bacteria, homologs for most of the *mam* and *mms* genes have been detected as well. However, with increasing phylogenetic distance to magnetospirilla, distinctive genes occur such as *mad*-genes in greigite–mineralizing deltaproteobacteria. Moreover, some gene functions are redundant and some deletion phenotypes are pleiotropic so that unique functions cannot yet be assigned to all of the listed genes. Biomineralization phenotypes owing to *nap*, *nir*, *nor*, *fnr, cbb3* and *fur* deletion are likely an indirect effect of perturbed cellular redox balance or iron homeostasis

and proteins, and the complete entity comprising the mineral core plus the surrounding membrane was termed 'magnetosome' (Balkwill et al. 1980; Gorby et al. 1988). The presence of a similar magnetosome membrane was later confirmed in *Mmag*, *M. gryphiswaldense* and apparently all other MTB.

The biosynthesis of magnetosomes was subsequently revealed to be a complex, step-wise process which can be genetically dissected (Raschdorf et al. 2016; Cornejo et al. 2016; Uebe and Schüler 2016): First, the magnetosome membrane is invaginated from the cytoplasmic membrane. Second, a set of specific magnetosome proteins is sorted to the magnetosome membrane. Third, iron is transported into the magnetosome membrane vesicle and mineralized as magnetite crystals. Fourth, a magnetosome chain is assembled, positioned, and partitioned during cell division. All steps are highly controlled by a distinct set of about 35 genes, which by proteomic and comparative genomic studies were identified to be clustered within a conserved magnetosome gene island (MAI, (Ullrich et al. 2005; Schübbe et al. 2006)). Genetic studies revealed that these so-called *mam* and *mms* genes in fact do control nearly all features of magnetosome biosynthesis (Murat et al. 2010; Lohsse et al. 2011; Lohsse et al. 2014) (Table 1). Transfer of these genes into the photosynthetic Alphaprotebacterium *Rhodospirillum rubrum* resulted in its "magnetization"; that is, it caused the biosynthesis of magnetosomes resembling those of the donor *M. gryphiswaldense*, including the formation of well-ordered linear magnetosome chains, and the accumulation of cells near the pole of a magnet.

Thus, this demonstrated that the MAI genes are necessary and sufficient to confer magnetosome biosynthesis to this hitherto non-magnetic microbe (Kolinko et al. 2014).

3 Formation of Magnetosome Membrane Vesicles

Magnetosome vesicles are formed by the invagination of the cytoplasmic membrane and seemingly remain connected to the cytoplasmic membrane in *Mmag*, but apparently become pinched off at later stages of biogenesis in *M. gryphiswaldense* (Fig. 2).

Formation of the magnetosome membrane is independent of magnetite biomineralization, as shown by the presence of empty vesicles in iron-starved cells or biomineralization-defective mutants. Likewise, vesicles are formed when cells are cultivated under aerobic conditions which suppresses magnetite biomineralization likely due to inappropriate redox conditions (Heyen and Schüler 2003; Li et al. 2012, 2013). In both strains, these invaginations originated simultaneously from several nonspecific cellular locations, as was revealed by tracking de novo magnetosome biogenesis by time-lapse fluorescence microscopy and cryo-electron tomography (Raschdorf et al. 2016; Cornejo et al. 2016).

Under optimal growth conditions, cells contain up to 100 magnetosome particles per cell. However, the molecular mechanisms which ensure an optimal number and size of magnetosomes are not well understood, but seem to depend on the expression levels of biosynthetic genes, as simultaneous overexpression of almost all *mam* and *mms* gene clusters substantially increased the number (and size) of magnetosomes in *M. gryphiswaldense* (Lohsse et al. 2016).

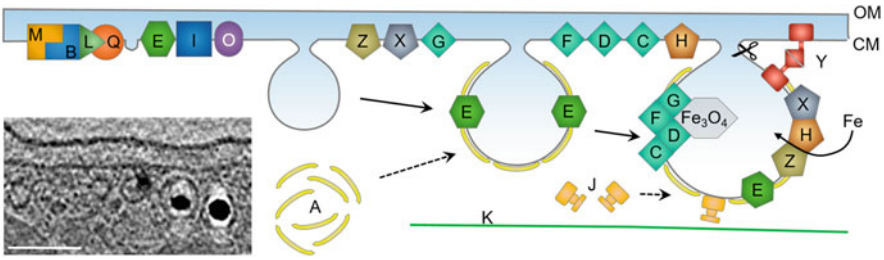

Fig. 2 Key proteins and steps of magnetosome vesicle biogenesis. Essential membrane-bound Mam-proteins (labeled with respective letters, see also Table 1) are thought to tightly interact at the cytoplasmic membrane and eventually facilitate formation and growth of vesicles. Later, further proteins that function in iron transport, redox control, and magnetite precipitation are recruited. Soluble proteins are associated with the periphery of the vesicles and play either a role in magnetosome membrane assembly such as MamA or they are involved in positioning and mobility of the vesicles, e.g., MamJ and MamK. In *M. gryphiswaldense*, vesicles eventually become pinched off the cytoplasmic membrane by an unknown mechanism

The magnetosome membrane has a similar lipid composition as the cytoplasmic membrane, but comprises a distinct set of proteins, with different functions in magnetite biomineralization which are encoded by *mam* and *mms* genes (Gorby et al. 1988; Grünberg et al. 2004). Magnetosome proteins are present in different quantities, from one or few up to 120 copies per particle (Grünberg et al. 2004; Raschdorf et al. 2016). The high protein content of the magnetosome membrane suggests a crowded composition and a tight packing with transmembrane domains of integral proteins. It has been proposed that a lipid raft-like association of magnetosome-membrane proteins takes place prior to the magnetosome invagination (Raschdorf et al. 2016). How proteins are specifically targeted to the magnetosome membrane is not known, and no conserved motifs that encode sorting signals to the magnetosome membrane have been found.

The four proteins MamB, MamI, MamL, and MamQ were identified as key factors in the early biogenesis of the magnetosome membrane (Murat et al. 2010; Lohsse et al. 2014; Raschdorf et al. 2016). Among them, elimination of only MamB completely abolished the formation of regular magnetosome membranes, while mutants of MamI, MamL, or MamQ still contained fewer immature vesicles in *M. gryphiswaldense* (Raschdorf et al. 2016). The crucial role of the cation diffusion facilitator (CDF) protein MamB in membrane biogenesis is independent from its function in iron transport, but involves interactions with other magnetosome proteins, including the paralogous CDF transporter MamM, and the protease MamE, which acts in control of protein sorting to magnetosomes (Uebe et al. 2011, 2018; Hershey et al. 2016a, b). From available genetic and biochemical data, a model for magnetosome membrane formation has been proposed, in which MamB may serve as landmark protein witch interacts with a subset of proteins at the inner cell membrane (Fig. 2). This initial protein complex then recruits further interaction partners that by protein crowding eventually induce lateral pressure to generate membrane curvature (Raschdorf et al. 2016).

4 Biomineralization of Magnetite Crystals

Compartmentalization of biomineralization by the magnetosome membrane provides a specialized "nanoreactor" in which the iron, redox, and pH environments of biomineralization can be strictly regulated for the formation of single crystals of magnetite. Most available evidence supports a model in which extracellular iron is first imported into the cytoplasm by generic transporters. Subsequently, iron is transported from the cytoplasm into magnetosome membrane vesicles by magnetosome-specific transporters MamB and MamM (for ferrous iron), which are members of the Fe/Zn-transporting subfamily of divalent metal CDF proteins (Uebe et al. 2018), MamH and MamZ (for ferric iron), which are members of the major facilitator superfamily (MFS) (Raschdorf et al. 2013). The proper Fe^{2+}/Fe^{3+} ratio for production of the mixed-valence iron mineral magnetite inside magnetosome membrane vesicles is thought to be regulated by MamE, MamP,

MamT, and MamX which are constituents of the magnetosome membrane (Fig. 2) (Grünberg et al. 2004). These proteins each contain two or three conserved MTB-specific CXXCH *c*-type cytochrome haem-binding motifs denoted the "magnetochrome" domain that may oxidize magnetosomal Fe^{2+} for biomineralization (Siponen et al. 2013; Jones et al. 2015). In addition, redox balance for magnetite biomineralization is also poised by the activity of cellular electron transport chains. For instance, magnetite formation is linked to dissimilatory nitrate reduction, and cells of *M. gryphiswaldense* are impaired in magnetosome biomineralization in the absence of nitrate, or upon deletion of genes encoding the periplasmic nitrate and nitrite reductases Nap and NirS, as well in cells lacking the fumarate and nitrate reduction regulator protein Fnr. In a similar manner, inactivation of the terminal oxidase Cbb3 involved in aerobic respiration caused pleiotropic effects on magnetosomes under microaerobic conditions, probably by disturbing the redox balance required for proper magnetite biomineralization (Li et al. 2012, 2013; Müller et al. 2014).

After nucleation of the magnetite crystal, several magnetosome proteins regulate their maturation into particles of defined size and shape in a positive (MamG, MamF, MamD, MamC, MamS, MamR, MamN, Mms6, and MmsF) or negative (Mms36 and Mms48) manner (Fig. 2). However, the understanding how they exactly interact with the surface of the nascent magnetite crystals is just emerging (Scheffel et al. 2008; Lohsse et al. 2011; Rong et al. 2012; Nudelman et al. 2018).

5 Structure, Assembly, and Positioning of Magnetosome Chains

During maturation, magnetosomes become organized and assembled into chains. Essential active parts of this assembly and positioning machinery consist of dedicated cytoskeletal proteins which have been identified some years ago. In *M. gryphiswaldense* and related magnetotactic bacteria, the magnetosome chains become concatenated by the joint action of the actin-like MamK, which polymerizes into cell-spanning dynamic filaments (Fig. 1) and MamJ, an adaptor protein with less-understood function (Komeili et al. 2006; Scheffel et al. 2006; Katzmann et al. 2010; Draper et al. 2011). In *Mmag*, both proteins exist as two paralogs with overlapping but also slightly different functions causing less pronounced phenotypes upon deletion compared to *M. gryphiswaldense* (Rioux et al. 2010; Abreu et al. 2014). *mamK* mutants fail to assemble wt-like continuous magnetosome chains but contain either disordered (in *Mmag*, (Komeili et al. 2006)) or short and fragmented chains in *M. gryphiswaldense* (Katzmann et al. 2010) (Fig. 3). Magnetosome chains connected to MamK filaments are only formed in the presence of MamJ, a poorly characterized cytoplasmic protein. It consists of a central acidic repetitive (CAR) domain, which is largely dispensable (Scheffel and Schüler 2007), and seems to be weakly structured (Nudelman and Zarivach 2014). The *mamJ* deletion mutant

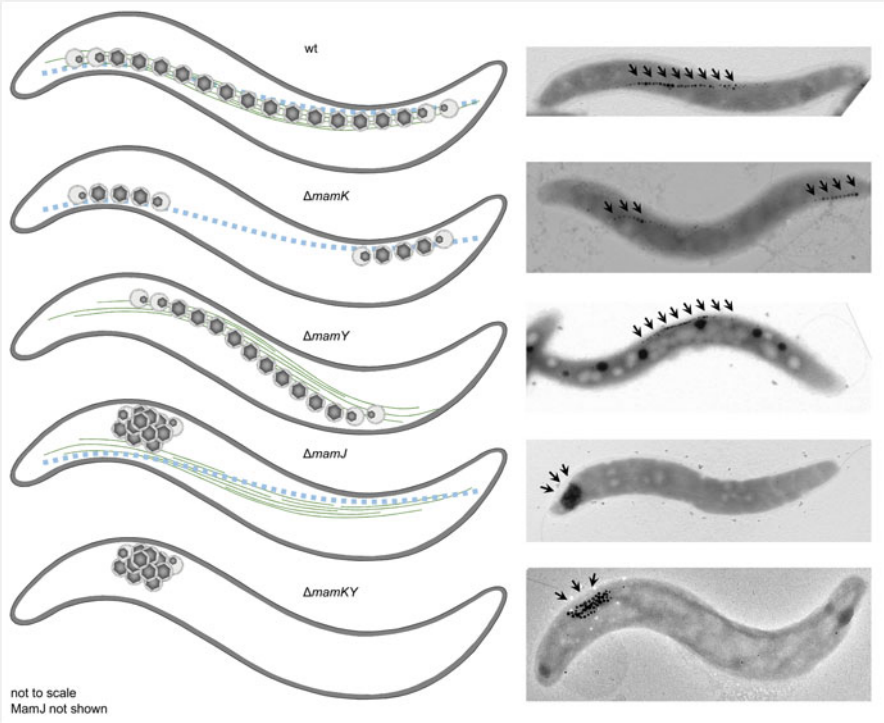

Fig. 3 Phenotypes of *mamK, Y, J*, and *KY* deletion mutants in *M. gryphiswaldense*. In the WT, magnetosomes are attached to cytoplasmic MamK filaments and to membrane-bound MamY structures via MamJ, thereby forming a straight and continuous chain. In the *mamK* mutant, chains are fragmented and off-center, but still attached to MamY and therefore at the geodetic cell axis. In the *mamJ* mutant, the magnetosomes are not attached to any structure and agglomerate by their own magnetic attraction. The *mamY* mutant shows continuous chains that are detached from the geodetic cell axis and in the *mamKY* double mutant; no chain stabilizing structure is present, resulting in agglomerated magnetosomes as in the *mamJ* mutant

phenotype in *M. gryphiswaldense* is striking as magnetosomes are completely disorganized and cluster irregularly due to their unconstrained magnetic interaction or form magnetic flux-closed rings, even in the presence of MamK (Scheffel and Schüler 2007; Bennet et al. 2015; Kiani et al. 2018) (Fig. 3). In *Mmag*, which contains two MamJ paralogs, the phenotype is less pronounced but magnetosome chain formation is also perturbed (Draper et al. 2011). These phenotypes and suggested MamK-MamJ interactions (Scheffel and Schüler 2007) led to the early model of an only two-part cytoskeletal structure, consisting of a presumably rather static backbone made of MamK filaments and MamJ, which attaches magnetosomes to that scaffold. However, this model recently proved incomplete in at least two aspects: First, the magnetosome chain was revealed to be highly dynamic; and second, localization of the chain in spirilla is much more controlled than initially assumed.

MamK has been analyzed extensively in vitro and the pure protein was found to polymerize into filaments when adenosine triphosphate (ATP) or guanosine triphosphate (GTP) are present (Sonkaria et al. 2012; Ozyamak et al. 2013; Bergeron et al. 2017). Recently, the crystal structure of the protein and molecular details of its polymeric form have been solved (Löwe et al. 2016) and underpinned its structural relatedness to eukaryotic actin proteins. In vivo studies suggest that MamK filaments not only concatenate magnetosome chains but also expedite splitting of the chain during cell division by distinct localization at the division plane: In magnetospirilla, cytokinesis occurs by unidirectional indentation and asymmetric septum formation at the division plane, resulting in a buckling-like deformation of the dividing cell (Staniland et al. 2010). Localization of the magnetosome chain opposite to the unilateral growing septum by MamK results in a leverage-like mechanism, which has been interpreted as specific adaptation required to overcome the magnetostatic interactions between separating daughter chains (Katzmann et al. 2011).

In vivo studies analyzed the dynamics of polymeric MamK filaments in its cellular context. By fluorescence recovery after photo bleaching (FRAP) experiments, it was found that MamK treadmilling speed in *M. gryphiswaldense* is about 300 nm/min (Toro-Nahuelpan et al. 2016) and depends on its ATP hydrolysis capacity. Similar observations were made in *Mmag* (Pradel et al. 2006; Draper et al. 2011; Abreu et al. 2014). Interestingly, dynamics of the MamK filaments was found to also depend on MamJ, which therefore seems not only necessary to tether magnetosomes to MamK filaments but also for MamK turnover rates.

The dynamics of MamK filaments in *M. gryphiswaldense* already suggested that a magnetosome chain is no static structure and that whole magnetosomes are moved along the track. In fact, active movement of the organelles seems a crucial prerequisite to assemble a chain: Magnetosome vesicles emerge more or less randomly at the cytoplasmic membrane (Raschdorf et al. 2016). Mature magnetosomes, however, are regularly found in chains suggesting an active collecting and positioning mechanism, although spontaneous incorporation of maturing magnetosomes based on their increasing magnetism may also play a role (Klumpp and Faivre 2012). The function of MamK in *Mmag* seems somewhat different, but still, MamK is needed to restrict movement and to position magnetosomes (Grant et al. 2018). There is, however, other evidence for active translocation of magnetosomes: When *M. gryphiswaldense* cells divide, each daughter cell receives exactly half the number of magnetosomes from the mother cell (Toro-Nahuelpan et al. 2016), indicating that cells distribute their magnetosomes with highest possible precision to their offspring. This is achieved by strict positioning of the chain center at the cell division site. After cytokinesis, the daughter chains undergo repositioning from the new cell poles to midcell, and they are maintained at this position during growth by an unknown mechanism. In mutants with severely impaired dynamics of MamK, chain dynamics is also perturbed (i.e., chains are not efficiently re-localized to midcell), leading to unequal distribution of the organelles (a phenotype that is also seen in *mamK* and *mamJ* deletion mutants) (Katzmann et al. 2011; Toro-Nahuelpan et al. 2016). Yet, the molecular mechanism by which magnetosomes move along MamK filaments is still unknown. Photobleaching experiments suggest that MamK filaments in

M. gryphiswaldense nucleate close to the cell poles and grow toward midcell, i.e., in the direction where magnetosomes migrate. Interestingly, the treadmilling speed of MamK filaments seems much higher than the speed of magnetosomes (Toro-Nahuelpan et al. 2016), suggesting that magnetosomes are not tightly coupled to MamK oligomers. On the other hand, cargo-carrying motor proteins reminiscent to myosin, which walks along actin filaments in eukaryotic cells, have not been identified in MTB. Potential factors that control nucleation of MamK filaments at the cell poles and their polarity are also unknown. It is also not clear what happens if the filaments of opposite polarity meet at midcell and if MamK filaments stop growing at all. For example, it has been observed that filaments that reach the opposite cell pole bend and turn, sometimes even under physiological expression levels (Komeili et al. 2006; Katzmann et al. 2011; Toro-Nahuelpan et al. 2016).

Furthermore, MamK and other cytoskeletal elements of the magnetosome chain were recently found to be linked to the generic cytoskeleton by the coiled-coil protein CcfM, suggesting an intricate network of magnetosome chain assembly determinants and cell shape control in magnetotactic spirilla (Pfeiffer et al. 2020).

6 Three-dimensional Chain Positioning, Motility Axis, and Magnetotaxis

Magnetotaxis differs from conventional chemotaxis paradigms known from, e.g., *E. coli*. Here, chemotactic swimming resembles a three-dimensional trial-and-error walk where periods of straight movement are interrupted by tumbling pauses where cells turn randomly before they resume straight swimming. These so called run-and-tumble sequences are biased by chemosensory signal cascades which control the frequency of runs and tumbling by interaction with flagellar motor proteins in response to detected gradients of nutrients, repellents, or electron acceptors (reviewed, for example, in (Bi and Sourjik 2018)). Magnetospirilla and all other characterized MTB so far are also motile by flagella, and aero- or even phototaxis has been described (Chen et al. 2010; Popp et al. 2014). So, what is the benefit of bearing a magnetosome chain in addition to extensive chemosensory networks and how does magnetotaxis feed into motility of MTB?

Magnetotaxis could, for example, be beneficial for a bacterium if it combined the positional information provided by the intracellular compass with decisions on locomotion, i.e., on run-and-tumble frequencies (conveyed by MamK, as suggested by (Philippe and Wu 2010)). However, up to now, neither deviant chemotaxis patterns in a *mamK* mutant nor direct evidence for a biochemical signal transduction between magnetosome chain and flagellar motor has been provided. This and the lack of any canonical signal transduction motif (as, for example, in kinases or methylases) in the magnetosome gene clusters suggests that magnetotaxis functions in a different way and exploits magnetic forces directly.

It has been shown that the force generated by a single magnetosome in the geomagnetic field is too weak to align a cell effectively (Frankel and Blakemore 1980). On the other hand, as described above, multiple disorganized magnetosomes within a cell agglomerate by magnetic attraction, likewise resulting in a net cellular magnetic moment close to zero (Kirschvink 1982; Kobayashi et al. 2006). Hence, to serve as an efficient magnetic field receptor, single magnetosomes become concatenated into a chain which in the model organism *M. gryphiswaldense* consists of ~45 particles (Zahn et al. 2017), adding the single magnetic moment of each unit to a functional magnetic dipole. This suggests that the number of magnetosomes per cell is controlled so that the chain forms a compass strong enough to passively align whole cells to the geomagnetic field, akin to a compass needle (Frankel and Blakemore 1980; Rosenblatt et al. 1982a, 1982b; Moskowitz et al. 1988). Correspondingly, bigger cells that belong to other phyla such as members of the nitrospirae or multicellular MTBs tend to possess a multitude of magnetosomes and chains (Jogler et al. 2011; Leão et al. 2017), which increases the magnetic force for their alignment. Therefore, it is believed that the force which aligns a magnetosome chain to the magnetic field is mechanically transmitted to the cell body and used to align whole cells passively (Kobayashi et al. 2006). As a result, there is limited need to stop the movement for tumbling in magnetospirilla. Their motility axis is preset by the position of flagella and arrangement of the magnetosome chain. The alignment to the geomagnetic field then reduces three-dimensional swimming to a linear movement along the vertical inclines of the earth's magnetic field; and by the integration of chemotactic responses such as aerotaxis, magnetotactic bacteria in stratified environments are efficiently guided to their preferred oxygen concentration. However, recently it became clear that in particular spirilla have evolved additional sophisticated means to optimize their magnetic navigation.

For efficient magnetotaxis, the magnetosome chain must adopt and maintain a very distinct position in the cell. First, a fixed position is important because a flexible, "floating" magnetosome chain could move within the cell rather than aligning it. A physical connection of magnetosomes to cytoplasmic content such as DNA (as described for carboxysomes, carbonosomes, and polyphosphate inclusions) seems therefore not sufficient. Tethering the chain to rigid and more static structures such as the cell envelope would meet this requirement much better. Second, for efficient magnetotaxis, the magnetic moment of the magnetosome chain must perfectly match the swimming direction of the cell, which is predefined by the position of flagella on the cell surface (Frankel and Blakemore 1980). Spirilla are propelled by polar flagella and hence move along the longitudinal cell axis. This propulsion is accompanied by fast rotations of the cell body. If swimming direction and magnetosome chain were misaligned, cells would tumble when they swim because two forces pulled in slightly different directions. Third, positioning of the linear magnetosome chain must safeguard that it is maintained straight. Straightness is necessary to maximize the net magnetic moment of the chain similar to a corresponding bar magnet. Strikingly, the chains of MTB seem to regularly meet all these criteria, even in helical cells of magnetospirilla. This is intriguing

since unlike rod-shaped bacteria, spirilla lack any straight cell surface to support a rod-like magnetoreceptor. However, this question has remained unaddressed for a long time, and mechanisms for magnetosome chain positioning in curved cells have been unknown until recently. The first glance on the intriguing proficiency of magnetotactic spirilla to accommodate a straight magnetoreceptor in helical cells was possible through an in-depth analysis of the magnetosome protein MamY and the *mamY* mutant in *M. gryphiswaldense.*

Initially, three-dimensional analysis of magnetosome chain positioning in *M. gryphiswaldense* wt cells revealed that the chain tightly follows a path along the cytoplasmic membrane with highest convex curvature. This path coincides with the shortest connection between the cell poles and hence represents the geodetic axis of the helix. Importantly, this path also coincides with the cellular motility axis. Upon the deletion of *mamY*, magnetosome chains lose their straight appearance and detach from the inner (convex) curvature of the helical cell shifting from the geodetic path to the outer (concave) curvature (Fig. 3). This indicates that MamY is involved in tethering the magnetosome chain to a trail that is perfectly congruent with the motility axis. Consequently, when *mamY* is deleted and magnetosome chains are displaced, the ability of the cells to align to the magnetic field drops similar to the *mamK* mutant (Pfeiffer and Schüler 2019). Another indication for the scaffolding function of MamY is the phenotype of a *mamYK* double mutant. This strain lost its ability to form magnetosome chains completely and phenocopies a *mamJ* mutant where all magnetosomes agglomerate (Fig. 3).

MamY, initially proposed to be involved in vesicle formation in *Mmag* (Tanaka et al. 2010), is a protein of the inner and the magnetosome membranes in *M. gryphiswaldense*, The protein self-interacts and forms higher ordered structures at the membrane. Upon a certain size, these polymers are supposed to become curvature sensitive and further enrich along the membrane with highest positive curvature, eventually forming an extended assembly reaching from pole to pole and following the geodetic cell axis. With its cytoplasmic domain, MamY recruits the magnetosome chain made by MamK and J and forces it to the geodetic cell axis (Toro-Nahuelpan et al. 2019).

The function of MamY could also explain why in the mamK mutant there are still short magnetosome chains: The magnetosomes are likely attached to MamY structures but are not concatenated into coherent chains because the cytomotive filaments of MamK are missing. Correspondingly, the short chains of the *mamK* mutant are still observed at sites of inner positive cell curvature. The formation of short chains instead of clusters could be explained by magnetic attraction of the particles rather than by active assembly (Klumpp and Faivre 2012).

Taken together, MamY seems the key to (1) connect the magnetosome chain to the cell envelope, ensuring efficient force transmission and cell alignment, (2) keep the magnetosome chain straight to maximize its magnetic moment, and (3) fit it to the cellular motility axis. Finally, it reconciles the different phenotypes of the *mamK* and *mamJ* mutants.

Altogether, a sophisticated "magnetoskeleton" can now be defined which to date consists of three cytoskeletal factors dedicated for magnetotaxis (Fig. 4). The actin-

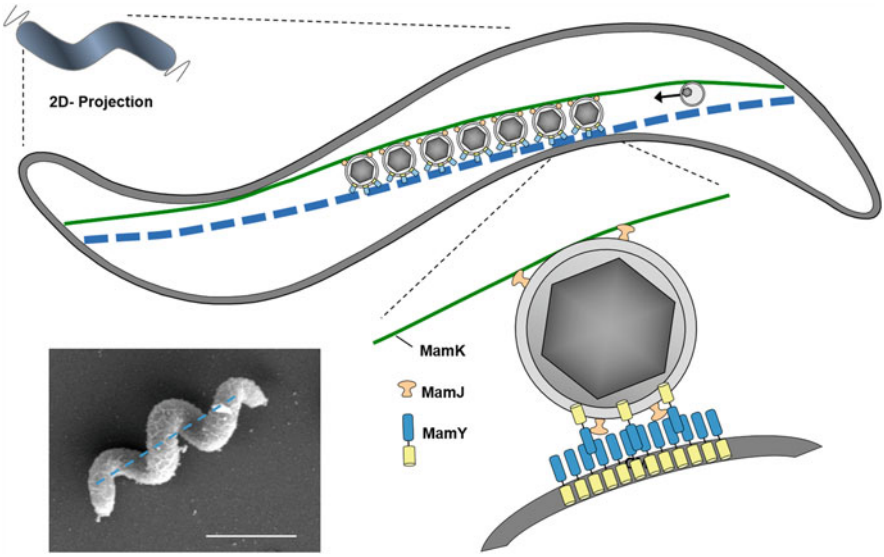

Fig. 4 Scheme of the current view on the tripartite magnetoskeleton in *M. gryphiswaldense*. The actin-like MamK (green) polymerizes in cell-spanning dynamic filaments. Magnetosomes are attached to this structure with the help of MamJ (beige). MamY, however, concentrates along the inner positive membrane curvature and in the magnetosome membrane and recruits the magnetosome chain to the geodetic cell axis. Note that the scheme represents a 2-dimensional projection of a helical cell meaning that in reality, the magnetosome chain stays close to the cytoplasmic membrane. The inset shows a scanning electron microscopy image of an *M. gryphiswaldense* cell to highlight the corkscrew-like cell morphology. The geodetic path is indicated as dashed line. Bar: 1μm

like MamK and its adaptor MamJ represent the dynamic part of the magnetoskeleton as they actively concatenate magnetosomes and position the chain at midcell, thereby also ensuring precise splitting and equipartitioning of the magnetoreceptor upon cell division. The static MamY structure by contrast is responsible to identify and to tether the dynamic assembly to the geodetic cell axis, i.e., to fix it along the shortest path connecting the cell poles. This straightens the "compass needle" within the helix and aligns it with the motility axis, thereby perfectly superimposing the earth's magnetic field vector on swimming movements.

These recent results highlight that magnetosomes—in contrast to other bacterial organelles—do not function as single entity but require dedicated cytoskeletal elements to form a dynamic and distinctly localized higher ordered structure suitable for perfect magnetic navigation.

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