



Graphical Structural Biology Review

Current view of iron biomineralization in magnetotactic bacteria

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ABSTRACT

Biomineralization is the process of mineral formation by living organisms. One notable example of these organisms is magnetotactic bacteria (MTB). MTB are Gram-negative bacteria that can biomineralize iron into magnetic nanoparticles. This ability allows these aquatic microorganisms to orient themselves according to the geomagnetic field. The biomineralization process takes place in a specialized sub-cellular membranous organelle, the magnetosome. The magnetosome contains a defined set of magnetosome-associated proteins (MAPs) that controls the biomineralization environment, including iron concentration, redox, and pH. Magnetite formation is subjected to a tight regulation within the magnetosome that affects the nanoparticle nucleation, size, and shape, leading to well-defined magnetic properties. The formed magnetite nanoparticles have unique characteristics of a stable, single magnetic domain with narrow size distribution and high crystalline structures, which turned MTB into the subject of interest in multidisciplinary research. This graphical review provides a current overview of iron biomineralization in magnetotactic bacteria, focusing on Alphaproteobacteria. To better understand this complex mechanism, we present the four main steps and the main MAPs participating in the process of magnetosome formation.

Introduction

Biomineralization, the formation of minerals by living organisms, is a well-described process in all kingdoms of life. Although biomineralization covers many elements, most studies focus on calcium-based minerals. Iron is a fascinating biomineralization element that, in contrast to calcium, can create magnetic minerals. MTB are a diverse group of aquatic, magnetic responsive, gram-negative bacteria that can biomineralize iron into magnetic nanoparticles (Amor et al., 2020). MTB organize the magnetic nanoparticles into a chain that creates a sufficient magnetic dipole moment to orient themselves according to the geomagnetic field. It is hypothesized that this ability reduces their random movement to a single dimension, which allows them a better way to navigate toward their optimal habitat around the oxic-anoxic interface, referred as magnetotaxis (Müller et al., 2020).

MTB biomineralize iron into the single domain magnetic nanoparticle, magnetite (Fe_3O_4) and/or greigite (Fe_3S_4) (Staniland and Rawlings, 2016). This process takes place in a unique sub-cellular membranous organelle, the magnetosome. The resulting magnetic nanoparticles are not uniform among all MTB and vary in shape and size (Fig. 1A). The nanoparticles size is usually in the range of $\sim 35 - 120$

nm, which fits well with the size of a single magnetic domain (Nudelman and Zarivach, 2014).

Magnetosome formation in MTB is genetically controlled and involves a large set of specialized genes. These genes are usually organized in operons, located in a genomic island known as magnetosome island (Fig. 1B) (Lohße et al., 2014). These genes encode, primarily, membrane proteins and are named magnetosome membrane-associated (Mam) and magnetic particle membrane-specific (Mms) proteins in *Alphaproteobacteria*.

Most of our knowledge is based on two fresh-water cultivated *Alphaproteobacteria*, *Magnetospirillum magneticum*, and *Magnetospirillum gryphiswaldense*. These bacteria share many conserved genes and a common magnetosome formation mechanism. In both, the magnetosome formation is based on four main steps: 1) Protein sorting and membrane invagination, 2) Magnetosomes alignment into a single or multiple chains 3) Ion transport and magnetosome inner environment control, and 4) Iron nucleation and crystal shape and size control. The last three steps are described separately to simplify the mechanism, while they most likely occur simultaneously and not sequentially. In this brief graphical review, we will discuss the main findings in the field of MTB and highlight the four magnetosome formation steps from the

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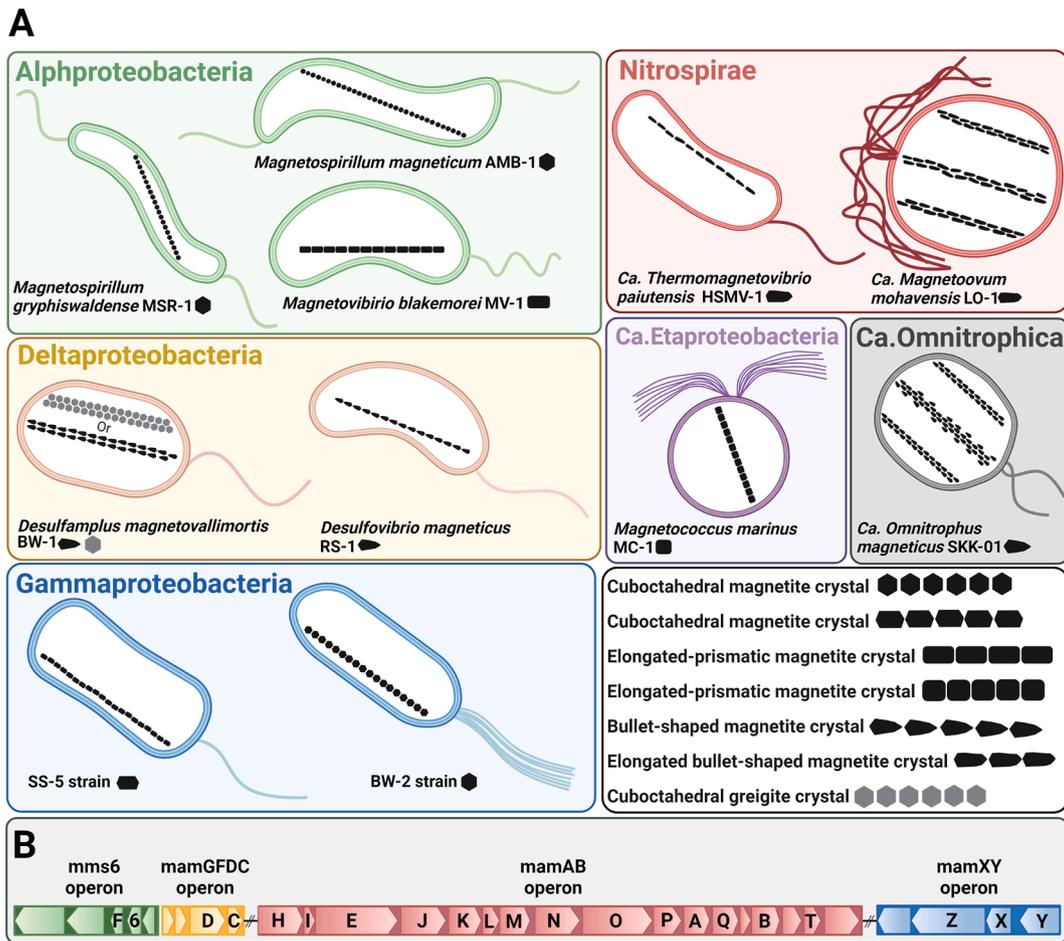


Fig. 1. A) Schematic representation of magnetotactic bacteria (MTB) from different phyla and classes. MTB divide into different types based on their genetics. Additional differences exist in their morphological characteristics, such as cellular shape, magnetosome chain arrangement, number of chains, number of flagella, magnetic crystal composition (magnetite or greigite) and crystal shape (Cuboctahedral, elongated-prismatic, bullet, elongated bullet). B) Four operons from the “magnetosome island” of MSR-1. The genes marked by a single letter represent the genes and their encoded proteins that are discussed in this review. Created with BioRender.com.

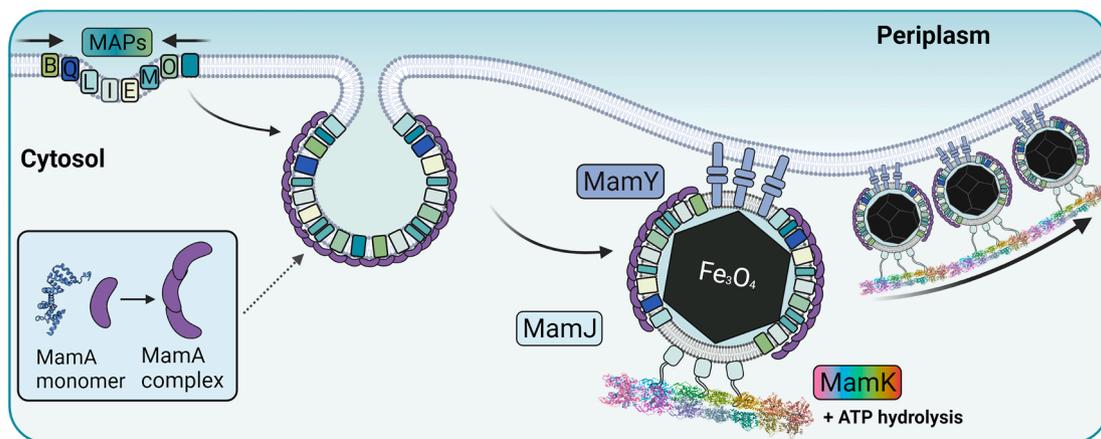


Fig. 2. Suggested model of protein sorting, membrane invagination, and magnetosome assembly into an organized chain. Proteins solved structures are in ribbon representation. MamB, M, L, Q are essential for the magnetosome membrane formation (MamM in MSR-1 whereas MamI in AMB-1) where MamB is the most crucial. MamB is also suggested to be involved in the recruitment of other MAPs (Magnetosome-associated proteins). The minimal protein complex MamLQBIEMO enables a proper invagination, whereas magnetite biomineralization requires additional MAPs. MamA complex covers the entire magnetosome membrane, interacts with other MAPs, and mechanically supports the formed organelle membrane. MamK, MamJ, and MamY are taking part in the chain organization. MamK, an actin-like protein (PDB: 5JYG), is organized as a double-stranded and non-staggered long filament composed of MamK monomers. The double-strand assembly involves the lateral contacts between monomers. MamK is also an ATPase that utilizes ATP for its polymerization. MamJ acts as an anchor that connects the MamK filament to the magnetosomes membrane. MamY, a membrane-embedded protein, can sense and localize to convex parts of the inner cell membrane. MamY can oligomerize and, as such, link the magnetosome and inner cell membrane. Created with BioRender.com.

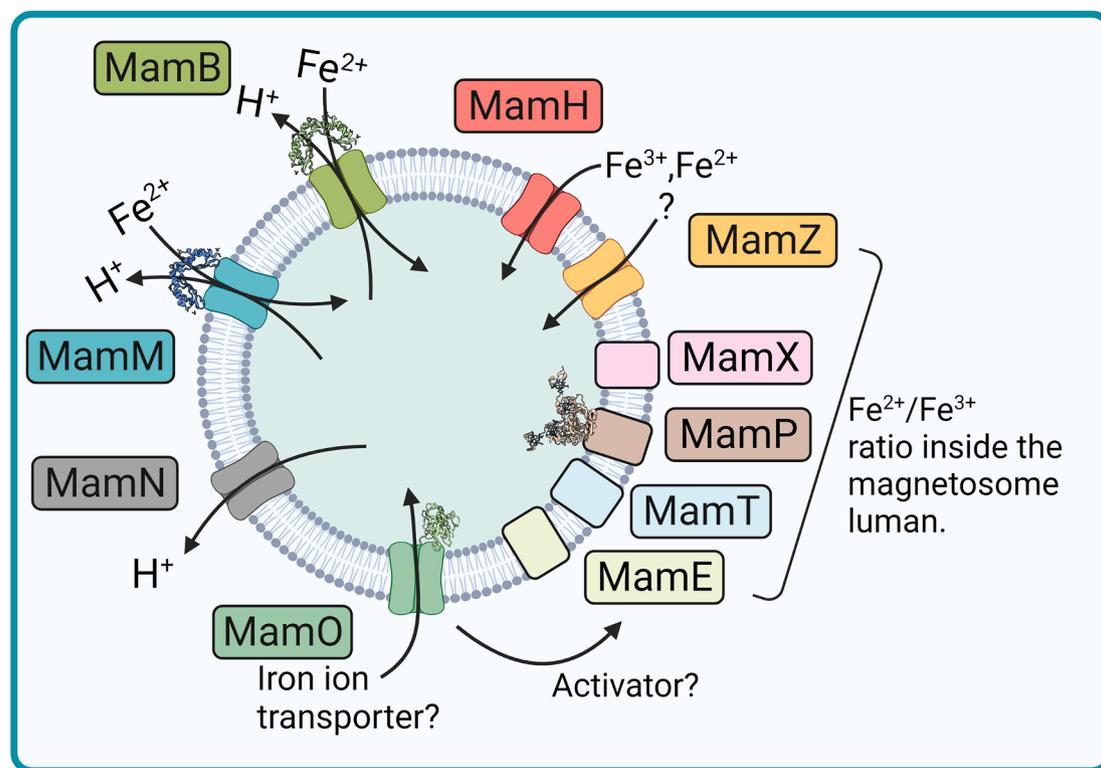


Fig. 3. Different magnetosome-associated proteins (MAPs) are suggested to control the magnetosome lumen environment through ion transport, pH regulation, and $\text{Fe}^{2+}/\text{Fe}^{3+}$ ratio. Proteins solved structures appear in ribbon representation (MamM PDB: 3W5X, MamB PDB: 5HO5, MamO PDB: 5HM9, MamP PDB: 4JJ0). MamM and MamB are iron transporters that import divalent iron ions while exporting protons, thus increase the iron content and pH levels in the magnetosome lumen. Another iron transporters set is predicted based on the homology to MSF proteins (MamH and MamZ) and domain homology to a TauE-like protein (MamO). This domain might also activate MamE in a non-catalytic manner. However, it is still uncertain whether they function as transporters and which ions they transport. MamN is suggested to be involved in the pH regulation inside the magnetosome lumen based on homology to Na^+/H^+ antiporter. The maintenance of a certain $\text{Fe}^{2+}/\text{Fe}^{3+}$ ratio is suggested to be carried out by the set of proteins MamE, MamT, MamP, MamX, and MamZ.

Alphaproteobacteria biomineralization perspective.

Protein sorting and membrane invagination

In biomineralization, compartmentalization is the key in producing and maintaining the compatible chemo-physical environment required for the reaction. Thus, in many organisms, a dedicated compartment with a controlled environment is created. In MTB, the magnetosome's defined compartment includes all proteins required to control magnetite formation (Raschdorf et al., 2016). It was shown that although the magnetosome's membrane derives from the cytoplasmic membrane, some differences exist in the fatty acid ratios (Ardelean et al., 2009) (Grünberg et al., 2004). However, the main difference comes from the unique magnetosome proteins composition. The magnetosome contains only magnetosome-associated proteins (MAPs), without any proteins of the MTB inner membrane that are not magnetosome-specific. In addition, MAPs cover much of the magnetosome membrane surface in high concentration, indicating a structured protein-lipid complex rather than freely diffusing proteins in a membrane (Raschdorf et al., 2018).

Genetic studies in *Alphaproteobacteria* showed a very specific subset of MAPs (Fig. 2), including MamB, MamM/I, MamL, and MamQ, crucial for magnetosome membrane formation (MamM in MSR-1 whereas MamI in AMB-1). Deletion of these genes leads to magnetosome null phenotype (ΔmamB) or immature magnetosome vesicles ($\Delta\text{mamM,L,Q}$) in MSR-1 (Raschdorf et al., 2016). While in AMB-1, besides ΔmamB , deletions of *mamI*, *mamL* and *mamQ* resulted in magnetosome null phenotype as well (Murat et al., 2010).

MamB, apart from its iron transport activity which will be discussed later, is defined as a hub protein that acts as a nucleation site for other

MAPs. A point mutation in MamB, which prevents iron transport, resulted in empty vesicles with a defined size, similar to the wild-type vesicles, suggesting that vesicles formation and maturation is magnetite independent (Uebe et al., 2018).

A mutant that lacks the *mamAB* operon, with an artificial minimal gene cluster, *mamLQBIEMO*, was shown to allow membrane invagination but did not result in magnetite synthesis. However, this gene cluster was insufficient for magnetosome membrane formation upon additional deletion of *mms6* and *mamGFDC* operons (Raschdorf et al., 2016). This indicates that although those seven proteins are crucial, other MAPs are also essential for magnetosome membrane formation. Surprisingly, in AMB-1, the forming invaginations were seen attached to the cell membrane throughout the whole process. In contrast, invagination intermediates were rarely found in MSR-1, where it seems that only one direct step shifts the inner membrane into a complete vesicle (Uebe and Schüler, 2016). Based on all these data, a current hypothesis for *M. gryphiswaldense* is that MAPs assemble into a unique lipid-raft-like complex that, upon a dynamic fluctuation or unknown physical force, flips out of the membrane in a single step yielding a well-defined vesicle (Fig. 2).

Another interesting protein suggested to be involved in protein sorting is MamA. MamA is a highly conserved cytoplasmic protein that assembles into a protein complex, covering the entire magnetosome membrane (Zeytuni et al., 2011) (Fig. 2). It was suggested that MamA interacts with other magnetosome membrane proteins such as Mms6 and is involved in the organization of MAPs in the membrane. Yet, deletion of this gene did not lead to a defined phenotype, and it seems that magnetosome formation and its organization was not affected. This result suggests that MamA might play a role in magnetosome

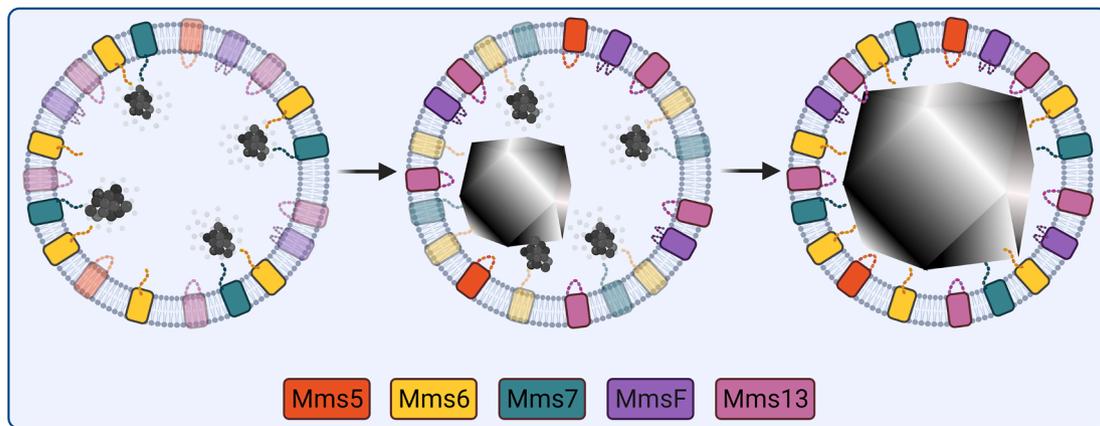


Fig. 4. A suggested model for nucleation and crystal shape and size control. Some proteins that were found to participate in each step are highlighted. In the first step, nucleation initiation occurs by forming nanometer-size pre-nucleation clusters on the C-terminal regions of Mms6 and Mms7 (MamD), followed by fast agglomeration to form magnetite. In addition, Mms6 and Mms7 (MamD) were found to strongly bind divalent iron cations, which implies their ability to increase the local iron ion concentration. In the second step, the nanoparticle continues to grow. At the same time, its size and shape are tightly regulated by Mms proteins. Three of these proteins are Mms13 (MamC), MmsF and Mms5, which interact with the growing crystal by acidic residues found in their inter-lumen loops. This regulated process results in the formation of a full-sized cubo-octahedral crystal with magnetic properties. The proteins in the figure appear in the order of their abundance in the magnetosome membrane. Created with BioRender.com.

stabilization by providing mechanical support to the formed organelle membrane (Nguyen et al., 2016).

Cellular arrangement of magnetosomes

Vesicle formation is just the first step toward magnetotaxis. Each magnetosome contributes only slightly to the total cellular magnetic dipole needed to orient the MTB. Thus, magnetosomes accumulation in an organized way is required. MTB exhibit different magnetosome chain organizations. Most of the current data is based on spirilla *M. magneticum* and *M. gryphiswaldense* having a single elongated magnetosome chain (Fig. 1A). One of the first genes that were connected to the magnetosome organization is *mamK* (Komeili et al., 2006). MamK is an actin-like protein that can assemble into a long protein filament. MamK polymerization is an ATP-dependent dynamic process that treadmill the linked magnetosomes from their inner membrane emergence sites to the correct cellular location (Fig. 2) (Ozyamak et al., 2013). In *Magnetospirillum* species, MamJ, an unstructured adaptor protein, links the magnetosome membrane with the MamK filament and affects MamK dynamics to create the full magnetosomes chain (Fig. 2) (Draper et al., 2011) (Ozyamak et al., 2013). MamY is an additional protein that participates in *Magnetospirillum* magnetosome positioning. MamY is an integral membrane protein localized in the inner bacterial and the magnetosome membranes and can oligomerize and self-interact via its cytoplasmic domain. MamY senses the highest convex part in magneto spirilla and vibrio membranes and follows this convex line to form a straight magnetosome chain accordingly (Fig. 2) (Toro-Nahuelpan et al., 2019).

Ion transport and magnetosome inner environment control

Once the magnetosome compartment is created, ion transport, in and out of the vesicle, is required for the formation of the correct mineral. MamB and MamM are two transporters that import divalent iron cations from the cytosol to the magnetosome lumen (Fig. 3). These proteins belong to a highly conserved cation diffusion facilitator (CDF) protein family, found in all life domains, taking part in maintaining the metal ion homeostasis while exploiting the proton motive force. Previous studies showed that deletions of *mamM* and *mamB* resulted in the absence of magnetite and in decreased intracellular iron content. Additionally, deletion of *mamM* affected *mamB* stability (Uebe et al., 2011).

Additional proteins involved in ion transport are the major facilitator superfamily (MFS) homologous proteins, MamH and MamZ. MFS proteins can transport small molecules, such as ions, across the membrane, suggesting MamH and MamZ transport iron into the magnetosome lumen (Fig. 3). While fewer and smaller crystals were seen upon deletion of *mamZ* or *mamH*, the deletion of both genes resulted in a more severe effect, as almost no regular crystals were seen (Raschdorf et al., 2013). Another protein with suggested transport activity is MamO. MamO structure prediction showed similarity to a TauE-like transporter domain. Proteins from the TauE family were shown to be involved in ion transport. This domain might also be required to activate MamE in a non-catalytic manner since no physical interaction between them was reported (Hershey et al., 2016) (Fig. 3).

Besides iron transport, it is necessary to regulate the chemical conditions inside the magnetosome for controlled crystal nucleation and growth. An optimal, alkaline environment is required during magnetite formation (Uebe and Schüler, 2016). As mentioned above, MamB and MamM contribute to this process by exporting protons while importing iron ions. However, this contribution is not sufficient since the amount of iron mineralized during magnetite formation is significantly smaller than the number of protons released to the magnetosome lumen during this process. Therefore, another solution is required to maintain the basic environment for magnetite formation by exporting protons (Barber-Zucker and Zarivach, 2016). A protein suggested to participate in pH regulation is MamN, due to its homology to Na^+/H^+ antiporter (Fig. 3). Deletion of *mamN* results in empty vesicles, which further supports its suggested role (Komeili, 2012).

Crystal formation also requires a specific ratio of $\text{Fe}^{2+}/\text{Fe}^{3+}$. MamP, MamX, MamT and MamE contain an MTB-unique heme-binding c-type domain called magnetochrome. Magnetochromes are thought to play a role in the iron redox state by maintaining a certain $\text{Fe}^{2+}/\text{Fe}^{3+}$ ratio (Li, 2021) (Fig. 3). Deletion of these genes caused defects in crystal biomineralization (Li, 2021). In vitro experiments showed that MamP soluble domain contains an iron oxidase activity which participates in ferrihydrite formation (Siponen et al., 2013). Based on structure prediction, sequence analysis, and physiological characterization, MamZ also contains a YedZ-like ferric reductase domain. Together with its suggested transport activity, MamZ might be bi-functional (Raschdorf et al., 2013).

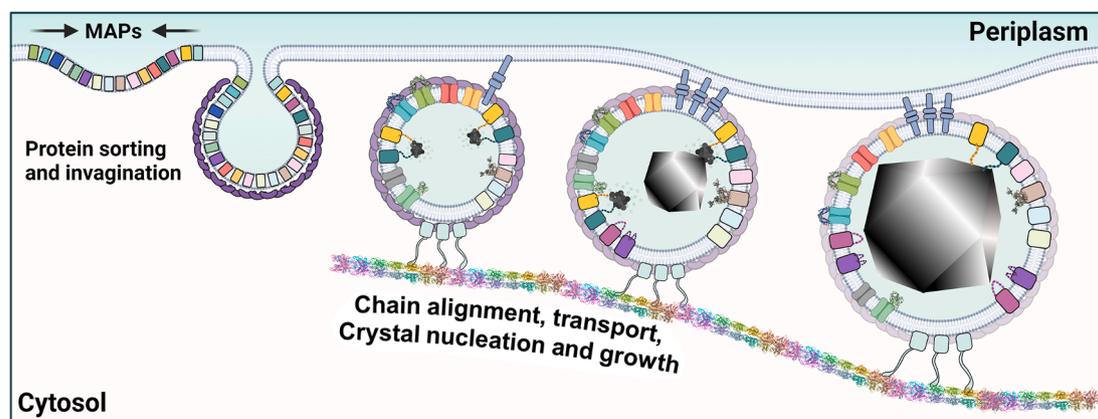


Fig. 5. An overview of the suggested magnetosome formation mechanism in Alphaproteobacteria. The first step of the mechanism is proteins sorting and invagination of the inner bacterial membrane, creating a defined compartment with a unique protein composition. This step is followed by three additional steps: chain alignment, transport and crystal nucleation and growth. It is still unclear whether they occur sequentially or simultaneously. The magnetosome provides an iron biomineralization compatible environment and contains most of the proteins essential for magnetite biomineralization control. Under optimal conditions, a single magnetite crystal is synthesized in every magnetosome, with specific size and shape properties. Some key proteins participating in this mechanism are colored based on previous figures. Created with BioRender.com.

Magnetite nucleation and crystal shape and size control

Once reaching optimal conditions, a single magnetite crystal per magnetosome is synthesized with species-specific morphology, such as cubo-octahedra, elongated hexahedra, and bullet shapes (Arakaki et al., 2014) (Fig. 1A). Nucleation and growth of such crystals have two suggested models. The first assumes that magnetite biomineralization occurs by direct co-precipitation of soluble Fe^{2+} and Fe^{3+} , while in the second, magnetite is formed through phase transformation of mineral precursor phase (Uebe and Schüler, 2016). Previous cryo-TEM studies showed that magnetite nucleation and growth, in solution, proceed through a fusion of clusters, or primary-particles of 1–2 nm, rather than atomic accretion (Baumgartner et al., 2013).

Iron co-precipitation assay showed Mms6 and Mms7 have strong binding affinities to Fe^{2+} ions suggesting they initiate nucleation by increasing local metal concentration (Nudelman et al., 2018). Mms6 is the most abundant protein in the magnetosome and was shown to participate in magnetite nucleation *in vivo* and *in vitro* (Raschdorf et al., 2018) (Staniland and Rawlings, 2016). When taking the nucleation models in mind, the high Mms6 abundance might suggest that many pre-nucleation clusters are formed on Mms6's C-terminal that, upon release, fuse to form the magnetite nucleus. Magnetite growth continues upon the agglomeration of these clusters on the crystal surface (Fig. 4).

Magnetite magnetic properties depend on the size and shape of the crystal, and therefore, control over these parameters is crucial (Müller et al., 2020). Mms5, Mms6, Mms7 (MamD), and Mms13 (MamC) were found to promote crystal growth (Fig. 4) (Arakaki et al., 2014). These proteins are embedded in the magnetosome membrane, with a well-defined hydrophobic transmembrane region, which likely plays a role in their membrane sorting and self-assembly (Arakaki et al., 2014). Hydrophilic regions that contain acidic amino acids and are exposed to the magnetosome lumen are responsible for the iron-binding ability. Differences in the surface recognition among the Mms proteins might account for sequence and structural variations of these hydrophilic regions (Arakaki et al., 2014).

Deletions of *mms* genes do not affect the number of crystals but affect their size and morphology (Arakaki et al., 2014). It is believed that Mms proteins are precisely positioned within the magnetosome membrane to interact with specific magnetite faces and cooperatively control the resulting crystal size, shape, and orientation. Previously, it was shown that Mms proteins have different effects on magnetite growth by altering the growth rate of each crystal face. Deletions of *mms5* and *mms13* resulted in slightly smaller crystals than the WT, and deletions of *mms6*

and *mms7* resulted in smaller elongated crystals. These findings indicate that this protein set is required to produce full-sized cubo-octahedral crystals. In addition, genome analyses showed that *mms* genes are only present in MTB which produce cubo-octahedral crystals (Arakaki et al., 2014). Mms6 is also involved in magnetosome protein recruitment as indicated by its interactions with MamA and the reduction of Mms5, 7, and 13 levels in the magnetosome in its absence (Staniland and Rawlings, 2016).

MmsF is another major player in the control of magnetite biomineralization. Deletion of *mmsF* in AMB-1 did not show any difference in magnetite growth rate until it reaches ~25 nm length when the growth starts to stall (Fig. 4) (Murat et al., 2012). This indicates that MmsF is most likely required during crystal maturation.

Concluding remarks: while the overall process of magnetosome formation seems to be well understood (Fig. 5), there are still many missing points to fully understand the magnetosome formation mechanism. For example, specific molecular details such as protein-protein interactions, protein structures and their related functions are still scarce. Based on the current knowledge, we assume that proteins are well organized in the membrane as a protein-lipid complex which significantly impacts all aspects of magnetosome formation including the control over the organelle size and shape and over the resulted mineral.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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