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REVIEW - THE AMAZING LITTLE MAGNETS: MAGNETOTACTIC BACTERIA

SUMAIYA A. SHAIKH AND RATNA TRIVEDI

DEPARTMENT OF MICROBIOLOGY,

SHREE RAMKRISHNA INSTITUTE OF COMPUTER AND APPLIED SCIENCES,

SURAT-395 005

sunnu_1935@yahoo.in ; drratnatrivedi@gmail.com

ABSTRACT:

Magnetotactic bacteria (MTB) were first discovered by Richard P. Blakemore in 1975, and this led to the discovery of a wide collection of microorganisms with similar features i.e., the ability to internalize Fe and convert it into magnetic nanoparticles, in the form of either magnetite (Fe_3O_4) or greigite (Fe_3S_4). Studies showed that these particles are highly crystalline, monodisperse, bioengineerable and have high magnetism that is comparable to those made by advanced synthetic methods, making them candidate materials for a broad range of bio-applications. In this review article, the history of the discovery of MTB and subsequent efforts to elucidate the mechanisms behind the magnetosome formation are briefly covered. The focus is on how to utilize the knowledge gained from fundamental studies to fabricate functional MTB nanoparticles (MTBNPs) that are capable of tackling real biomedical problems.

KEY WORD: *Magnetotactic bacteria (MTB); magnetosome; MTB nanoparticles (MTBNPs).*

INTRODUCTION:

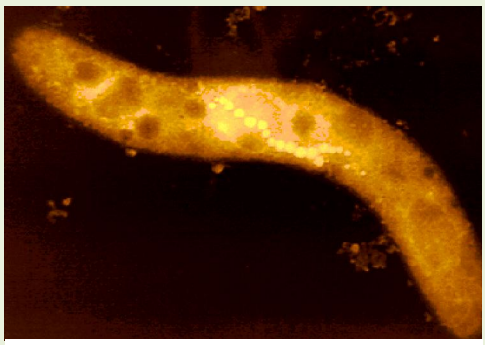

Figure 1Magnetotactic bacteria with chain of magnetite crystals.

Magnetotactic bacteria (MTB) were first discovered by Richard P. Blakemore in 1975 [1] when he was looking at some coccoid bacteria and found a large population of them migrating in one direction, which could be reversed under the influence of an external magnetic field. Subsequent studies showed that those bacteria were all capable of taking up Fe sources and converting them *in vivo* to magnetic nanocrystals, in the form of either magnetite (Fe_3O_4) or greigite (Fe_3S_4). In the early days of MTB research, most studies were conducted to address questions such as how the magnetic crystals were made and aligned, how the MTB controlled the biomineralization, and why bacteria containing such organelles evolved. Nowadays, however, with the rapid development of nanoparticle-based biomedicine, new possibilities for exploiting novel biomaterials have arisen, which encourages us

to take a second look at these "old" magnetic materials, but with a new question in mind: could we take advantage of the inexhaustible labor of MTBs to fabricate biomaterials with specific magnetic and biological properties, by precise genetic and proteomic manipulation.

General features of MTB

MTBs as a whole share some common features. All the reported MTBs are gram-negative members of the domain bacteria. Moreover, all MTBs have only the respiratory form of metabolism, metabolizing short-chain organic acids as carbon sources [3,4]. MTBs are virtually a heterogeneous prokaryote collection constituted by members from different conventional phylogenetic groups, they are inevitably varied in many respects. For example, MTBs with different kinds of morphologies have been reported, including coccoid, rod shaped, vibrioid, spirilloid, and even multicellular [1,5,6]; furthermore, the MTB-NPs that are imbedded in them can differ in size, shape, and orientation [5,7] Despite this versatility among strains, the properties of MTB-NPs are highly strain-specific.

Thomas-Keprta et al. [8–10] have identified six properties that they claimed as collectively unique for MTB-NPs, which are: (1) unusually truncated hexa-octahedral morphology; (2) few crystallographic defects; (3) elongated habit; (4) narrow size distribution, restricted mainly to the single domain field; (5) high purity; and (6) alignment in chains, with the last being the most distinguishing one [11]. It has now become a general consensus that the significance of aligned magnetic crystals is that it allows maximization of magnetization. By aligning in a head-to-tail manner, the MTBs aggregate their internal magnetic dipole moments, making themselves more susceptible to an external magnetic field [12].

The bacterial movement that Blakemore observed was a vivid demonstration of the migration of MTBs along the geomagnetic field line, which is one-way, with the specific direction determined by which hemisphere they are in. In particular, MTBs found in the Northern Hemisphere are mostly north-seeking MTBs, whilst those found in the Southern Hemisphere are mostly south seeking. As for those living at the equator, their movements are found evenly distributed between the two polarities [4,7,13,14]. However, such a simple generalization was recently contravened by the finding of a distinct population of south-seeking bacteria in the Northern Hemisphere [7,15]. This geomagnetic field governed migration is believed, to facilitate their search for optimal living environments in complex chemical gradients, such as aquatic columns with stratified sediments. MTBs, especially those producing magnetite crystals, are found to populate in the oxic-anoxic transition zone.

In demonstration by Whiteman et al., wild-type *Magnetospirillum magneticum* AMB-1 cells and their nonmagnetic mutant counterparts were put in an environment with an advancing oxygen gradient. It was found that in an applied magnetic field, the wild-type AMB-1 cells migrated faster to the preferred oxygen concentration than either wild-type cells in a zero field or the nonmagnetic cells in any field [16]. Such observations indicate that, besides undergoing geomagnetic field regulation, MTBs are capable of

sensing crucial environmental changes, such as oxygen concentration, and correspondingly adjusting their direction of motion to remain within the optimal living conditions. In other words, the migration of MTBs is decided by multiple elements with the motif of finding the best living conditions. It is single-dimensional, but is not necessarily single-directional. In this sense, the traditional terminology "magnetotactic" is incomplete. For those MTBs which hold positions in the oxic-anoxic zone, both the magnetotaxis and the aerotaxis contribute; hence, the more appropriate designation is "magneto-aerotactic" [5].

Interestingly, the identical converse migrations of the MTBs can be powered by different engines. For magnetotactic spirilla, the bidirectional movement is powered by the two polar flagella at both ends of the cells. However, in the case of magnetotactic cocci, turning-around is achieved by reversing the rotation direction of the flagella. In both hemispheres, counterclockwise rotation of magnetotactic cocci will induce motion of the particle towards the pole, whereas clockwise rotation will reverse the direction of motion, which helps the MTBs stay within the zone for optimal growth.

Magnetosome Associated Proteins and Lipids

MTB-NPs are born with a magnetosome membrane (MM) that stabilizes the particles under the physiological environment. The MM is mainly composed of phospholipids, 50% of which is phosphatidylethanolamine, similar to that of the cell membrane (CM) [17]. Analysis of the complete genome sequence of AMB-1 identified 78 MM proteins that are also prevalent in the CM [18,19]. These similarities led to the surmise that the MM might originate from the CM rather than being generated internally as an independent vesicle [18].

Authentic proof was obtained by electron cryotomography (ECT), which allows visualization of the sample in a three-dimensional manner without fixation or other pretreatment, thereby giving more detailed and dynamic information [7,20–22]. Komeili et al. actually captured the invigilating MM, which confirms the above hypothesis [20,23]. Meanwhile, the observation of empty or partially filled MMs in iron-starved or "premagnetic" cells suggests that the MMs are formed *prior to* the particles and likely work as nanoreactors in which the iron resources are accumulated and subsequently converted into particles under controlled conditions [17,24].

ECT imaging also helps in understanding the formation of chain-like assemblies of the magnetosomes. The magnetite crystals imbedded within these liposomes are beyond the superparamagnetic region [24], and therefore have a tendency to aggregate due to strong magnetic interactions. They are actually linearly aligned, there must exist another stabilizing force or scaffold upon which the particles are positioned. The genome sequence of AMB-1, which consists of a single circular chromosome of 4,967,148 bp and 4559 predicted open reading frames (ORFs), has been completely deciphered [19]. Of the genes that encode for MM proteins, 48 have been identified as MTB-specific, 13 of which are believed to take part in the MTB

formation.[19]. Previously, a 130 kb magnetosome genomic island was identified, which is referred to as the "magnetosome island" (MAI) [24,25–27]. Most of the identified magnetosome specific proteins (such as MamA, MamB, MamC, MamD, and MamE) were found grouped into gene clusters within the MAI [7]. Knowing the genome sequence is valuable in allowing interrogation of the protein functions at genomic and proteomic levels, which, however, is nontrivial. One approach is to knock out the gene of interest, and deduce the protein function from the abnormalities displayed by the resulting mutant, which are probably caused by the protein absence. As we know that the MamJ must contribute to the connection between magnetosomes and the cytoskeleton filament, and although the filament remains intact, the absence of MamJ as the "glue" causes dissociation of the magnetosomes from the string; without the holding tension, the magnetic forces bring the magnetosomes together [21,28].

In the observation made by Wu et al., who labeled MamK with dual fluorescent probes and tracked their formation, finding that the MamK protein nucleated at multiple sites in the cytoplasm and gradually assembled into mosaic filaments [29]. And it was found that gene *mamK* alone is efficient in directing the synthesis of linear filaments in *E. coli* [29]. Based on these observations, a rationale was suggested for the magnetosome chain formation, in which MamK is described as the main component of the cytoskeleton filament, and MamJ is closely associated with MamK and helps maintain the magnetosomes on the filament.

Despite the recent breakthroughs, what has been learned might be just the tip of the iceberg, and it is still too early to claim a full understanding of the MTB biomineralization and chain assembly at genomic and proteomic level. There are so many uncertainties that we are still unable to answer some basic questions, such as exactly how the magnetosome vesicle formation is initiated, how the Fe is accumulated and how the magnetosomes interact with the filament, not to mention the detailed descriptions of the respective and collective functions of the different MM proteins. However, with new state-of-the-art techniques and the successful sequencing of MTB genomes [19], such studies are making rapid progress. More importantly, the results obtained from these fundamental studies have already began to increase interest in magnetosomes as a novel class of materials.

The Magnetosomes- Magnetic Crystals

Compared with conventional magnetic particles made by chemical synthesis, MTB particles have many interesting attributes.

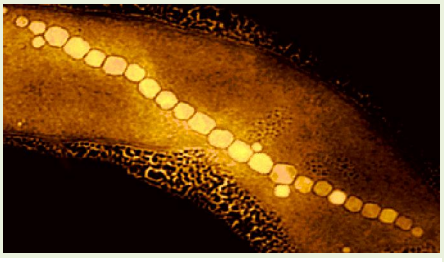

Fig. 2- Chain arrangement of magnetosomes in MTB.

Better shape control

In laboratory synthesis, it is more difficult to control the shape of magnetic nanoparticles than other materials, such as quantum dots or noble metals. Most of the chemically synthesized magnetite particles

are spherical or polygonal or simply a mixture. On the contrary, the morphology of MTB-NPs are species-specific and vary among strains, with cuboidal, parallelepipedal, and tooth, bullet- or arrowhead shapes all being reported [5,30,31].

MTB-NPs are typically highly crystalline with few defects

Though it is possible to synthesize magnetic nanoparticles with good crystallinity, it typically requires high-temperature treatment; MTBs, however, can achieve this at room temperature. MTB-NPs are always constituted of a combination of octahedral, dodecahedral, and cubic forms [32,33]. How the shape control is achieved is unclear so far, but it could be due to the selective inhibition of specific faces by adsorption of certain organic molecules.

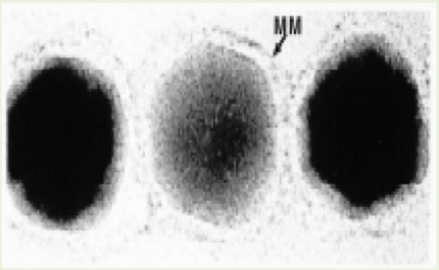

Fig.3- MTB-NPs with the surrounding magnetosome membrane

Biologically catalyzed particle formation

Recent studies showed that it only takes 30 min for MTB to form mature magnetite crystals: in the first 15 min, the crystals grow to the desired size, but with a nonmagnetic surface layer constituted by hematite; then in another 15 min, such hematite phases are completely converted to magnetite, with a concurrent increase in magnetization [35]. The composition of the MTB-NPs is highly conservative [36]. Unlike chemical synthesis, in which magnetite alloys can be easily made by mixing the Fe precursor with other metal salts, efforts to make doped MTB-NPs by simply growing MTB with multiple cations are usually fruitless: the cells can selectively take up iron from even limited supplies to make pure magnetite particles [37]. The mechanism of this specific uptake is still unknown. As a matter of fact, there is hardly any proof of the origin of such a distinct iron uptake pathway in MTB [38]. Fe(II) can be assimilated through a central ferrous transporter and simple diffusion, or, alternatively, from reduction of Fe(III). On the other hand, Fe(III) uptake is probably facilitated by forming complexes with certain chelating agents called siderophores produced by MTBs, most of which are catecholates and hydroxamates [5]. The organic substrate for ferric conjugation can be ferritin; but the substrate for ferrous conjugation is unknown.

However, strict biogenic control over the particle characteristics is based on the assumption that the optimal growth factors are satisfied. Otherwise, the bio-mineralization process is not necessarily as robust and can be dramatically influenced by many external parameters [39]. The actual particle composition depends upon the surroundings: those growing in the oxic–anoxic transition zone predominantly yield magnetite particles whilst those growing in the anaerobic region, where sulfide supply is abundant, yield exclusively greigite particles [40]. Compared with greigite nanoparticles, magnetite nanoparticles have higher magnetization and thus are more useful for potential practical applications in bio-separation, hyperthermia and as contrast agents in MR imaging. So, we'll focus the discussion on magnetite MTBs only.

Production and purification of MTB-NPs

Unlike the production of other common biomaterials, the purification step, which usually takes considerable effort, is a minor issue for MTB-NP production. Owing to their magnetic features, the MTB-NPs can be easily concentrated and separated, in an innate state, along with the lipid layer and the MM proteins. In contrast, the growth of MTB under laboratory conditions is non-trivial. One of the biggest issues is that most MTBs prefer complex chemically stratified aquatic habitats and vertical redox gradients, which are very hard to mimic in the laboratory [2]. The most common and compliable MTB strains are AMB-1, MRS-1, and MC-1. In a study performed by Schuler et al., in order to find the optimal growth conditions, all three strains were cultivated in a modified dual-vessel laboratory fermentor [34].

Surface modification and bioapplications of MTB-NPs

The superb magnetic properties of MTB nanocrystals, such as monodispersity, high crystallinity and close-to-bulk magnetization, allow them to compete with or even surpass the synthetic ones made by state-of-the-art synthetic routes. Their innate physiological compatibility, i. e., their nontoxicity and stability, is preferable to the synthetic analogues. In addition, MTB-NPs disperse well in water owing to their innate lipid coating, whereas the synthetic particles need to be rendered water soluble, which is usually nontrivial and can be extremely difficult for those with sizes beyond the superparamagnetic range. One major concern, in the context of bioapplications, is the functionalization of the particles. The lipid layer on the particles provides a nice platform, which permits the immobilization of biomolecules through a variety of bionconjugation techniques. For specific bioapplications, the particles usually have to be loaded with biomolecules, such as DNA, proteins, and peptides, in order to be equipped with the relevant pathophysiological capabilities.

On each MTB particle, about 120 streptavidins could be loaded by adopting the lipid insertion method, whereas chemical conjugation only gave up to 40 streptavidins per particle. In a similar manner, other kinds of amphiphilic molecules can also be immobilized onto the lipid coating layer. since streptavidin has four identical binding sites, they can serve as bridge molecules to allow the introduction of another biotinylated biospecies.

Although it is convenient, it is not mandatory to take advantage of the lipid coating layer. Just as for functionalization of synthetic particles, exotic coating layers can be added. For instance, incubating MTB particles with aminopropyltriethoxysilane results in silane crosslinking and coagulation, yielding in silica coated particles that are hydrophilic and aminated. Matsunaga et al. immobilized glucose oxidase and uricase onto such particles by using glutaraldehyde as the crosslinking agent. Compared with conjugates made from synthetic magnetites or zinc ferrite particles, such particles showed enzyme activities about 40 times higher, and could be used for 5 cycles without loss of catalytic activity [41]. The high magnetization and surface-to-volume ratio ensure that MTB-NPs are effective agents in magnetic separation. For

example, they have been applied to extract heavy metal cations, such as plutonium (Pu), from waste water, due to their superior loading capacity [42]. But the association between particles and biospecies can be a nonspecific physical interaction. A better approach is to make the particles "smart" by loading them onto molecules which have a unique match with the target and will recognize and bound with it exclusively when in proximity. The streptavidin immobilized MTB particles, derived from the various biotinylation approaches mentioned above, are good starting materials, since they allow conjugation with a variety of antibodies for rendering specific targeting capability.

MTB particles have also been utilized as drug carriers. Li et al. loaded doxorubicin (DOX) onto MTB-NPs through covalent attachment and evaluated the ability of these particles to inhibit tumor growth. In a pilot study performed on H22 tumor-bearing mice, these DOX loaded MTB-NPs showed a comparable tumor suppression rate to DOX alone (86.8% vs 78.6%), but with much lower cardiac toxicity and meanwhile the other related studies are going on.

Conclusions and perspectives

Since Richard P. Blakemore first discovered MTB under a microscope some 30 years ago, considerable progress has been made in understanding the mechanism and construction of such natural magnetic particle machinery. On the other hand, however, harnessing such particles and utilizing them as tools in versatile bio applications, is still in its infancy. The greatest hurdle is availability However, progress has been made on scaling up the production and it is now possible to make more than 10 mg of MTBNPs from each liter of culture media per day. Furthermore, there are many attributes of MTB-NPs that make them potentially important, at least as a complement to synthetic magnetic nanoparticles. First of all, their sizes are in a range that is difficult to achieve by artificial synthetic approaches. Secondly, the MTB-NPs are innately coated with a lipid layer that confers physiological solubility and stability, which is critical for bio-applications and is sometimes the bottleneck for synthetic magnetic nanoparticles. And Last but not the least, their functions can be manipulated at the genomic and proteomic levels. Although most of these studies are still at the proof-of-concept level, the MTB-NPs have already demonstrated the potential to work as well as, or in some cases even better than, synthetic analogues. Ongoing efforts could lead to more exciting findings that may further enrich and empower this platform.

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