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A Review on Magnetotactic Bacteria and Magnetosomes: Recent Trends and Multivalent Advances

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Abstract: Magnetosome are forthwith one of the potential biosolutions for researchers exploring different aspects related to biomedical and biotechnology applications. Magnetotactic bacteria (MTB) are members of prokaryotes. They appear in different morphoforms and produce unique organelles called Magnetosomes (MS). The magnetosomes help bacteria in survival through imparting unique properties to navigate across the earth's geomagnetic field. The whole bacteria as well as magnetosomes prove suitable tool for multivalent applications, thus they turn out to be a challenge to researchers with respect to production yield. The discovery of a new wild type, magnetosome-over producing MTB strains allowing higher yield of magnetic nanoparticles is therefore critically needed to achieve a sustainable production of biologically derived magnetic nanoparticles. Therefore, is the necessity to explore biota in search of magnetotatic bacteria, and subsequently their multifaceted metabolism and iron-biomineralization process. Through this review, we focus on the diversity of Magnetotactic bacteria and their potential applications of magnetosomes in different sectors including biomedicine. Various research on this study is to emphasize the wide range of applications of these bionanomagnets in biomedical research, as well as recent breakthroughs and future research directions using magnetotactic bacteria in biomedicine.

Keywords: Magnetotactic Bacteria, Magnetosome, Hyperthermia, Biomineralization

1. Introduction

Magnetotatic bacteria (MTB) belong to the prokaryotic group of microorganisms that make use of Earth's geomagnetic field to orient, navigate, and reach the most optimal microenvironment in their habitat [1]. All MTB have the tendency to synthesize intracellular iron containing magnetic nanoparticles (MNPs) particularly magnetite (Fe_3O_4) and greigite (Fe_3S_4) [2] that measure typically in the range of 30-120 nm [3] generally arranged in one or more chain-like structures in the specialized organelles called the 'magnetosomes' [4]. The magnetosomes are large in size present in single magnetic domain nanoparticles which confer the ability to perform magnetic movement. MNPs exhibit marked stability at the physiological temperature. Magnetosomes containing MNPs improve the cellular magnetic dipole's ability to navigate using the earth's geomagnetic field lines, analogous to a compass. This property of MTB is called as "Magnetotaxis". Magnetotaxis enables the navigation of bacteria in a more favorable environment in between oxic-anoxic transition zones (OATZ), which typically contains oxygen levels around 1%. MTBs generally occur in chemically stratified water bodies, and are typically the members of rare microbial community of the sediment ecology. MTB has been found in a variety of ecosystems, including lakes, ponds, soils, deep sea sediments, fresh water bodies, estuaries, lagoons, intertidal zones, mangrove swamps, and a few more uncommon severe settings [5, 6].

2. Diversity of MTBs

MTB are found all over the world. However, there are currently just a few MTB strains available in pure culture form, eg- *Magnetospirillum gryphiswaldens* MSR-1, *Magnetospirillum magneticum* AMB-1, *Magnetospirillum magneticum*MGT-1, *Magnetovibrio* sp. MV-1, *Magnetococcus*sp, MC-1; marine magnetic spirillum QH-2, *Magnetospirillum* sp. WM-1 and *Magnetospirillum magnetotacticum* MS-1 which are similar to the alphaproteobcateria, while *Dsulfovibrio magnetic* RS-1 is similar to the Delta-proteobacteria [7]. Therefore, little is known regarding the diversity of MTBs, and their distribution across various environments.

3. Physiology of Magnetotactic Bacteria and Magnetosomes

The physiology of MTB is important for the heavy metals absorption, particularly to reprocessing of the elements from the environments having high abundance of sulfur, iron, carbon, and nitrogen [8]. A few other non-magnetotactic organisms also have the ability to synthesize nanoparticles; for instance, *Penicillium*-gold, *Fusariumsolani* are well known for their ability to convert a solution of silver ions in silver nanoparticles [9]. however, this phenomenon is highly different from the one implemented by MTBs during intracellular synthesis of magnetic nanoparticles in highly specialized cellular structures. When MTB cells are lysed the magnatosome crystals mostly present in the form of stable residues at sites. This causes a reduction in the magnetization of those sediments. Magneto fossils (fossil macrosome crystals containing magnetite) have been found in a variety of places, including deep marine sediments, and have been dated to be roughly 50 million years old. Magnetosome fossils discovered on a metero rock ALH 84001 have been used as proof of life on ancient Mars. [10]. The magnetic properties of MTB are strongly linked to the crystal structure, magnetosome size, and unique orientation of the magnetosomes [11].

4. Molecular Mechanism of Magnetosome Synthesis

Magnetosome membrane (MM) is derived from cytoplasmic membrane, which is composed of many proteins that are absent from cytoplasmic membrane [12]. These specific proteins of MTB are indicated by the prefix like "*Mam*". *Mam* proteins though share similar function of magnetic-nanoparticles synthesis in MTBs, they vary with the species. However, all many of the mam, and other proteins located on magnetosome membrane are yet to be identified and explored in details [13, 14]. The biomineralisation of magnetosome crystals, chain organisation, and crystallographic direction are all governed by *mam* proteins [12]. Mam proteins that resemble proteins from the tetratricopeptide repeat (TPR) protein family based on amino acid sequence [15].

The recent years have thrilling advances in defining the molecular basis of magnetosome synthesis. In different species of MTB set of magnetosome genes present in core region form genomic islands through which it is conserved. Keen analysis of genetic, biochemical, and cell biology of is needed to reveal the process of MS formation and functioning [12]. Cloning approach can be a potential tool for detailed characterization of physiological role of the genes involved in MS formation. Magnetotactic bacteria *M. magnetotacticum* MS-1, for example, was used to clone the mam 22 gene and In *M. gryphiswaldense* MSR-1 and *M. magneticum* AMB-1, a gene encoding a homologous protein mam A was discovered. Factors controlling crystal maturation during magnetosome formation revealed substantial information in *Mangetococus* sp. *MC-1* [12].

The pH, temperature, iron, carbon, oxygen, nitrogen, sulphur, redox potential, genes, proteins, and the overall eco consortium all influence the biosynthesis of magnetosome basic factor. These parameters have a significant impact on bacterial cell physiology, as well as the microstructural and physical features of magnetite crystals generated in MTB [16].

5. Isolation and Cultivation of MTB for MNPs Production

To trap these bacteria and scale up their production, a variety of approaches are used, including enrichment media that mimic the natural habitat to create optimal micro-environmental conditions for MTB development and magnetosome synthesis. Richard Blakemore initially observed MTB with magnetotactic response [1]. He employed a simple approach of layering sediment samples with sea water in glass jars and incubating them under ambient light conditions. The magnetotactic response of MTBs was used to differentiate them from the enriched samples. For this experiment, a drop of was brought in contact with an MTB-enriched sediment sample on a microscopic slide to allow fast-moving MTB from the enriched sample's northern border to reach the drops, which were then collected using a micropipette. Moench and Knetzka succeeded in developing an enrichment method for growing MTB in the laboratory. MTB was cultivated in the lab by layering new oxidation sediment in beakers or glass jars. The pond's secondary influent and duckweed were added. A considerable number of magnetococci were observed and collected using a magnet after jars were capped to avoid evaporation and incubated with subdued sunlight at 20 to 27°C for 1 to 2 months. The 'Capillary racetrack' (CRT) method for isolation and purification is a more popular and widely used method that uses a single pipette sealed at one end [17]. The unusual characteristics of MTB, such as its microaerophillic or obligatory anaerobic nature, as well as its finicky and varied nature, make it difficult to cultivate under controlled settings, posing a challenge to researchers [18, 19]. MTBs are classified into several phyla based on their physiology and shape. MTB is a type of bacteria that belongs to the domain bacteria. They are polyphyletic, with members belonging to the Alpha proteobacter, Delta proteobacter, Gamma proteobacter, and Nitrospira phyla. Planctomycetes-Verrucomicrobia [20]. Within the candidate division, single cell examination reveals a unique uncultivated magnetotactic bacteria OP3 [21].

In the maritime environment, an uncultured, greigite-forming, multi-celled magnetic prokaryote has been discovered, and it has been linked to sulphate-reducing bacteria belonging to the delta proteobacteria. Uncultured MTB from other phyla, as well as extremely large rod-shaped bacteria with five magnetite chains, each containing 200 particles, were isolated from several microcosm sediments (REF). Both the freshwater bacteria candidates *Magnetobacterium bremense* (MHB-1) and the strain designated candidates *Magnetobacterium bavaricum* share 91 percent sequence homology; both belong to the phylum Nitrospira [5]. The majority of isolation and cultivation approaches rely only on MTB's active swimming activity. Magnetosome manufacture on a big scale is critical for MTB commercialization, and MS. Kundu and Kulkarni (2010) have reported for increased yield of strain MS-1 when grown in a modified MSGM supplemented with 25% nutrient broth. During growing in the modified MSGM, the morphology and properties of magnetosomes remained constant [22].

6. Applications of MTB

The unique property of MTB to synthesize magnetosome (MS) can be utilized in diversity of sectors including medicine, industry, and environment (Table 1). Iron-nanoparticles synthesized by MTBs have many advantages over the chemically, and physically synthesized ones. In this context, the magnetosomes have gained much attention for biotechnological and medical (cancer treatment) application. Magnetosomes in chains have an extremely stable structure that is sustained even after the bacteria are disrupted during MS isolation. This structure is intriguing because it inhibits aggregation and allows for greater internalisation of human cells [23]. Due to their low targeting ratios, magnetic nanoparticles produced from the whole MTB have also been shown to be a feasible alternative to synthesised nanoparticles. Tumors reject the treatment due to the hypoxic environment. When MTB- *Magnetococcus marinus* strain MC-I was injected into SCID tumours in mice and magnetically guided, up to 55 percent of MC-I cells entered into the hypoxic zone of HCTII6 colorectal xenografts [24]. Polyethylenimine (PEI), used in traditional gene therapy or DNA vaccination is associated with certain drawbacks including toxic effect. However, polyethylenimine coated on bacterial magnetic particles (BMPs) can potentially reduce the toxic effects. The BMPs-PEI complexes bind to DNA. When such complex is inserted in to the mice, their efficiency is enhanced several folds [25].

Table 1. *Biotechnological applications of whole magnetotactic Bacteria [35]*

Sr. No.	Field	Application	Advantages	Disadvantages
1	Drug delivery	Targeted tumour treatment with drug-loaded nanoliposomes coupled to M. marinus cells	Uses the cell's inherent magnetotaxis to dispense cell lysis.	Due to other LPS, it may be immunogenic.
2	Bioremediation	Heavy metal removal and waste water treatment (Cd, Te, Se)	Magnetic crystal dopping is feasible, and minerals that have been removed can be recovered.	MTB growth in polluted media is poor, and biomineralization may be hampered.
3	Energy generation	Electromagnetic induction generates electricity in *Ms. Magneticum* AMB-1 cells and magnetosomes.	Technology based on renewable energy	Only a few millivolts are produced, which is costly.

7. Recovery of Magnetosome

Following MTB cultivation, magnetosomes must be extracted and purified for specialized applications. To recover the magnetosomes, the MTB cells after cultivation are harvested and the cells are lysed with the help of physical methods such as sonication and magnetosomes are collected using dynamic magnet. Magnetosomes are purified by washing with deionized water [26]. Purified MS can be implemented for variety of biomedical applications (Table 2).

Table 2. *Biotechnological applications of Magnetosomes [35]*

Sr. No.	Field	Applications	Funtionalization method	Advantages	Disadvantages
1	Drug delivery	Antitumor medication delivery: doxorubicin, cytrabine, daunorubicin, ganglioside delivery, antitumor gene delivery	Surface plasmid adsorption; chemical crosslinking with glutaraldehyde and ginipin/PLGA	Tissue specificity, targeted medication delivery, and reduced drug toxicity Functionalization is simple.	Endotoxin test required, possible activity change, unknown biologicafate
2	MRI contrast agent	Tumor detection diagnostics	There is no functionalization; the targeted peptide is chemically coupled.	Great affinity to target cells, high detection sensitivity, and may be employed as a therapeutic tool (through hyperthermia medication delivery).	Endotoxin testing is required since the biological destiny is unknown.
3	Hyperthermia	Tumors' treatment	In general, there is no functionalization.	Tissue specificity can be utilised as a diagnostic technique and has less negative effects than chemotherapy and radiotherapy.	Endotoxin is required since the biological destiny is unknown.

8. Applications of MNPs

Bacterial magnetosomes have been employed as image enhancers for cancer diagnostics in the laboratory. MS is also used as a medication carrier in tumor-targeted therapy. Nanoparticles generate heat that has an anticancer impact. Some cancers, such as lung cancer, can be treated using this approach. At normal human body temperature, chemically manufactured iron oxide nanoparticles have a super magnetic or ferromagnetic nature. Chemically produced nanoparticles have a lower specific absorption ratio (SAR) than magnetosomes in magnetic fields less than the threshold level. As a result, it is claimed that employing magnetosomes for cancer treatment is more favorable, and so interest in magnetic hyperthermia using magnetosomes has grown [27, 28]. Bacterial magnetosomes play an important function in the pharmaceutical industry. Because of their inherent biocomtability, magnetic property, and high surface area-to-volume ratio, it is emerging as a potential drug delivery vehicle with an iron oxide or iron sulphide core surrounded by a natural lipid membrane shell and the ability to combine therapeutic moieties with diagnostic agents. Bacterial magnetosomes with a negative charge are one of the most effective magnetic nanoparticles for medication delivery [29, 30]. Therefore, magnetosomes seems particularly well studied for the treatment of tumor using magnetic hyperthermia and for the application in diagnostic procedures. However, most of the MTB are Gram negative, and contain lipopolysaccharides (bacterial endotoxin) that may cause fever or septic shock. Lipopolysaccharides presence is therefore prohibited in medicinal products [31].

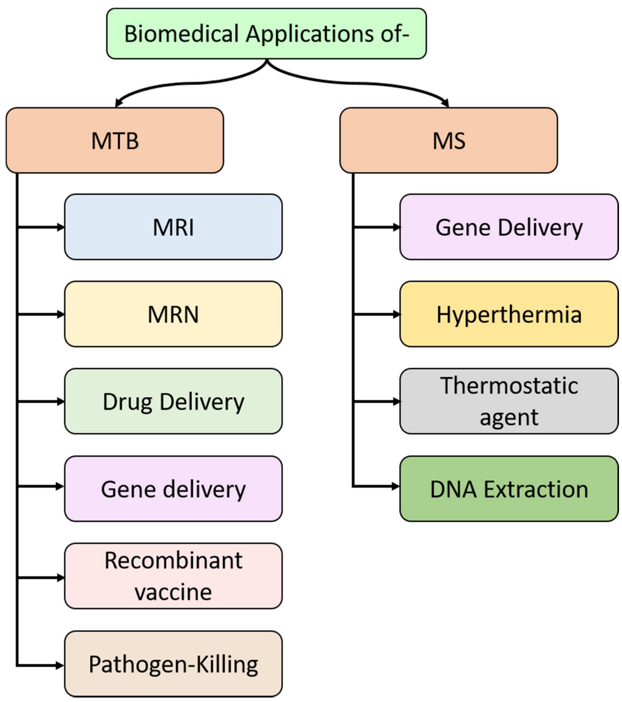

Figure 1. *Biomedical applications of magnetotactic bacteria and magnetosomes.*

Other important application of magnetosome is in hepatic cancer treatment. Doxorubicin is an effective drug, but has significant toxicity with around 80% mortality. When doxorubicin is conjugated with magnetosomes, it increases its antitumor activity to 87% and reduces the mortality to around 20%. The toxicity of drugs and the risk of mortality are greatly lowered due to the presence of numerous chemical moieties on the surface of magnetosomes [32].

9. Biological Interactions of MNPs

9.1. Cytotoxicity

Magnetosome suspension has a few harmful effects on mouse fibroblast H-22, HL-60, and EMT-6 cells, notwithstanding their bacterial origin. It has been proven that a magnetosome concentration of less than 1.3 mg/ml is safe to use [33]. When compared to the maximum dose of magnetosomes, 0.5 percent of body weight, acute toxicity of magnetosomes in mice and rats at dosages of 270,360, or 480 mg kg-1 of intravenously injected dosage form demonstrated no effect. The mice given the conventional chemical SPION, on the other hand, started to die at a lower amount of nanoparticle administered at 135 mg/kg.

9.2. Immunotoxicity

Because Fe3O4 is relatively insoluble, the toxicity of magnetosome is unlikely to be related to iron chemical toxicity. The dissolved iron ions, on the other hand, may be poisonous due to a Fenton reaction that produces hydroxyl radicals, which are potent oxidants; Fe3O4 does not have the same toxic effect. Magnetic fluid hyperthermia caused by chemically created nanoparticles and magnetic nanoparticles made naturally by MTB: magnetosomes. The efficacy of such a regimen is investigated using a glioblastoma xynograft model. Mice (U87MG cells) were injected individually with intra-tumoral magnetosomes and exposed to an alternating magnetic field for a week, with temperature measurements, TEM pictures, and Prussian staining procedure. When compared to control groups, patients exposed to the alternating magnetic field showed statistically significant suppression of tumour growth. The magnetosomes have a high transversal relaxivity, according to this study, and their successful transport to the targeted region is tracked using MRI. As a result, theranostic agent candidates for hyperthermia based on iron oxide nanoparticles could be microbially generated magnetosomes [34].

10. Conclusions

Magnetotatic bacteria and magnetosomes has scoop up multivalent dimensions in field of Microbial nanotechnology and interdisciplinary research. There is only limitation MTB isolation and cultivation at artificial laboratory condition. There is great need to develop new methods and experiments to transfer mgnegnetite production gene to desire bacteria.

Therefore, increased the yield of MS production will achieve and that's leads to additional benefit and possibilities to use of amazing nanomagnets in nanotechnology era. Because of the magnetic, physical, and optical features of MTB and magnetosomes, many researchers became interested in their possible use (s) in biotechnological and nanotechnological applications. Following investigations that finally led to more efficient and less expensive magnetosome purification processes, MTB and magnetosomes have now been tested in certain biotechnological and nanotechnological applications. Therefore, the review is mainly designed to enlist and assemble the multivalent application of these elusive bacteria and magnetosomes.

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