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Magnetotactic bacteria: nanodrivers of the future

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REVIEW ARTICLE

Magnetotactic bacteria: nanodrivers of the future

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Abstract

Magnetotactic bacteria (MTB) represent a heterogeneous group of Gram-negative aquatic prokaryotes with a broad range of morphological types, including vibrioid, coccoid, rod and spirillum. MTBs possess the virtuosity to passively align and actively swim along the magnetic field. Magnetosomes are the trademark nano-ranged intracellular structures of MTB, which comprise magnetic iron-bearing inorganic crystals enveloped by an organic membrane, and are dedicated organelles for their magnetotactic lifestyle. Magnetosomes endue high and even dispersion in aqueous solutions compared with artificial magnetites, claiming them as paragon nanomaterials. MTB and magnetosomes offer high technological potential in modern science, technology and medicines. This review focuses on the applicability of MTB and magnetosomes in various areas of modern benefits.

Keywords

Astrobiology, bio-indicators, biosensor, cancer, drug delivery, hyperthermia, magnetosomes, phase display, robotics, waste treatment

History

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Introduction

The term ''magnetotactic bacteria'' (MTB) although taxonomically indistinct, yet represents a morphologically, metabolically and phylogenetically diverse group of aquatic prokaryotes, passively aligned parallel to the Earth's geomagnetic field while they swim (Bazylinski & Frankel, 2004). MTB first came into light in 1975, when RP Blackmore was looking at some coccoidal bacteria and found a large population of them migrating towards the direction where an external magnetic field was applied (Blakemore, 1975). Such magnetically attracted cells pursued attention with time, and attracted scientists to discover a large collection of microorganisms with similar features (Balkwill et al., 1980; Blakemore et al., 1979; Farina et al., 1990; Schüler & Frankel, 1999).

MTB are a diverse group of Gram negative aquatic prokaryotes with a broad range of morphological types, including coccoid, rod, vibrioid and spirillum. MTB live in a redox transition zone between oxygen rich upper water and oxygen depleted sulphide rich lower water/sediment in an aquatic environment. The unique impression of MTBs is their unique nano-ranged intracellular protein bound magnetic inclusions ''magnetosomes'' that impart ''magnetotaxis'' to these cells (Arakaki et al., 2008). Magnetosomes confer superiority to chemical iron-oxide nanoparticles due to their immanent magnetic characteristics, uniform genetically controlled nano-morphology, narrow size distributions and biomembrane envelope.

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The potency of MTB is not only restricted to magnetosomes, but also includes the living cells. Therefore, both MTBs and magnetosomes are enjoying celebrity status due to their multi-dimensional applications including recovery and detection of biological entities (Amemiya et al., 2005), in cellular homeostasis disorder (Iskusnykh & Popova, 2010), as a contrast dye in MRI (Benoit et al., 2009), hyperthermia therapy for cancer (Liu et al., 2012), in sensitive immunoassays, high-performance DNA/mRNA recovery (Sode et al., 1993; Yoza et al., 2002), DNA discrimination analysis (Nakayama et al., 2003), drug delivery (Matsunaga et al., 1997), as carriers for enzymes (Matsunaga & Kamiya, 1987), nucleic acids (Takeyama et al., 1995) antibodies (Matsunaga et al., 2003; Nakamura & Matsunaga, 1993), as biosensors (Fouladi et al., 2007b), non-destructive domain analysis of soft magnetic materials (Harasko et al., 1995), to locate magnetic poles on meteoritic magnetic grains (Funaki et al., 1989), waste treatment and removal of heavy metals and radionucleotides from wastewater (Bahaj et al., 1998; Wu et al., 2006a) and in nanorobotics (Martel, 2006a). In addition, these might be tools for searching extra-terrestrial life (McKay et al., 1996).

The journey of MTB and magnetosome has been documented in various review papers (Alphandéry, 2014; Arakaki et al., 2008; Cristina et al., 2007; Hofer, 2013; Lang et al., 2007; Li et al., 2010; Martel, 2014; Matsunaga, 1986; Schüler & Frankel, 1999; Sun et al., 2011; Xie et al., 2009; Yoshino et al., 2010; Zhang et al., 2009). This review is an attempt to summarize the experimental findings and ideas adopted for applications of MTB and magnetosomes in various fields. While a number of research articles are being added day by day, there is no comprehensive review that sheds light on broader applicability of these amazing creatures. Although a

very specific focus was adopted for this review, the number of publications over the years, far exceeds the citation limit format and the author apologizes to those researchers whose contributions were unintentionally omitted. It is difficult to differentiate the applications of MTBs as these are all interlinked. To ease this study, applications have been divided into medical and commercial types and in sub headings. Various scientists used different names for the magnetic nanoparticles obtained from MTB, yet magnetosome was found to be the most common and hence used in this study.

Medical applications

G protein-coupled receptors expression

G protein-coupled receptors (GPCRs) are among the largest family of the total proteins encoded by the human genome and prime targets for drug discovery, treatment of cancer, endocrine, neural and many other disorders (Katritch & Abagyan, 2011). As GPCRs have large hydrophobic domains, their purification from cells is time-consuming and results in conformational losses. The GPCR with natural conformation was manufactured by expressing the GPCR gene in MTB (Matsunaga et al., 2004) as a chimeric gene coding for the GPCR and anchor protein from magnetite particle membrane proteins of their fragments. Yoshino et al. (2002) also displayed D1R GPCRs on to magnetosomes via display technique by fusing it to magnetosome's membrane specific protein Mms16. Expression of D1R was confirmed by anti-D1 antibody and binding activity of recombinant magnetosomes using bodipy-labeled SCH23390. Further, GPCRs was assembled into the lipid membrane of magnetosomes (Yoshino et al., 2004). Localization of Mms16 as an anchor molecule on magnetosomes was confirmed by luciferase fusion studies. Stable luminescence was observed from magnetosomes Mms16 fused with luciferase at the C-terminal region. D1R was also loaded on magnetosomes using Mms16 (Yoshino et al., 2004). This technique refined the native conformation of GPCRs without the need for detergent solubilization, purification and reconstitution after cell disruption.

Detection system/in immunoassay

Various technologies like fluorescence and chemiluminescence have been adopted for the detection of various biochemical assays. However, low labeling signals due to photo-degradation is a common problem. Magnetosomes are attractive materials for the assay system as a label due to their longer stability and life (Arakaki et al., 2004). Many standard immunoassays after magnetic alteration can be used for the determination of various biologically active compounds and xenobiotics, immunomangtic separation and pathogen detection (Li et al., 2010). Initially, the detection of mouse IgG was reported by Matsunaga et al. (1990). Further, a sensitive detection system was developed for protein streptavidin using biotin conjugated to magnetosomes with a detection limit of $1\,pg\ ml^{-1}$ (100 times more sensitive than a conventional fluorescent detection system) (Amemiya et al., 2005). In addition, a modular chemical approach of magnetosome modification was reported (Ceyhan et al., 2006) for attachment of the streptavidin and the resulting magnetosomes were suitable as probes for detection of complementary targets, nucleic acids and proteins that were specifically recognized by the magnetosome-bound DNA oligomers or antibodies. In another study, the quantitative detection of HBsAg (the surface antigen of the hepatitis B virus) was studied (Guo et al., 2006) using antibody-labeled magnetosomes via a chemiluminescence-immunoassay. This method produced highly sensitive results in comparison to routine methods. In an interesting study, Prunus necrotic ringspot virus and grapevine fan leaf virus were detected by fluoro-immunoassay using magnetosomes and a double antibody sandwich enzyme linked immunosorbent assay (Chen et al., 2009). The system showed six times higher efficiency than ELISA-based method. Interestingly, Hu et al. (2010) observed magnetosomes' intrinsic peroxidase-like activity similar to artificial magnetic nanoparticles and based on these findings, an immunoassay approach was developed to use magnetosomes as a peroxidase mimic catalyst and a magnetic separator. An immunoassay, using novel ''beads on beads'' composites, was performed by assembling magnetosome beads onto polystyrene microbeads (Matsunaga et al., 2007a). Also, fully automated detection of prostate-specific antigens was performed with a detection limit of $1.48\,ng\,ml^{-1}$. Wacker (2007) modified immuno-PCR (M-IPCR) technology for automatable high sensitive antigen detection. This M-IPCR was based on antibody-functionalized biogenic magnetosomes with similar principles to that of a sandwich immunoassay and was able to detect up to $320\,pg\,ml^{-1}$ r-HBsAg in human serum which was about 100-fold more sensitive than the analogous magneto-ELISA. Other studies described a fully automated immunoassay system for the detection of endocrine disrupting chemicals such as alkylphenol ethoxylates, bisphenol-A, alkylbenzene sulfonates (Matsunaga et al., 2003) and β-estradiol (Tanaka, 2004) using monoclonal antibodies chemically conjugated to magnetosomes.

The radioallergosorbent test (RAST) is a popular test for the detection of allergens. However, RAST is time consuming, complicated and gives results independent of clinical symptoms. A solid-phase fluoro-immunoassay using antibody immobilized on magnetosomes was developed (Nakamura & Matsunaga, 1993) for the rapid detection of mouse immunoglobulin G (IgG) (Nakamura et al., 1991). Another study (Nakamura & Matsunaga, 1993) reported highly sensitive detection of allergen using magnetosomes-immobilized fluorescein isothiocyanate. Very recently, a longitudinal surface plasmon resonance assay for the simultaneous detection of pefloxacin and microcystin-LR in seafoods has been developed using antibody-functionalized gold nanorods as signal probes and antigen-ovalbumin modified magnetosomes as signal amplification probes (Sun et al., 2013).

The measurement of auto-antibodies to thyroid-stimulating hormone receptors (TSHR) is important for the diagnosis of autoimmune thyroid disease such as Graves' disease (GD). Sugamata (2013) expressed recombinant hTSHR on the lipid-bilayer surface of magnetosomes using a tetracycline-inducible expression system. Further, it was suggested that hTSHR-displayed magnetosomes had potential for ligand-receptor interaction analysis in GD patients.

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The detection and removal of *E. coli* with a fluorescein isothiocyanate conjugated monoclonal antibody, immobilized on magnetosomes was also studied (Nakamura et al., 1993). In addition, MTBs were used to label macrophage cells for inflammation detection (Hartung et al., 2007).

Single nucleotide polymorphisms (SNPs) are the most common form of human genetic polymorphisms which provide powerful tools for identifying genes responsible for diseases such as cancer, hypertension and diabetes (Tomita-Mitchell et al., 1998). For data reliability, SNP analysis requires a large number of samples. Therefore, there is a need for high throughput and accurate multiple assay system for SNP analysis (Arakaki et al., 2008). Maruyama et al. (2004) developed a DNA thermal dissociation curve analysis protocol for an automated system with magnetosomes by developing a method for avoiding light scattering caused by nanoparticles during the use of fluorescent dyes as labeling chromophores. SNPs of aldehyde dehydrogenase-2 (Maruyama et al., 2004), epidermal growth factor receptor (Maruyama, 2007) and transforming growth factor beta-1 (Matsunaga et al., 2007b; Ota et al., 2003) genes have been successfully detected in the past. A semi-automated system for the large-scale detection of SNPs, has been developed (Matsunaga et al., 2007b), based on allele-specific oligonucleotide hybridization and thermal dissociation curve analysis using magnetosomes (Figure 1).

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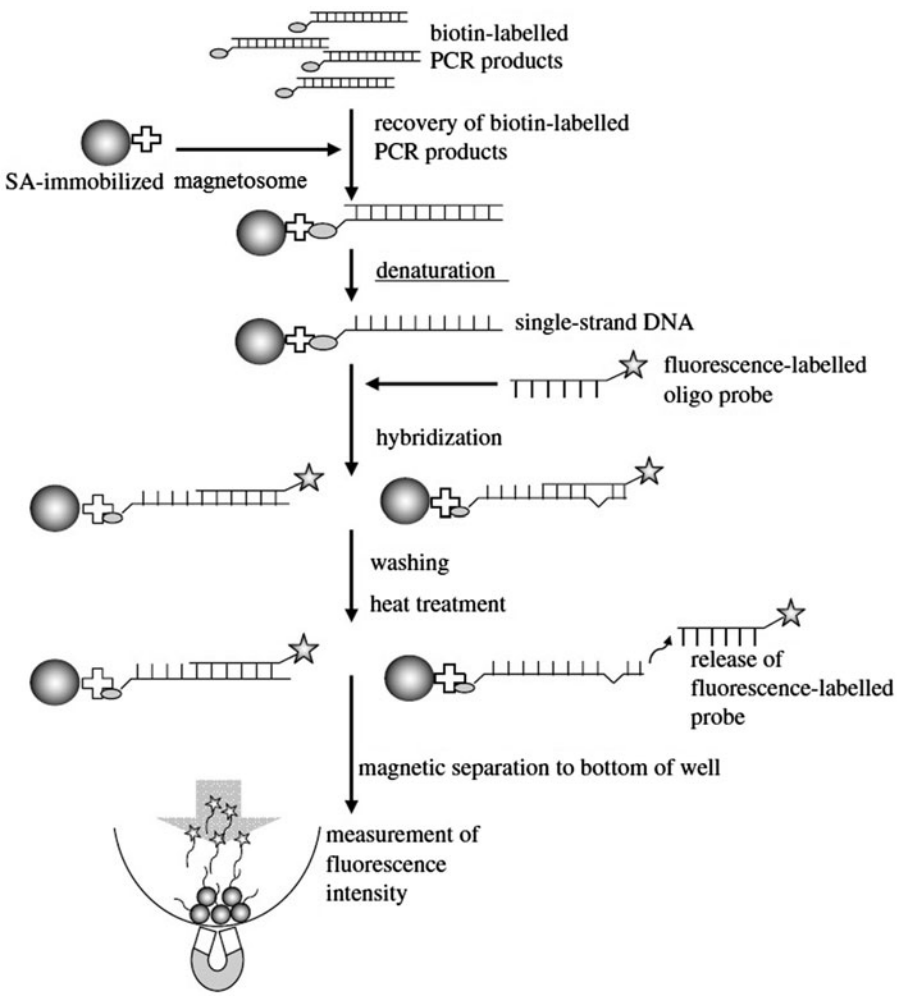
Figure 1. Schematic representation of SNP detection protocol. [Included and reproduced after permission from Arakaki et al. (2008)].



Phase display

Phage display is the technique for *in vitro* protein evolution and is a key tool in drug discovery. It is used to find new ligands (enzyme inhibitors, receptor agonists and antagonists), to target proteins (Bratkovic et al., 2005; Lunder, 2005), to determine tumor antigens (for use in diagnosis and therapeutic targeting) (Hufton et al., 1999) and in searching for protein–DNA interactions (Gommans et al., 2005) using specially constructed DNA libraries with randomized segments. A method of conjugating biotinylated liposomes with phospholipids on magnetic beads coated with streptavidin was introduced by Xie et al. (2006). Further, magnetosomes have been employed as a bacterial membrane model for phage biopanning (Tanaka et al., 2008). Approximately 4×10^{10} plaque-forming units of the library phage (complexity, 2.7×10^{9}) were reacted with magnetosomes. Six candidate peptides, which were highly cationic and could bind onto the magnetosome membrane, were obtained. They exhibited antimicrobial activity against *Bacillus subtilis* but not against *Escherichia coli* and *Saccharomyces cerevisiae* (Figure 2).

Display techniques of dopamine (GPCR) receptors, onto magnetosomes and their applications to ligand binding assays were also described (Yoshino & Matsunaga, 2009). By this system, it was possible to retain native conformation of membrane proteins without the need for detergent solubilization, purification and reconstitution after cell disruption. Furthermore, estrogen and anuclear receptors were also

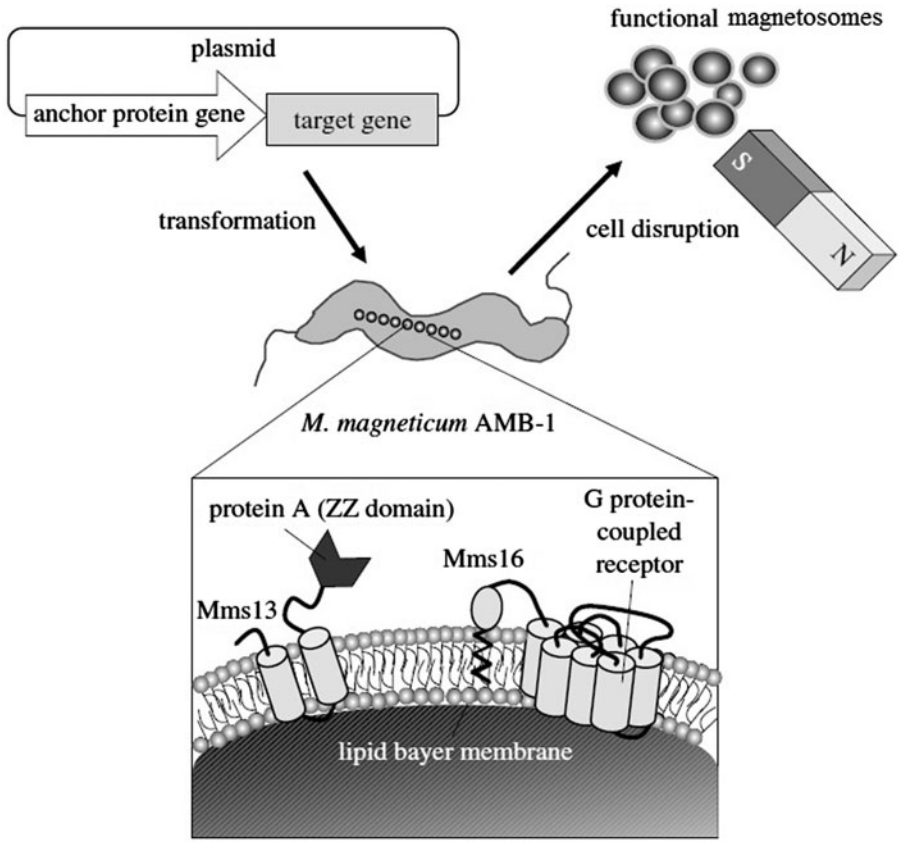


Figure 2. Schematic representation for the preparation of functional magnetosomes for protein display. [Included and reproduced after permission from Matsunaga et al. (2007a–c)].

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displayed onto magnetosomes. The assay using magnetosomes displaying an estrogen receptor could discriminate full agonists, partial agonists or antagonists (Yoshino & Matsunaga, 2009). In another study, to establish highly expressed protein display on magnetosomes, strong promoters were identified with a *M. magneticum* AMB-1 genome and proteome databases (Yoshino & Matsunaga, 2005) using a luciferase-reporter gene assay and 400 times higher luminescence intensity observed during experiment. Recently, it has been reported that protein displays can be designed using specific magnetosome membrane proteins as anchor molecules for the assembly of foreign proteins on the surface of magnetite magnetosomes. Many magnetosome membrane proteins were observed as anchor proteins, including MagA, MpsA, Mms16 and Mms13 (MamC, Mam12) (Lefèvre et al., 2011). Another interesting study of genetic functionalizing the membrane surrounding MTBs with a phosphohydrolase was conducted by Ginet et al. (2011). Membranes were engineered to purify, robust and recyclable biocatalysts to degrade ethyl-paraoxon (pesticide) and genetically fused to the opd gene from *Flavobacterium* sp. ATCC 27551 encoding a paraoxonase to MamC, in *M. magneticum* AMB-1. The MamC protein acted as an anchor for the paraoxonase to the magnetosome surface, thus producing magnetic nanoparticles displaying phosphohydrolase activity.

Gene delivery

Non-viral methods of gene delivery have been widely used in gene therapy and DNA vaccination. Xiang et al. (2007a,b) developed a novel non-viral delivery by coating polyethylenimine (PEI) onto the surface of magnetosomes. Magnetosomes–PEI complexes could bind DNA and provide protection from DNase degradation. The transfection efficiency of magnetosomes–PEI/DNA complexes was observed to be higher than that in PEI/DNA complexes. Interestingly, in contrast to PEI, the magnetosomes–PEI complex was less cytotoxic to cells *in vitro* and could deliver an exogenous gene to animals and allow it to be expressed *in vivo*. DNA vaccines are an attractive approach to generate antigen specific immunity. Tang (2012) used magnetosomes as carriers of a r-DNA composed of a secondary lymphoid tissue chemokine, human papilloma-virus type E7 and Ig-Fc fragment to generate a gene vaccine (BMP-V) for tumor immunotherapy. Efficient transfection of BMP-V *in vitro* and *in vivo* was achieved when a 600 mT static magnetic field was applied for 10 min. The treated mice tolerated BMP-V immunization well with no toxic side effects.

Magnetic cell separation

Separation of specific cells from mixed gentry, such as peripheral blood, umbilical cord blood and bone marrow, is a necessity for various therapeutic and diagnosis applications. Magnetic cell separation technology applying immuno-magnetic particles for the isolation of target cells from cell suspension received considerable attention. This technique combines antibodies and magnetic nanoparticles, against the target cell surface antigen and offers a rapid and easy way for sensitive and reliable capture of target biomolecules. For cell separation, nanomagnetic particles are preferred due to their sensitivity, rapidity, precision with no toxicity to the cells.

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Magnetosomes were bound with protein G and anti-CD monoclonal antibodies for direct magnetic separation of immune cells from blood (Takahashi et al., 2009). β-Lymphocytes or T-lymphocytes, which represent less than 0.05% in whole blood cells, were successfully separated at a purity level of more than 96%. Kuhara et al. (2004) developed a highly efficient magnetic cell separation system for Leukocytes using magnetosomes expressing protein A binding to the Fc fragment (anti-mouse IgG) with purity range of 97.5%. Stem cell marker (CD34) is the best identified surface antigen expressed on hematopoietic stem cells, which are known to be rare. CD34-positive cells were also separated by binding the protein A-magnetosome complexes with the antibody. The stem cells separated using magnetosomes maintained their capability of colony formation as hematopoietic stem cells without inhibition of their proliferation and differentiation abilities. Specific separation of target cells using magnetosomes was achieved by simple magnetic separation from cell suspensions using a permanent magnet with no special magnetic column (Kuhara et al., 2004). Yoshino et al. (2008) modified magnetosome expressing protein A for magnetic cell separation and achieved separation of monocytes and β-lymphocytes from peripheral blood.

Automated DNA extraction

DNA extraction using magnetic particles is receiving attention due to easy techniques. Arakaki et al. (2008) developed an automated DNA extraction method based on magnetosomes, which allowed highly accurate DNA recovery for subsequent PCR processes. In this method, pre-treatment by organic solvents was not required and therefore permitted DNA extraction within 30 min. In another study (Yoza et al., 2003), a cascading hyper-branched polyamidoamine dendrimer was synthesized onto the surface of magnetosome to allow enhanced extraction of DNA from fluid suspensions.

Cancer treatment

Cancer/tumor treatment is one of the most challenging tasks of modern medical science, due to peripheral toxicity by conventional therapies. General chemotherapy and radiotherapy produce unsatisfactory responsiveness, making new therapeutic strategies an immediate need to combat cancer. MTBs and their magnetosomes can serve cancer therapy in various ways.

Major parameters affecting blood-borne anticancer drug delivery to tumor sites are: the miss-formed angiogenesis capillaries supplying tumors, the high interstitial pressure inside solid tumors and the blood flow heterogeneity of vessels supplying the tumor. These parameters result in the increased time, diminution and non-uniform distribution of drugs to the target. Therefore, development of techniques, which can facilitate localization of drugs at the tumor site, would be an attractive option. Recently, MTB and magnetosomes have claimed their candidature as efficient drug carriers (Hopkin, 2004; Martel, 2006b; Munoz-Jimenez et al., 2010; Schüler & Frankel, 1999) due to their peculiar paramagnetic, nano-scale, narrow size distribution and membrane bounded characters (Bazylinski et al., 1994; Gorby et al., 1988; Grünberg et al., 2004; Hoell et al., 2004; Nakamura et al., 1991). Magnetoliposomes, containing *cis*-diammine-dichloro-platinum (II) (CDDP) prepared using magnetosomes, were evaluated for specific drug targeting and controlled release at the tumor site (Matsunaga et al., 1997) with 1.7 times higher capture volume than artificial magnetic particles. In addition, on application of a magnetic field, magnetoliposomes released their content over 2 h, suggesting that CDDP loaded magnetoliposomes, efficient antitumor activity and controlled drug release (Matsunaga et al., 1997).

Moreover, the use of entire flagellated bacteria to target tumors is also possible. Since MTBs can swim in the vasculature and reach tumor mass even in the absence of flow. These possess all the required components such as a flagellum, an internal magnetic sensor, an appropriate size and enough thrust for effective drug targeting in the human vasculature (Martel, 2006b). Martel (2006b) studied targeted delivery of therapeutics with controlled bacterial carriers in the human blood vessels. It was observed that the displacement path of a swarm of MTB could be controlled and modified under computer software. It was also demonstrated that MTB could swim efficiently in human blood for a few minutes with positive biocompatibility and could be detected by MRI (Martel, 2006a).

Novel nanocomposites of magnetosomes and semiconductor quantum dots were developed (Maeda et al., 2008) for targeting and identifying cancer cells. Two functional proteins, biotin carboxyl carrier protein (BCCP), derived from AMB-1 and protein G, derived from Streptococcus were displayed on magnetosomes. Using streptavidin–QD/protein G-BCCP-magnetosomes nanocomposites, magnetic manipulation and fluorescent labeling of lung cancer cells was demonstrated (Hoell et al., 2004). Chen et al. (2013a) proposed microwave breast tumor detection by loading a microwave contrast agent onto MTB. Multiple agglomerations of MTB released into the human breast could be tracked simultaneously and monitored using differential microwave imaging techniques. Further, the same research group (Chen et al., 2013b) used an anatomically realistic numerical breast phantom as a platform to demonstrate the feasibility of this tumor diagnostic method. Carbon nanotubes and ferroelectric nanoparticles were loaded onto the MTB.

Magnetic fluid hyperthermia

Magnetic fluid hyperthermia (MFH) involves injecting the fluid containing magnetic nanoparticles directly into the tumor site, and then generating the alternating magnetic field around the tumors in order to destroy them by heat dissipated by the nanoparticles. MFH could prevent unnecessary heating in healthy tissues because only the magnetic nanoparticles absorb the magnetic field energy (Timko et al., 2009). An important characteristic of magnetosomes is their ability to induce heat generation, when an oscillating magnetic field is applied to them. This feature conceives the idea that these magnetosomes might be helpful in the destruction of tumors through hyperthermia or thermoablation (Alphandery et al., 2011a).

Alphandery et al. (2011a) observed the heating efficiency of cobalt doped chains of magnetosomes for applications in

alternative magnetic field cancer therapy by hyperthermia. The hysteresis losses, magnetic properties and heating efficiency of the magnetosome chains were shown to be enhanced in the presence of cobalt. Further, a method for the treatment of tumor cells through heat generated by magnetosomes and by alternative magnetic field has also been described (Alphandery et al., 2011b). These magnetosomes were found to yield sufficient antitumoral activity in tumor-bearing mice. Alphandery et al. (2011c) studied heat generation by MTB cell, extracted magnetosomes and extracted individual magnetosomes without membranes exposed to an oscillating magnetic field. It was observed that the specific absorption rates of each of these three magnetic samples were larger than that reported for smaller super-paramagnetic nanoparticles. Further, it was observed that up to 100% of cancer cells were destroyed when MDA-MB-231 breast cancer cells suspension was incubated in the presence of magnetosomes, in an alternative magnetic field (Alphandery et al., 2011d). Recently, applications of magnetosomes were tested by sonication for MFH treatment of tumors (Alphandery et al., 2012). Liu et al. (2012) also studied the application of magnetosomes in MFH.

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Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging technique based on the principles of nuclear magnetic resonance primarily applicable in medical settings to generate high quality images of inside of human body. MRI plays a vivid role in the pre-clinical development of new drugs, diagnostics and their delivery systems. For ultrasensitive MRI, magnetic nanoparticles with maintained uniform size are desirable. Therefore, magnetosomes can be used as highly sensitive MR contrast agents. Herborn et al. (2003) characterized magnetosomes as superparamagnetic contrast agents for MRI. Lisy et al. (2007) assessed the use of fluorochrome-coupled magnetosomes (FCM) as a bimodal contrast agent for both MRI and near-infrared fluorescence (NIRF) optical imaging of cultured macrophages. Further, it was observed that macrophages could be labeled with FCM and imaged using both a 1.5 T MR scanner as well as with NIRF optical methods. Felfoul et al. (2007) studied MC-1 MTBs as biocarriers for drug delivery and showed that the magnetosomes embedded in each MTB could be used to track the displacement of bacteria with an MRI system *in vivo*. The ability of the *M. magneticum* AMB-1 to confer positive MRI contrast was determined *in vitro* and *in vivo* (Benoit et al., 2009). It was observed that AMB-1 could produce positive magnetic resonance imaging contrast and colonize mouse tumor xenografts.

Accurate delivery and localization of cells in order to target organs is a critical issue for successful cell-based therapies with stem cells or immune cells such as antigen-presenting dendritic cells (DC). Labeling with contrast agents before implantation facilitates accurate monitoring of cellular migration using MRI. Sebastian et al. (2009) investigated magnetosome's uptake into hematopoietic $Flt3^+$ stem cells and DC from mouse bone marrow and observed that the uptake of magnetosomes into cells increased magnetic activity. Even lower numbers of magnetosome-loaded cells were readily detected by MRI. Felfoul et al. (2010) investigated the influence of the magnetosome's chain and the MC-1 MTB cell on the MRI contrast and observed that magnetosomes were the predominant source of contrast in MRI over motion and the cell body. Goldhawk et al. (2012) reviewed the magnetosomes as a reporter of gene expression in MRI and found that their suitability and superiority for development of reporter gene expression for MRI. Vereda et al. (2009) also reported the use of magnetosomes as contrast agents for MRI. In their patent claim, Gambhir et al. (2010) disclosed the use of *M. magneticum* AMB-1 as the MRI contrast agent and a method of detecting tumors in a subject by MTB enhancement of the positive contrast of MRI. Afkhami et al. (2011) developed a method for encapsulating MTB MC-1 by MR navigation in a controlled release pattern and carried the resulting capsules to the vicinity of the capillary network where they could be released and guided towards the tumor.

Biocompatibility issues

Magnetotactic bacteria (MTBs) and magnetosomes are rapidly spreading their aura in medical science by various ways. However, it is necessary to assess their biocompatibility *in vitro* and *in vivo* before considering clinical applications. Until today, magnetosomes have rarely been employed as drug carriers *in vivo* mainly due to the indecipherable biocompatibility and pharmacokinetics. Magnetosomes are been predicted as being biocompatible due to their: (i) biological origin (Xiang et al., 2007b), (ii) negligible chemical toxicity (Häfeli & Pauer, 1999; Wagner et al., 2006) and (iii) insolubility of Fe_3O_4. On the other hand, associated toxic properties of magnetosomes may primarily be due to their: (i) nano-scale size, which leads to deposition and aggregation of nanoparticles in the body; and (ii) impurities (particularly proteins, nucleic acids and polysaccharides) associated with magnetosomes extracted from bacterial cells, which result immunotoxicity, (iii) protein contents on membrane (Grünberg et al., 2004; Jevprasesphant et al., 2003; Sun et al., 2010b). Yet magnetosomes are enclosed by a lipid bilayer and specific soluble and trans-membrane proteins. These lipids and proteins on magnetosomes surfaces may endow them with great potential for good biocompatibility.

Some research groups (Xiang et al., 2007b) evaluated biocompatibility and cytotoxicity of magnetosomes for mouse fibroblasts *in vitro* and observed that magnetosomes were not toxic. Interestingly, a novel technique for reconstruction of magnetosome membrane expressing protein-A (protein A-magnetosome) was developed to reduce cytotoxicity (Yoshino et al., 2008). In another study, magnetosomes without surface modification were incorporated into endothelial progenitor cells *in vitro*, and cells containing magnetosomes showed high viability (Kim et al., 2009). A target distribution of magnetosomes in sublingual vena of Sprague–Dawley (SD) rats was observed by Sun (2009) and the tissue distribution of magnetosomes in dejecta, urine, serum and main organs was examined. After injected into the sublingual vena, magnetosomes were only found in livers and no evidence of the existence of magnetosomes in the dejecta and urine was observed within 72 h following the intravenous

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administration. Histological examination of major organs from 40 mg kg^{-1} magnetosomes treated rats shown no remarkable pathological changes except for increased number of vacuoles in livers, and thicker interlobular septa in lungs (Sun et al., 2010b). In another study, MTT test, micronucleus test and hemolysis assay were carried out by Yan (2012) to evaluate *in vitro* cytotoxicity, blood toxicity and genotoxicity of magnetosomes. Under these conditions, magnetosomes showed no cytotoxic, genotoxic and hemolytic effects up to 4.0 mg ml^{-1} indicating good biocompatibility. Cytotoxicity studies conducted by Liu et al. (2012) using human breast cancer cells MCF-7 indicated that under alternative magnetic field magnetosomes exhibit a lower toxicity than metal nanoparticles. Recently, Taherkhani et al. (2014) observed that liposomal attachments to MTB formulation improved the biocompatibility of MTB, whereas attachment does not interfere with liposomal uptake.

Commercial applications

As immobilization career

The uniform nanosize of magnetosomes and the inhibition of aggregation by intact magnetosome membranes give a large surface: volume ratio and therefore these could be used as carriers of bioactive substances via immobilized on the surfaces of the particles (Xie, 2005). Immobilized biological molecules like enzymes, antibodies, oligonucleotides and other biologically active compounds have proven superior practical applications than individual molecules, due to extended stability and reusability (Maeda et al., 2008). Furthermore, immobilization of biologically active compounds on magnetosomes proved better because these can be: (a) targeted, directed to desired place and can be removed from the system by applying external magnetic fields, (b) used to express their activities in desired process and (c) used as affinity agents for capturing targeting or modifying target molecules or cells (Xie, 2005). Other properties include: (d) negatively charged surface and better dispersion due to polarized primary amino groups in the magnetosome bilayer lipid membrane, (e) easy function with diverse bioactive molecules due to the abundance of primary amino groups in the surface of magnetosomes, (f) potentially slow drug release (in case) from magnetosomes *in vivo* due to the digestible magnetosome membrane and (g) high biocompatibility.

Earlier, MTB were used as an immobilization carrier for enzymes and antibodies (Matsunaga & Nakamura, 1989) like anti-α-fetoprotein (Matsunaga, 1987). Later, immobilization of antibody onto magnetosomes was inspected (Xie, 2005) via immune-agglutination using antibody–magnetosome complexes, and was applied for the detection of carcino-embryonic antigen (CEA). It was observed that, 5 μg anti-CEA antibody–magnetosome complexes could detect CEA of 100 pg ml^{-1}. In another study, biotinylated magnetic nanoparticles were constructed by displaying biotin carboxyl carrier protein (BCCP) on the surface of magnetosomes (Maeda et al., 2008). In an analysis using tetra-methyl rhodamine isocyanate-labeled streptavidin, approximately 15 streptavidin molecules were shown to be immobilized on a single BCCP-magnetosomes (Maeda et al., 2008). Furthermore, gold nanoparticle–magnetosome composites were constructed via the biotin–streptavidin interaction. The lipid layer on the particles provided a platform, which permitted the immobilization of biomolecules through a variety of bioconjugation techniques (Xie et al., 2009). Specifically, on each MTB particle, about 120 streptavidins could be loaded by adopting the lipid insertion method, whereas chemical conjugation only gave up to 40 streptavidin per particle (Ceyhan et al., 2006).

Protein drugs are becoming common these days, but lack successful delivery in target areas as they readily become digested or disrupt during crossing of organs, cells and intracellular compartments, thus require a carrier to reach to the target site. Matsunaga & Kamiya (1987) immobilized glucose oxidase and uricase on magnetosomes. The activity of immobilized magnetosomes-glucose oxidase was observed 40 times higher than immobilized artificial magnetites or Zn-ferrite particles. Both glucose oxidase and uricase retained their activities and could be reused up to five times. The same research group also immobilized FITC conjugated anti-IgG antibodies on magnetosome, which were modified with glutaraldehyde or SPDP for the detection of allergen (Nakamura & Matsunaga, 1993; Nakamura et al., 1991, 1993). Tanaka & Matsunaga (2001) loaded Hemoglobin A1c onto modified magnetosomes. In another study, the homogenous chemiluminescence enzyme immunoassay using antibody bound Protein A–magnetosomes complexes was developed for detection of human IgG (Matsunaga et al., 2002).

Radiotherapy can be used to treat diseases, especially cancer, using radiation to weaken or destroy particular targeted cells (Kumar et al., 2009). Radioactive isotopes such as 99mTc, 131I, 123I and 111In were linked to magnetosomes with suitable chelates, radioactive labeled molecules such as nucleic acids and proteins, and by including the radioactive isotopes in the culture medium during magnetosome formation (Kumar et al., 2009). Magnetosomes, labeled with radioactive isotopes showed advantages in internal radiation of solid tumors due to their targeted delivery (Sun et al., 2011). The Matsunaga group immobilized biotin-labeled oligonucleotide probes onto magnetosomes, which were modified with sulfo-NHS-LC-LC-biotin and streptavidin (Ceyhan et al., 2006; Maruyama et al., 2004; Ota et al., 2003; Takeyama et al., 1995; Yoza et al., 2003). Takeyama et al. (1995) used magnetosomes as a DNA carrier for introduction into the cell. In this method, magnetosomes coated with plasmid DNA were used for the ballistic transformation of the marine cyanobacterium *Synechocystis*. In another experiment, DNA oligonucleotides were immobilized on magnetosomes and used for the detection of mRNA (Takeyama et al., 1995). Magnetosomes were also used to carry out magnetic separation of DNA (Yoza et al., 2002) by coating with 3-aminopropyltriethoxysilane, *N*-(trimethoxy-silylpropyl) isothiouronium chloride or 3-(2-(2-aminoethyl)-ethylamino)-propyltrimethoxysilane (AEEA). DNA binding efficiency increased with the number of amino groups present on the silane compounds and was 14-fold higher than with untreated magnetosome.

The activities of the most chemotherapeutic drugs suffer from the inability to accumulate selectively at the site of

action, and thus require an effective carrier. Sun (2007) Sun et al. (2008) loaded doxorubicin (DOX) onto bacterial magnetosomes (DBMs) in EMT-6 and HL60 cell lines to evaluate *in vitro* and *in vivo* anti-neoplastic effects of DBMs on hepatic cancer. The DOX–DBMs showed slower released of DOX into serum and maintained 80% stability after 48 h of incubation. In another study, a novel magnetic targeting anti-tumor drug delivery system was constructed with magnetosomes (Liu et al., 2013). In this study, methotrexate was loaded onto the magnetosome membrane using genipin, and this system showed high drug loading ratio (43.3–49.6%), high encapsulation efficiency (76.5–98%) and long-term release behaviors (over 2 months) without initial burst release. Recently, Taherkhani et al. (2014) reported attachment of liposomes to MTB through carbodiimide chemistry to make self-propelled agents as therapeutic carriers. About 70 nanoliposomes were found to be linked with MTB without compromising functionality and motility.

Biosensor applications

Fast pathogen detection is a genuine necessity in clinical diagnosis, disease control and the food industry. Conventional bacteria detection methods consume considerable time, especially at very low concentrations (or at early stages of bacteria growth), at which point detection is most vital. To accelerate the detection procedure, MTB can be used as bio-carriers, by binding it to microbeads coated with antibodies or bacterial-phages. The swimming directions of the MTB can be controlled by a directional magnetic field (Martel et al., 2006), which induces a torque on magnetosomes inside each MTB, acting like a compass. Under controlled external magnetic fields, the flagellated MTB propel the functional microbeads, effectively sweeping the aqueous sample (Lu & Martel, 2006b; Martel et al., 2006) to search for the targeted pathogenic bacteria. The MTB transports the pathogenic bacteria to the microelectrodes array, where the variations in electric impedance can be measured. The existence of a pathogen is indicated when the impedance variations increase beyond a certain threshold (Martel, 2008). Earlier, a glucose biosensor was constructed using the enzyme glucose oxidase, immobilized onto magnetosomes (Nakamura & Matsunaga, 1989). Another method reported the production of aligned multi-walled carbon nanotubes on the surface of a silicon chip using magnetosomes (Kumar et al., 2005). The technique could ultimately result in the integration of nanotubes into nanoelectric devices.

Lu et al. (2006) developed a preliminary design of MTB-based biosensor. Pathogenic bacteria were directed by MTB to an area where a micro-electrode array connected to a microelectronic circuit was used. This detected and recorded the number of the pathogenic bacteria by measuring variations of the impedance between the electrodes. Further, results showed that MTB could survive in the human blood and most of the media used to cultivate the pathogenic bacteria. In another study, an impedimetric detection system was proposed, where microbeads were attached to the MTB and were modified with a coating of an antibody or phage, specific to the target pathogenic bacteria. This experimental setup was able to detect 2 microbeads of 8 μm in the microchannel (Denomme et al., 2007). However, Fouladi et al. (2007b) fabricated a biosensor using MTB based on CMOS technology that consisted of an array-like structure of microelectrode pairs that can be selected independently. The system was able to differentiate deionized water, normal temperature bacterial media and hot bacterial media. In another study, Fouladi et al. (2007a) measured impedance via MTB-biosensor to detect the presence of pathogenic bacteria and observed that MTB could detect impedances ranging from about 3 kΩ to 100 MΩ. Lu et al. (2007) discussed the design and simulation of an impedance sensing platform based on the MicraGEM processes utilizing MTB. It was observed that a 10 μm microbead could be detected by measuring the variations of impedance between a pair of planar electrodes. Recently, an electrochemical immunosensor was developed to detect staphylococcal enterotoxin B based on magnetosomes, polyaniline nano-gold composite and 1,2-dimethyl-3-butylimidazolium hexafluorophosphate ionic liquid. High sensitivity and stability at 4 °C was observed reaching up to 60 days (Wu et al., 2013) and could be regenerated four times using NaOH elution. MTB particles were also observed to serve as imaging probes with the detection limit of as low as 1 pg ml^{-1}, about 100 times more sensitive than fluorescence-signal-based detection techniques (Amemiya et al., 2005).

Toner

Toner is a powder, used in laser printers and photocopiers to form the printed text and images on the paper. In its basic form it is a mixture of carbon powder, iron oxide and sugar. Since magnetosomes are extremely fine, high purity and uniform size iron oxide particles, they have considerable scope in high quality toner development. Kishi et al. (1987a,b) used magnetosomes of *Aquaspirillum magnetotacticum* as a magnetic substance for toners with enhanced qualities. Further, Kishi et al. (1988b) deposited magnetosomes in an electroconductive magnetic toner, working as an electroconductive material to the periphery of the toner particles. This electroconductive magnetic toner was capable of providing an image of superior quality. In the same year, magnetosomes were used as magnetic carrier particles of a two component developing agent in toner by Kishi et al. (1988c). Further, single-component magnetic color electrostatographic toner was made by Kishi et al. (1988a) incorporating in color toner particles and magnetosomes.

Wastewater treatment and heavy metal recovery

The large quantity of wastewater generated from various industries which contains metal ions also causes several health and environmental problems. Traditional metal removal methods, such as chemical precipitation, solvent extraction and ion-exchange from wastewater are less effective under very low metal ion concentration (Bahaj et al., 1994). As MTB have the ability of absorbing the metal ions, thus precious metals can be recycled from wastewater (Wang & Sun, 2005). MTB-based magnetic field technology shows great application potential in the area of wastewater

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treatment for many advantages, such as high efficiency, low power, low cost and no secondary pollution etc.

Among preliminary studies, Bahaj and coworkers (Bahaj et al., 1993a,b; Bahaj & James, 1994, 1993) studied the application of MTB in environmental cleanup through metal loading. In these studies, up to 100% separation efficiency was achieved within 24 h (Bahaj & James, 1994). Further, Cd recovery by a sulfate-reducing MTB, *Desulfovibrio magneticus* RS-1, was investigated by Arakaki et al. (2002) and >95% of Cd at an initial concentration of 1.3 ppm was recovered during operation. Ren et al. (2004) studied the biosorption of Cr(III) by MTB. Another study (Wang & Sun, 2005), reveals the 100% removal of Pb(II), Cr(III), Cu(II) and Zn(II) along with appreciable removal of Cr(VI), Fe(III), Fe(II) and Ni(II) from activated sludge via application of MTBs. Gold and silver trapping was also possible by uncultured MTB from microcosms (Keim & Farina, 2005). Song et al. (2007b) applied MTB as biosorbents for the adsorption of Au(III) and Cu(II) ions from aqueous solution. With initial metal concentrations of 500 mg l^{-1}, maximum biosorption capacity of 1 g of MTB (dry mass basis) for Au(III) and Cu(II) were calculated as 505.2 mg of Au(III) and 493.1 mg of Cu(II). Wu et al. (2006b) observed that pH 1–5, biomass concentration 2 g l^{-1}, and 20–200 mg l^{-1} initial Ag(I) concentration were most favorable for Ag(I) adsorption by MTB in wastewater. Further, Wu et al. (2006a) paid stress on parameters affecting sorption process and observed that the most efficient adsorption of Pd(II) was under pH 1–5, biomass concentration 6 g l^{-1}, Pd(II) initial concentration 20 and 80 mg l^{-1} and within 30 min. Adsorption of Au(III), Cu(II) and Ni(II) ions from aqueous solution by MTB in single and ternary systems had been investigated (Song et al., 2006a). It was observed that competitive biosorption from ternary component systems enhanced the Au(III) adsorption, together with significant inhibition for Cu(II) and Ni(II). Further, time dependence studies showed that the adsorption equilibriums of Au(III) and Cu (II) were achieved within 5–10 min during biosorption of MTB (Song et al., 2007a,b, 2006b). In an interesting study (Song et al., 2008b), maximum Au(III) biosorption capacity of MTB isolate *Stenotrophomonas* sp. was 506, 369 and 308 mg g^{-1} l^{-1}, dry weight biomass at the initial pH values of 2.0, 7.0 and 12.0, respectively. When thiourea was used as the desorbent to recover gold from the MTB biomass (Song et al., 2008b). Jiang et al. (2007) achieved 100% Pb(II) removal via biosorption by MTB from the activated sludge. Song et al. (2008a) investigated the Pd(II) and Al(III) adsorption from waste solution by MTB. Competitive biosorption on MTB from the Pd–Al system displayed a unique phenomenon that the adsorption of Pd(II) was reinforced and that of Al(III) was prohibited. In another study, Sun et al. (2009) adsorbed Au(II) and Cu(II) from artificial wastewater solution with MTB. Au(II) was recovered at pH 2, and the corresponding desorbing agent was thiourea, while to recover Cu(II), the pH was maintained at 5, and the corresponding desorbing agent was EDTA. Furthermore, Sun et al. (2010a) treated activated sludge with the help of enriched MTB-11s and observed selective adsorption of Ag(I), Cu(II) and Co(II). Tanaka et al. (2009) applied M. magneticum AMB-1, in the recovery of Au(III) from plating waste and approximately 42 and 100% of Au(III) was precipitated from growth medium containing 10 μM gold and from a mixture of plating waste/growth medium containing 0.4 μM gold, respectively. Further, Song et al. (2011a) built a magnetic separator model to study adsorption of Au(III) by MTB. While Song et al. (2011b) studied biosorption of Ni(II) by MTB in aqueous solution. Wang et al. (2011) observed the competitive biosorption of Ag(I) and Cu(II), on M. gryphiswaldense (MSR-1), for reference to the succeeding selective reinforced processes in binary ion systems. In binary ion biosorption, Cu(II) was observed to promote the adsorption of Ag(I) while Cu(II) itself reduced or inhibited correspondingly. Cai et al. (2011) used *M. gryphiswaldense* MSR-1 to reduce Au(III) to a zero-valent metal in a water environment, and, to accumulate them into spherical nanoparticles on the cell surface through biosorption. Recently, Song et al. (2012) studied treatment of Au(III) loading wastewater, using external magnetic field and MTB with nearly 100% biomass removed at the magnetic intensity of 1200 GS in 100 min. Cheng et al. (2012a) investigated the effects of microscopic intermolecular forces on the adsorption of Cu(II) by MTB and observed that adsorption of Cu(II) was the combined results of both the electrostatic attraction and the particle's thermal motion. Further, a model cell of MTB, used in the wastewater treatment process, was developed by the same research group (Cheng et al., 2012b). Recently Song et al. (2013) studied the biosorption of Au(III) by MTB via surface complexation, ion exchange, electrostatic attraction and oxidation–reduction reaction. The biosorption of Au(III) and Cu(II) ions in both single and binary systems by *M. gryphiswaldense* MSR-1 was investigated by Li et al. (2013). The biomass exhibited the highest single Au(III) and Cu(II) ion adsorption yields at 25 °C, pH 2.5 and 5.0, respectively, and a biomass concentration of 10 g·l^{-1} (3.83 g·l^{-1}, dry basis).

Robotics/actuators

The construction of micro-robots, with dimension ranges of 1–2 μm, using artificial components is difficult due to several technological mannerisms. Therefore, it is needed to identify a biological entity with an embedded power and propulsion system. One such natural entity that could help in this respect is the MTB (Martel, 2012). Technically, MTBs can be considered as micro-robot as they possess efficient molecular motor, sensory and actuation capabilities as well as an embedded remote control interface. Motile MTB can, in principle, be considered for the implementation of actuation and propulsion and can be used to propel and steer micro-devices and nanorobots under computer control to reach dreary sites in the human body. For example, MC-1 MTB can propel themselves with flagella generating a thrust exceeding 4.0 pN (Lu & Martel, 2006b), which exhibit escalating mobility and allow this MTB to swim in water at room temperature, without load at speeds often exceeding 200 μm s^{-1}. This property, coupled with appropriately oriented computer-controlled magnetic fields, may be applied on the nanometric scale (Lu & Martel, 2006b).

Lu & Martel (2006a) developed a microfluidic system to assess and control the swimming direction of MTB in micro-channels and used it as carriers in microsystems such

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as lab-on-chip. In another study, bacterial actuation and manipulation was demonstrated, where *M. gryphiswaldense* was used to push 3 μm beads at an average velocity of 7.5 μm s^{-1} along pre-planned paths by modifying the torque on a chain of magnetosomes in the bacterium (Martel et al., 2006). Use of a MTB-based micro-actuation method for propelling an untethered aqueous micro-robot under a controlled embedded electronic system may allow minimized electrical power. In this direction, the preliminary design of a photo-voltaic cell to capture energy from an incident light source in order to control the direction of motion of a micro-robot propelled by MTB was described by Andre & Martel (2006). According to the estimate, a total of four cells with an efficiency of 12.5% should provide up to 100 μA of photonic current to the electronics embedded in each untethered micro-robot from an incident source of green light. Martel et al. (2008b) showed that a combination of various types of nanorobots could be more efficient to enhance targeting in the smallest blood vessels found in the human microvasculature. Furthermore, they (Martel et al., 2008a) used MTB to propel and steer micro-devices and nanorobots under computer control to reach remote locations in the human body near the arterio-capillar entry. Presently, micro-robotics is facing a shortfall of poor kinematic dexterity. To overcome this problem, Yang et al. (2009) developed a bionic micro-robot under joint control of internal and external signals with the motion of MTB for reference and observed that both the velocity and attitude of the micro-robot could be controlled flexibly. Martel et al. (2009b) described a flagellated nanomotor combined with magnetosomes as an effective integrated propulsion and steering system for nanorobots. It was designed for targeting locations only accessible through the smallest capillaries in human body and trackable via MRI. Moreover, Martel et al. (2009a) described many medical robotic platforms for enhanced performance through additional software/hardware subsystems suited for medical interventions in the microvasculature modules. This allowed enhanced targeting efficacy and operations in very difficult locations such as tumor lesions, which was only accessible through complex microvasculature networks.

Interestingly, in a recent study, Martel & Mohammadi (2010) observed that a swarm of computer-controlled flagellated MTB acting as natural micro-robots could perform many of the same complex collective tasks envisioned with these futuristic self-propelled artificial micro-robots. The ability of MTB to penetrate 3D multi-cellular tumor spheroids through openings present in the tissue was studied by Mokrani et al. (2010). This specific *in vitro* model reproduced the loose cellular junctions and the gaps present in most tumors which showed that MTB could navigate in such environments using a computer-guided magnetic field and could be a promising micro-robot for drug delivery.

Magnetic resonance targeting (MRT) is an emerging approach in medical robotics that could enhance target interventions deep in the human body. It applies MRI for gathering and tracking data to determine the position of microscale entities to guide them towards a specific site in the body accessible through the vascular network. Martel (2010) studied micro-robotic navigable entities for MRT to target colorectal tumors, consists of 1–2 μm MR-trackable and controllable MTB with propelling thrust force provided by two flagella bundles per cell exceeding 4.0 pN, a 10-fold increased value over typical flagellated bacteria. Further, Felfoul et al. (2011) reported the navigation of MTB ($300\ \mu m \cdot s^{-1}$ without any external power) towards a solid tumor using a computer controlled set of magnetic coils. Recently, MTB-micro-robots were constructed by Ma et al. (2012), by attaching microbeads through immunoreactions. The system was fully capable of directing and monitoring the movement of the MTB-micro-robots. Recently, Khalil et al. (2013b) studied closed-loop control strategy for MTB-based micro-robot. In their work, response of MTB to a field-with-alternating-direction was investigated and strategy was developed to perturb the vibrational and rotational modes of its flagella, hence decreasing its velocity. Further, a targeted drug delivery system was developed using magnetic micro-robots for increasing the therapeutic indices of drugs (Khalil et al., 2013a). A closed-loop motion control of micro-robots under the influence of controlled magnetic fields has been developed.

Micro- and nano-manipulators

The principal goal of remote manipulation is to extend human ability in remote locations (Ignat et al., 2007). MTB represents a remarkable micro-robotic element for a distinct manipulator class, as the magnetosome could be controlled with a 3D system using magnetic levitation. Also, the magnetosome can be assimilated with the multi-joint type moray arm (Shugen et al., 2002), which is characterized by a mechanism integrating a powerful prismatic joint (slider) at the arm as is defined by the curvature. Ignat et al. (2007) developed a mechano-magnetic manipulator based on *M. gryphiswaldense* with the intention to develop micro or nano-optical scanners where the optical beam is scanned and controlled by the motility of magnetic bacterium in outer magnetic field.

In geology, paleontology and astrobiology

One of the most interesting applications of MTBs is in geology, paleontology and astrobiology (Yan et al., 2012). Due of their high abundance and remarkable ability to accumulate and precipitate iron and/or sulfur minerals, MTB are assumed to draw their key impact on biogeochemical cycling of iron and sulfur in natural sediments (Simmons & Edwards, 2007). Fossilized magnetosomes, produced by MTB, were suggested as paleo-environmental indicators in the sedimentary and rock records (Chang & Kirschvink, 1989). Fossil magnetite from MTBs is supposed to be well preserved in freshwater sediments (Snowball et al., 2002). The fossilized MTB are observed as a key carrier that can provide information about the origin of the geomagnetic field and properties of the deep Earth, history of plate motions and magnetic reversals, and even magnetic proxy records of paleo-environmental and paleo-climate (Bazylinski & Schübbe, 2007). In addition, based on the magnetotactic and micro-aerophilic behavior of MTB, the oxygen depletion in bottom sediments and overlying water can be predicted by tracking their position and magnetic strength using a magnetic sensor (Schüler & Frankel, 1999).

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As bio indicator

The origin of life remains one of the greatest enigmas in science, but equally enigmatic is the question, whether life exists elsewhere in the infinite universe. For centuries people have speculated about the possibility of life on Mars knowing about the planet's proximity and similarity to Earth. The ALH84001 meteorite was found in December 1984 in Antarctica. The sample was probably ejected from Mars about 17 million years ago and spent 11 000 years in or on the Antarctic ice sheets. The meteorite ALH84001 is a shocked igneous rock of probable Martian origin. It contains chemically and isotopically heterogeneous carbonate globules (Thomas-Keprta et al., 2000) associated with which are organic and inorganic structures that have been interpreted as possible fossil remains of ancient Martian biota (McKay et al., 1996).

Analysis of ALH84001 revealed some evidence that suggests existence of microbial life on Mars approximately 4 billion years ago (McKay et al., 1996). It was suggested that carbonate globules in meteorite ALH84001 contained the fossil remains of Martian microbes and observed that Martian magnetite was both chemically and physically identical to terrestrial, biogenically precipitated, intracellular magnetites produced by MTB MV-1 (McKay et al., 1996). Specifically, both magnetite populations were single-domain, chemically pure and exhibited a unique crystal habit, truncated hexaoctahedral. They suggested that these magnetite crystals in the Martian meteorite ALH84001 were likely produced by a biogenic process. Moreover, these types of magnetite particles are not known or expected to be produced by abiotic means either through geological processes or synthetically in the laboratory (Thomas-Keprta et al., 2000, 2001). Thomas-Keprta et al. (2000, 2001) argued that these Martian magnetite crystals are in fact magnetofossils. It was suggested that about 25% population of ALH84001 magnetic crystals are identical to biologically produced crystals Thomas-Keprta et al. (2001). Ardelean et al. (2008) also focused on possible contributions of MTB to the terraformation of Mars or other planets. Although, there are credible arguments and supports for both the non-biogenic and biogenic hypothesis for the origin of the magnetite particles in ALH84001 meteorite, yet if it's biological origin is proved, such magnetofossils would constitute evidence of the oldest life forms known.

Perspectives

The above literature demonstrates the tremendous medical, biotechnological, environmental, astrobiological, industrial and nanotechnological potentials of MTBs. Although most of these studies are still at the proof-of-concept stage and it showed only one type of potential application. Yet these findings indicated, in near future, that it would be possible to develop multifunctional magnetosomes for various applications. The biocompatibility results to date are also encouraging, which indicates their positive possibilities as future heroes in medical and nano-sciences. However, numerous fundamental questions, that have remained unsolved thus far, have prevented an application of magnetosomes at the technical scale. There has been no commercial application of MTBs so far, mainly because they are difficult to obtain in large quantity (Lu & Martel, 2006b), due to their fastidious nature. Loosening of magnetosomes and their softness is also a critical issue and a very few species have been be cultured in the laboratory. The isolation of MTBs remains a critical issue. Even to date, there are only two reports in the literature demonstrating the ability to culture these bacteria on solid/agar based media (Naresh et al., 2010; Schultheiss & Schüler, 2003). More research in this field is clearly required to isolate other MTB candidates, to better understand the process of magnetosomes formation and their effect in the host cell or organism. If these obstacles are overcome, MTBs will surely drive future nanotechnology developments!

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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