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Advances in Biomedical Applications of Magnetotactic Bacteria and Their Biosynthesized Magnetic Nanoparticles–Magnetosomes (Postprint)

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Abstract

In recent years, magnetotactic bacteria and their biologically synthesized magnetosomes have gradually gained recognition for their excellent biosafety and have been utilized in bioengineering and medical application research. Compared with artificially chemically synthesized magnetic nanoparticles, magnetosomes extracted from magnetotactic bacteria exhibit advantages such as biomembrane coating, high biocompatibility, uniform particle size, and high magnetism. Due to the chain-like arrangement of magnetosomes within their cells, magnetotactic bacteria possess the ability to swim along magnetic field lines and have also been applied in various research applications. Therefore, this review summarizes the characteristics of magnetotactic bacteria and magnetosomes, with particular emphasis on the latest research progress in their applications in bioengineering and medical fields.

Full Text

Preamble

Magnetotactic Bacteria and Their Biosynthetic Magnetic Nanoparticles–Magnetosomes: Research Progress on Biomedical Applications

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Abstract

In recent years, magnetotactic bacteria and their biosynthetic magnetosomes have gained recognition for their excellent biosafety and have been increasingly utilized in bioengineering and medical applications. Compared with chemically synthesized magnetic nanoparticles, magnetosomes extracted from magnetotactic bacteria offer several advantages, including a biomembrane coating, high biocompatibility, uniform particle size, and strong magnetic properties. Additionally, magnetotactic bacteria themselves have been applied in various studies due to their ability to swim along magnetic field lines, enabled by the chain-like arrangement of magnetosomes within their cells. This review summarizes the characteristics of magnetotactic bacteria and magnetosomes, with particular emphasis on recent research progress in their bioengineering and medical applications.

Keywords: Magnetotactic bacteria; Magnetosomes; Magnetic nanoparticles; Biomedical applications

Introduction

With the advancement of nanotechnology, an increasing number of nanomaterials have been synthesized for healthcare applications. Magnetic nanoparticles, in particular, have found widespread use in modern scientific fields including biomedicine, magnetic fluids, catalysis, magnetic resonance imaging, data storage, and environmental protection [1-5]. Interestingly, compared with chemically synthesized magnetic nanoparticles, a biologically produced magnetic nanoparticle with a biomembrane coating—magnetosomes—has gradually attracted attention and been investigated for various applications [6-8].

Relative to artificially synthesized magnetic nanoparticles, magnetosomes exhibit high yield, good dispersibility, high crystallinity, and stable single magnetic domain crystals, all encapsulated by a biomembrane that confers excellent biocompatibility [9,10]. Magnetotactic bacteria that synthesize magnetosomes possess the ability to align with and swim along magnetic field lines due to the intracellular chain-like arrangement of magnetosome crystals, making them valuable for diverse applications. This review focuses on recent advances in the properties of magnetosomes and magnetotactic bacteria, as well as their latest applications in drug targeting, tumor therapy, biological separation, and imaging.

Background and Properties of Magnetosomes

In 1975, Blakemore [8] reported in *Science* on a magnetically sensitive bacterium capable of swimming along magnetic field lines, which he named magnetotac-

tic bacteria (MTB). Through electron microscopy, Blakemore [8,11] first observed magnetite magnetosomes within these bacteria. Magnetotactic bacteria are widely distributed in oxic-anoxic interfaces (OAI) of freshwater and marine environments, as well as in moist sediments [12]. Although their isolation and purification remain challenging, eleven strains have been successfully cultured axenically, serving as the primary research models for investigating magnetotaxis and magnetosome synthesis [13-18].

Magnetosomes are magnetic particles synthesized intracellularly by magnetotactic bacteria. Their composition is relatively uniform, consisting primarily of Fe O , with some containing Fe S . With the exception of one strain discovered by Bazylinski et al. [19] in 1995 that could synthesize both types simultaneously, most magnetotactic bacteria produce only one type of magnetosome. Magnetosome crystals typically range from 35–120 nm in size, classifying them as stable single-domain particles [20] with high coercivity [21]. In most bacterial species, magnetosomes arrange in chains with inter-particle distances of 3–18 nm [22,23].

The biomineralization of magnetosomes is a complex process that can be divided into four main steps: cytoplasmic membrane invagination, iron ion uptake, crystal nucleation and growth, and chain assembly [24-26]. Magnetosomes are coated with a biomembrane composed primarily of lipids and containing 20–40 different proteins [27,28]. These membrane proteins are not only crucial for understanding magnetosome synthesis mechanisms but also highly relevant for applications. Unlike synthetic magnetic nanoparticles, magnetosomes can be functionalized through genetic engineering and chemical conjugation to express specific proteins or antibodies on their surface, thereby imparting additional functionalities.

Currently, magnetosomes used in nanomedical research are primarily derived from two magnetotactic bacterial strains: AMB-1 and MSR-1. MSR-1 can now be cultivated at large scale in fermenters, enabling industrial-scale production of magnetosomes [29,30].

Applications of Magnetotactic Bacteria

The ability of magnetotactic bacteria to swim along magnetic field lines enables their use as bacterial microrobots for targeted therapy, enhancing the precision of drug and physical treatments while reducing drug dosage. Martel et al. utilized polar magnetotactic bacteria MC-1 attached to 3 m polystyrene microspheres and controlled their movement through a micro-electromagnetic array system [31]. They also demonstrated micro-assembly and manipulation of 5,000 magnetotactic bacteria to successfully construct a micro-pyramid from micron-scale glass bricks [32]. Felfoul et al. [33] exploited the magneto-aerotactic properties of these bacteria, injecting drug-loaded MC-1 bacteria near tumors. Through magnetic field navigation, 55% of the bacteria penetrated tumor hypoxic regions, thereby improving the therapeutic efficacy of nanoliposomal drug delivery.

Chen et al. [34] constructed a *Staphylococcus aureus* separation system by modifying the surface of magnetotactic bacterium MO-1 with rabbit anti-MO-1 polyclonal antibodies. Experiments demonstrated that magnetotactic bacteria could carry *S. aureus* to designated locations under magnetic control, laying the foundation for subsequent pathogen detection. In follow-up studies, Chen et al. [35,36] investigated the bactericidal effects of MO-1 against *S. aureus*, achieving significant antimicrobial efficacy in animal experiments through both alternating magnetic field hyperthermia and oscillating magnetic field-mediated mechanical forces.

Magnetosomes for Tumor Hyperthermia

Magnetic particles exposed to alternating magnetic fields generate heat through magnetic hysteresis loss and eddy current effects, raising the temperature of surrounding tissues and inducing tumor cell apoptosis [37,38]. Like other magnetic nanoparticles, magnetosomes release heat under alternating magnetic fields. Timko et al. [39] found that magnetosomes exposed to a magnetic field of 5 kA/m at 750 kHz exhibited a specific absorption rate (SAR) as high as 1.7 × 10 W/kg, demonstrating excellent magnetothermal conversion capability. MARTINEZ-BOUBETA et al. [40] improved the shape of artificially synthesized crystals by mimicking bacterial magnetosomes, comparing single-domain cubic magnetic nanoparticles with similarly sized spherical particles. They found that cubic nanoparticles exhibited higher magnetothermal conversion efficiency, which was confirmed through Monte Carlo simulations at the atomic level showing that cubic particles possess greater anisotropy and a stronger tendency for chain-like arrangement—factors contributing to their higher SAR values.

Magnetosome properties vary depending on bacterial culture conditions [41], which consequently affects SAR values and shape characteristics [42]. When AMB-1 bacteria were cultured in standard medium supplemented with additional vitamins or ferric quinate, the average magnetosome diameter increased from 47 nm to 52 nm and 58 nm, respectively, with corresponding increases in SAR. Le et al. [43] coated magnetosomes with poly-L-lysine, achieving a SAR of 4 × 10 W/kg, compared to only 2.6 × 10 W/kg for chemically synthesized iron oxide particles. Additionally, doping magnetosomes with cobalt has been reported to increase coercivity and thereby enhance SAR [44]. Experiments showed that when exposed to an alternating magnetic field of 80 mT at 183 kHz, cobalt-doped magnetosome chains exhibited SAR values increased from 4 × 10 W/kg to 5 × 10 W/kg. Studies on AMB-1 indicate that heat generation in alternating magnetic fields primarily originates from magnetic moment reversal and physical rotation of magnetosome chains [45,46].

In tumor hyperthermia, elevating tumor temperatures to 41–46 °C alters biomembrane function and status, activates lysosomal activity, and inhibits DNA, RNA, and protein synthesis, thereby killing tumor cells [47,48]. When cancer cells were co-incubated with magnetosomes and exposed to a 198 kHz magnetic field at 20–30 mT intensity, cancer cell proliferation was inhibited,

with chain-like magnetosomes showing superior antitumor effects [49]. Alphandéry et al. [43,50] injected chain-like magnetosomes extracted from AMB-1 into subcutaneous tumors in mice. Through alternating magnetic field heating at 100 kHz and 60 mT, tumor temperatures reached over 50 °C, and three 20-minute hyperthermia sessions resulted in complete tumor disappearance. To further improve safety, Alphandéry et al. coated magnetosome crystals with poly-L-lysine for hyperthermia experiments. Under a 202 kHz, 27 mT magnetic field, tumor temperatures rose to 42 °C, and tumors completely disappeared 68 days after tumor cell inoculation, with mice surviving up to 350 days post-inoculation [51].

Photothermal therapy represents another approach to tumor hyperthermia, where nanoparticles absorb light energy and convert it to heat, raising tumor temperatures for therapeutic effect [52]. Studies have shown that iron oxide nanoparticles irradiated with near-infrared light achieve good results in both cellular and mouse models [53,54]. Magnetosomes, primarily composed of Fe O , can similarly convert light energy to heat. Intratumoral injection of 0.4 mg magnetosome solution followed by 808 nm infrared irradiation at 1.5 W/cm² for 3 minutes elevated tumor temperatures to 57 °C, resulting in complete tumor disappearance [55]. Plan et al. [56] modified magnetosomes with RGD peptides and found that their photothermal efficiency was 100–1000 times higher than their magnetothermal efficiency in cellular experiments.

Magnetosomes for Drug Targeting

Magnetosomes exhibit excellent biocompatibility and low toxicity while being responsive to external magnetic fields, making them ideal drug carriers [57]. Their intact biomembrane coating exposes numerous amino groups, enabling conjugation of amino-containing drug molecules via bifunctional linkers. Additionally, various functional groups on the magnetosome membrane can be used to attach other molecules such as targeting ligands and imaging probes, conferring diagnostic and therapeutic functionalities [58,59].

Sun et al. [60] conjugated doxorubicin (DOX) to magnetosome particles (DBMs) using glutaraldehyde. In vitro cytotoxicity assays demonstrated that DBMs exhibited toxicity against HL60 and EMT-6 cells through proliferation inhibition and c-myc expression suppression, consistent with DOX' s antitumor properties. Animal experiments revealed tumor inhibition rates of 86.8%, 78.6%, and 4.3% for DBMs, DOX, and magnetosomes alone, respectively, in H22 tumor-bearing mice, with mortality rates of 20%, 80%, and 0%. While both DBMs and DOX effectively inhibited tumor growth, DBMs showed significantly lower toxicity than free DOX [61]. Guo et al. [62] found that poly-L-glutamic acid modification of magnetosomes increased DOX loading efficiency by 81.7% and enhanced cytotoxicity against HepG2 and MCF-7 cells.

Tang et al. [63] developed a gene vaccine (BMP-V) using magnetosomes as a carrier composed of secondary lymphoid tissue chemokine, HPV-E7, and pSLC-

E7-Fc recombinant DNA. After 10 minutes of exposure to a 600 mT static magnetic field, BMP-V achieved effective transfection both in vitro and in vivo. In a mouse tumor model, subcutaneous injection of BMP-V followed by magnetic field exposure induced systemic HPV-E7-specific immunity and inhibited tumor growth. Dai et al. [64] constructed a BMs–PEI–siRNA complex using polyethyleneimine (PEI) as a crosslinker, which efficiently delivered siRNA into tumor cells and significantly inhibited HeLa cell growth. These results demonstrate that magnetosomes can serve as gene carriers to induce systemic immune responses, offering new strategies for gene therapy and genetic vaccination.

Cheng et al. [65] developed a targeted thermosensitive combination drug delivery system based on magnetosomes, complexing DOX, heat shock protein HSP70, shPlk1, and magnetosomes to simultaneously provide chemotherapy, gene therapy, and hyperthermia. In vitro antitumor experiments showed that this composite drug exhibited significantly enhanced tumor inhibition under alternating magnetic fields compared to other treatments.

Magnetosomes for Biomedical Imaging

Purified magnetosomes with high crystallinity and good dispersibility in physiological environments serve as excellent contrast agents. Studies have confirmed that magnetosomes exhibit T transverse relaxivity at 17.2 T that is four times higher than commercial iron oxide contrast agents [66]. Additionally, fluorescent fusion magnetosomes can be used for both magnetic resonance imaging (MRI) and near-infrared fluorescence (NIRF) imaging [67,68].

Tang et al. [69] labeled magnetosomes from *Magnetospirillum* MSR-1 with a red fluorescent membrane probe (DiI) and imaged the liver, stomach, intestine, lungs, and spleen in mice using fluorescence imaging. Boucher et al. [70] injected RGD-modified magnetosomes intravenously into mice with glioblastoma, observing rapid accumulation in tumor regions within 2 hours and enhanced imaging at tumor sites via MRI, validating the feasibility of bioengineered MRI molecular imaging probes. Schwarz et al. [71] demonstrated that magnetosomes can label hematopoietic stem cells and dendritic cells for MRI-based tracking. Benoit et al. [72] directly injected low-magnetism AMB-1 magnetotactic bacteria labeled with Cu into tumor-bearing mice, with positron emission tomography (PET) showing AMB-1 accumulation in tumor regions 4 hours post-injection while decreasing in other organs. The magnetosomes within these bacteria also enhanced T -weighted MRI contrast. Xiang et al. [73] functionalized magnetosomes with P75 peptide for targeting EGFR and HER2, showing that modified magnetosomes primarily accumulated in tumor regions with minimal presence in liver and kidneys, significantly enhancing MRI tumor imaging and providing a potential tool for cancer diagnosis and tracking.

Magnetosomes for Biological Separation

Magnetosomes possess large surface areas, high magnetization, and easily modifiable surface biomembranes with abundant functional groups, making them widely applicable for protein separation, pathogen concentration, and purification [74,75].

Huang et al. [76] used magnetosomes for rapid enrichment and detection of phosphopeptides. Without modification, magnetosomes could immobilize Fe^{3} and Zr on their membrane to enrich phosphopeptides via interaction with positively charged metal ions. Magnetosomes could also directly enrich specific phosphopeptides from -casein digests through direct interaction, offering a new approach for phosphopeptide purification. Wacker et al. [77] modified magnetosomes with antibodies for antigen detection via immuno-PCR technology, achieving a detection limit of 320 pg/mL for hepatitis B surface antigen (HBsAg)—approximately 100-fold improvement over enzyme-linked immunosorbent assays. Li et al. [78] constructed magnetosome-polyclonal antibody complexes that specifically captured *Salmonella* with superior sensitivity and shorter detection times compared to conventional methods. Xu et al. [79] engineered a recombinant magnetotactic spirillum by fusing functional genes with magnetosome membrane protein genes to functionalize magnetosomes, achieving capture of 1×10 target cells per milligram.

Conclusions and Outlook

In recent years, numerous nanomaterials have been developed for biomedical applications. As biomineralized magnetic nanoparticles, magnetosomes offer advantages over synthetic particles including uniform size distribution, homogeneous composition, and biomembrane coating, making them widely applicable in diagnostics, therapeutics, and detection. Despite these benefits, magnetosome research spans multiple disciplines and faces several challenges that must be addressed:

1. **Scaling up production to industrial levels.** Industrial-scale production is a prerequisite for practical magnetosome applications. Significant differences exist between laboratory and industrial production methods, requiring the development of industrial cultivation equipment and optimization of culture conditions based on existing laboratory experience.
2. **Comprehensive safety evaluation.** Biomedical materials require extensive safety validation before application. While several studies have reported low toxicity of magnetosomes, comprehensive assessment of long-term toxicity and other safety parameters is still needed.
3. **Enhancing functionality.** Functionalization through magnetosome membrane modification can improve properties such as dispersibility and in vivo retention time, expanding their therapeutic potential.

With continued research advances, magnetosomes are poised to transition from laboratory to clinical applications, ultimately benefiting human health.

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