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REVIEW

Physiological origin of biogenic magnetic nanoparticles in health and disease: from bacteria to humans

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Abstract: The discovery of biogenic magnetic nanoparticles (BMNPs) in the human brain gives a strong impulse to study and understand their origin. Although knowledge of the subject is increasing continuously, much remains to be done for further development to help our society fight a number of pathologies related to BMNPs. This review provides an insight into the puzzle of the physiological origin of BMNPs in organisms of all three domains of life: prokaryotes, archaea, and eukaryotes, including humans. Predictions based on comparative genomic studies are presented along with experimental data obtained by physical methods. State-of-the-art understanding of the genetic control of biomineralization of BMNPs and their properties are discussed in detail. We present data on the differences in BMNP levels in health and disease (cancer, neurodegenerative disorders, and atherosclerosis), and discuss the existing hypotheses on the biological functions of BMNPs, with special attention paid to the role of the ferritin core and apoferritin.

Keywords: biogenic magnetic nanoparticles, biomineralization, ferritin, magnetoferritin, genetic control, neurodegenerative disorders, cancer

Introduction

Living organisms have a genetically programmed ability to synthesize a wide spectrum of minerals and other inorganic substances in a process known as biomineralization.[1–3] Biosynthesis of so-called biogenic magnetic nanoparticles (BMNPs) from inorganic iron compounds is of particular interest, because of the magnetic properties of BMNPs.

BMNPs have been the object of intensive research since 1975, when they were first detected in magnetotactic bacteria (MTB). MTB exhibit magnetotaxis, or movement in response to a magnetic field, which makes them migrate along geomagnetic field lines.[4,5] In later studies, BMNPs were found in a large number of organisms of all three domains, ie, prokaryotes, archaea, and eukaryotes (Table 1).

Formed in the process of biomineralization, crystalline BMNPs are nanocrystalline forms of antiferromagnets or ferrites, such as magnetite, maghemite, or greigite (Table 2).[6–9] From the point of view of magnetic properties, there are two types of BMNPs, with and without remanent magnetization: those without remanent magnetization include antiferromagnetic BMNPs and ferrite BMNPs in the superparamagnetic (SPM) phase; remanent magnetization is displayed by ferrite BMNPs in single-domain (SD) and multidomain (MD) states. As a rule, ferrite BMNPs, besides being very sensitive to applied magnetic fields, are permanent nanomagnets, showing remanent magnetization in a wide temperature range (Table 2) and generating a stray

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Table 1 Properties of BMNPs in different organisms

Organism	Mineral/amorphous material	Size (nm)	Shape-controlled (+), other (–)	Domain structure	Localization			References
					Intracellular (+), extracellular (–)	In chain (+), other (–)	Membrane-bound (+), other (–)	
Magnetotactic bacteria	Magnetite and/or greigite	10–40, 35–120*	+	SD	+	+	+	4, 5, 9, 26, 27, 69–71
Bacteria with MSIs	Magnetite, greigite, lepidocrocite, or amorphous materials	–	–	SD, SPM	+, –	+, –	+, –	39
Archaea	Magnetite	~100*	–	SPM	+	–	–	39
Algae protists	Magnetite			SD				41
Worms	Magnetite	~20		SPM				35
Mollusks	Magnetite			SD				9, 72
Armored snails	Greigite			SD				42
Honeybees, butterflies, ants	Magnetite	500*–1,000*	–	SD	+	–		33, 44, 45
Termites	Magnetite	~10	–	SD, SPM		–		34
Lobster	Magnetite?			SD				46
Newts	Magnetite			SD				47
Fish	Magnetite	25–60	–	SD		+		36, 48–53, 73
Sea turtles	Magnetite?			?				54
Birds	Magnetite, maghemite	~1,000*	+, –	SPM, SD	+	+, –	+	38, 55, 74, 75
Bats	Magnetite?			SD				59
Dolphins, whales	Magnetite			SPM, SD, MD				60
Humans	Magnetite, maghemite hematite	<1,000	–	SPM, SD, MD	+	+	+	61–63, 76

Note: *Size of BMNP clump, not single NP.
Abbreviations: BMNPs, biogenic magnetic nanoparticles; MSIs, magnet-sensitive inclusions; SD, single-domain; SPM, superparamagnetic; MD, multidomain.

Table 2 Magnetic iron minerals found in BMNPs

Oxide	Chemical structure	Magnetic character	T_C (K)	Saturation magnetization ($A \cdot m^2 kg^{-1}$)	References
Magnetite	Fe_3O_4	Ferrimagnetic	850	92–100	77
Maghemite	γ-Fe_2O_3	Ferrimagnetic	820	60–80, 56–74	81
Hematite	α-Fe_2O_3	Ferrimagnetic	956	0.3–0.4	82
Ferrihydrite	$Fe_5HO_8 \cdot 4H_2O$	Antiferromagnetic	~350[a–c]	0.1–1	83, 84
Wüstite	FeO	Antiferromagnetic	~203[a]	–	84
Greigite	Fe_3S_4	Ferrimagnetic	<625	59	85
Goethite	α-FeOOH	Antiferromagnetic	400[a]	0.01–1	9, 84

Notes: [a]T_N, Néel temperature, which describes transition from paramagnetic to antiferromagnetic phase; [b]two-line, X-ray diffractometry of ferrihydrite crystals usually shows two or six lines;[84] [c]at 300 K.
Abbreviations: BMNPs, biogenic magnetic nanoparticles; T_C, Curie temperature.

magnetic field, which in their vicinity is approximately four orders of magnitude stronger than the magnetic field of the Earth. The puzzle of the role of BMNPs in living organisms has not been solved to date, and it remains to be established whether they are involved in any biological functions other than the navigation of MTB under a geomagnetic field. Geomagnetic navigation of some migratory birds and other animals can also be explained by an alternative cryptochrome model.[10]

The genetic control of BMNP biomineralization has only been studied in detail in MTB, with the corresponding biomineralization proteins identified.[11–15] However, the physiological origin of BMNPs in other organisms, including humans, has attracted much attention for more than 30 years. The problem is very important, since elevated BMNP levels are associated with a number of human diseases, including neurodegenerative disorders and cancer.[16–21] Until recently, there had been only one hypothesis: that ferrihydrite present in the ferritin core might be a precursor of biogenic magnetite. Indeed, ferrihydrite has been proved experimentally to be a transient mineral in the formation of magnetite in cells of MTB[22] and in chiton teeth.[9] Still, ferritin has not been found experimentally to participate in biomineralization of BMNPs. Another hypothesis on the physiological origin of BMNPs in prokaryotes, archaea, and eukaryotes, including humans, recently predicted by bioinformatic methods, postulates a common genetic mechanism of BMNP biomineralization based on homologues of biomineralization proteins of MTB.[23] In this review, we outline experimental and theoretical investigations of the role of biomineralization proteins, especially ferritin, in the physiological origin of BMNPs, and we point out the importance of environmental pollution only as another source of MNPs in the human body. Our intention is to aid in better understanding of the cellular production of BMNPs for efficient treatment of a number of diseases representing an urgent problem that our society is facing now and will face in the future. In the following sections, we discuss the physicochemical properties of BMNPs, the genetic control of BMNP biomineralization, the physicochemical characteristics of natural and synthetic ferritin, and the question of whether the ferritin core is a precursor of BMNPs.

Physicochemical properties of BMNPs

BMNPs in MTB magnetosomes

MTB synthesize NPs of magnetic crystals enclosed in a membrane, a structure known as a magnetosome vesicle. Single-crystal magnetite or greigite is incorporated in the magnetosome membrane, which besides phospholipids contains a number of magnetosome-associated proteins (Figure 1A).[12,24,25] Magnetosomes in MTB are arranged in chains,[4–6] bearing dozens of separate magnetite NPs of size 10–135 nm[26,27] (see Figure 1B and C). These BMNP chains follow the long axis of the bacterium, and are attached to its membrane.[11] The NPs in a chain may have different crystal geometries, including octahedral, cubic, hexagonal prismatic, bullet, teardrop, and arrowhead morphologies (see examples in Figure 1D).[28–30] BMNPs are not the byproduct in MTB, but the process of biomineralization of BMNPs is energy-consuming.[31]

BMNPs in bacteria, archaea, and multicellular organisms

BMNPs have been observed in many prokaryotes, archaea, and eukaryotes (Figure 2, Table 1).[4–7,9,32–40] However, as already mentioned, for the first time BMNPs have been revealed in MTB that are characterized by the ability to "taxi" or navigate under a geomagnetic field. That is why historically the idea of magnetotaxis was transformed into an

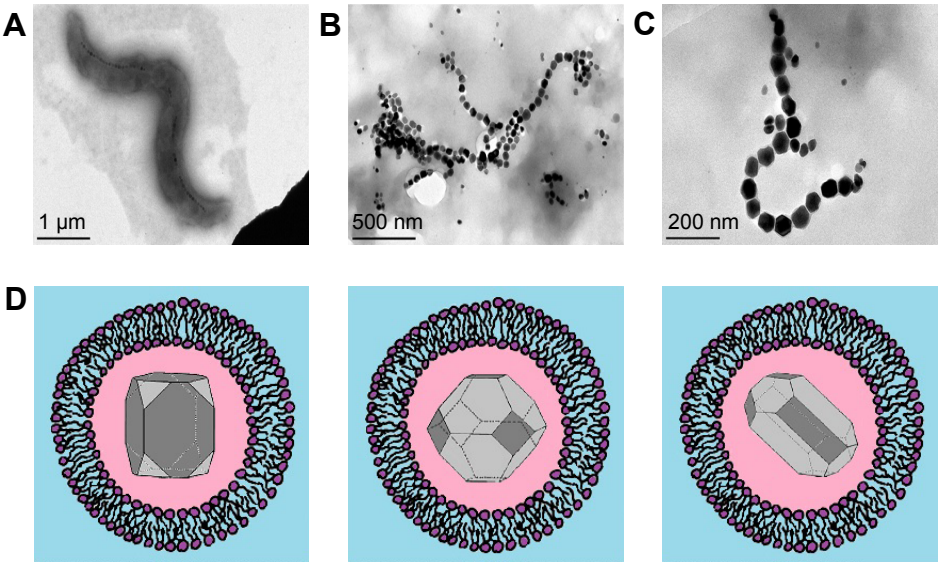

Figure 1 (**A**) TEM of magnetotactic bacterium (*Magnetospirillum* strain AMB1); (**B**) BMNP chain in a magnetotactic bacterium; (**C**) zoomed BMNP chain, showing several hexagonal grains (TEM courtesy of B Leszczyński); (**D**) schematic representation of BMNPs in a magnetosome vesicle. BMNPs of typical shapes observed in magnetotactic bacteria, each surrounded by lipid bilayers.
Abbreviations: TEM, transmission electron microscopy; BMNP, biogenic magnetic nanoparticle.

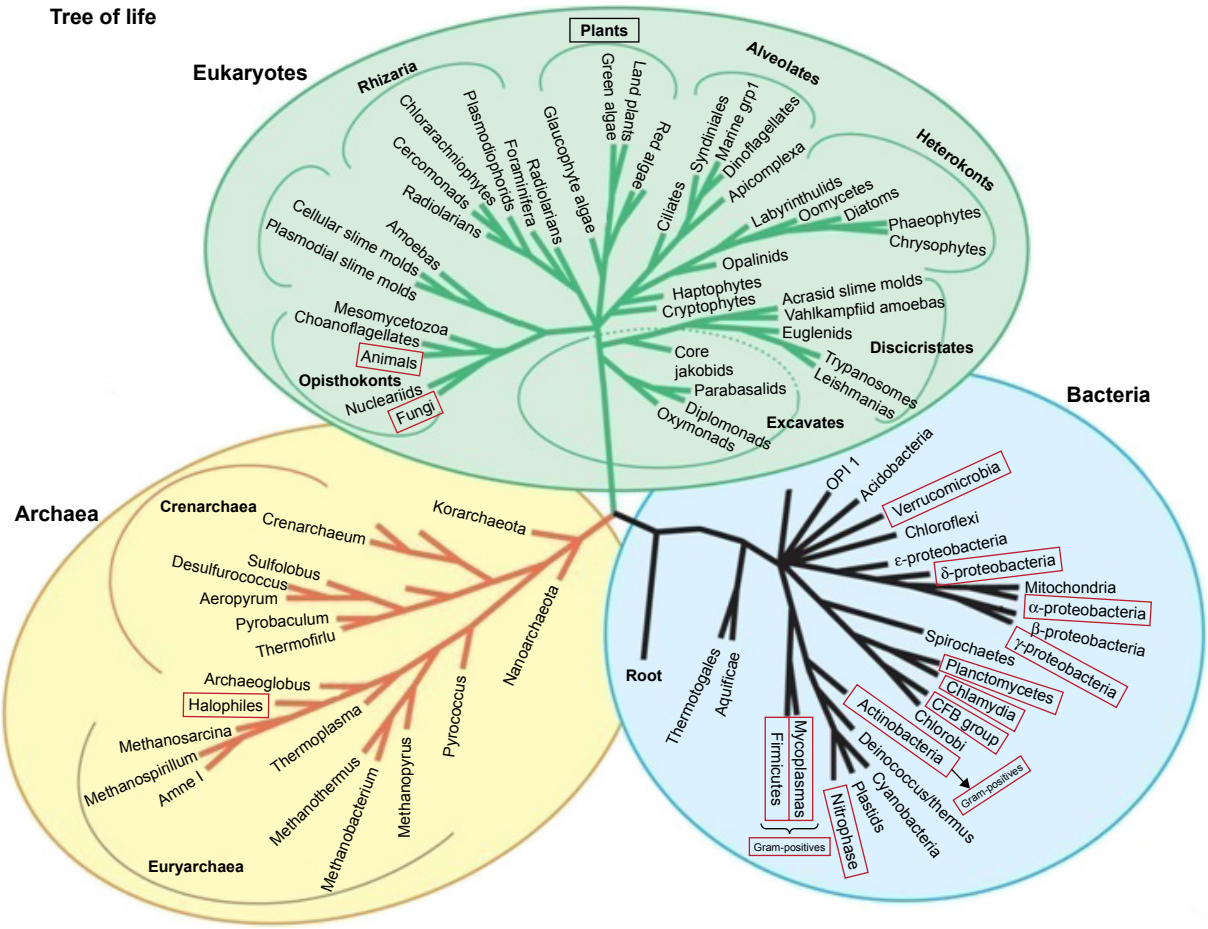

Figure 2 Taxa in which BMNPs have been observed experimentally.
Notes: Red boxes, BMNPs found in representatives of the given taxa; black rectangle, reported presence of biogenic magnetite in an unclear form (either phytoferritin or botanic BMNPs).
Abbreviation: BMNPs, biogenic magnetic nanoparticles.

idea of magnetoreception as a basic function of BMNPs in other organisms. However, many bacteria with BMNPs[39] are immovable, and some multicellular organisms with BMNPs are not able to migrate long distances.[35] Consequently, the question about the physiological origin of BMNPs and properties of BMNPs in organisms should be considered from a broader aspect, independently of their ability to navigate Earth's magnetic field.

More specifically, BMNPs have been found experimentally in algae, protists,[41] worms,[35] chitons,[37] armored snails,[42] ants, butterflies,[43–45] honeybees,[33,44] termites,[34] lobster,[46] newts,[47] fish,[36,48–53] sea turtles,[54] birds,[38,55–58] bats,[59] dolphins, whales,[60] and humans.[8,16,17,22,61–67] Table 1 provides general information on BMNPs in different organisms.

The phenotypic manifestation of BMNPs in multicellular organisms, archaea, and non-MTB differs in many ways from that of BMNPs in MTB. As a rule, BMNPs in multicellular organisms vary in shape, size, and other properties, and are not enclosed in magnetosome vesicles.[39,68] In archaea, in which the surroundings of BMNPs have been adequately investigated, magnet-sensitive inclusions have been found, which are surrounded by a homogeneous matrix with organic (mainly protein) components.[39] The absence of vesicles or a similar organic matrix consisting of protein filaments around magnetite BMNPs[68] has also been observed in human cells. In multicellular organisms, most BMNPs display remnant magnetization and are SD structures. However, MD and/or SPM phases have also been observed in some multicellular organisms (Tables 1 and 2).

In magnetite, transition from the SPM to SD phase typically occurs in the size range 25–30 nm,[77] and transition from SD to MD around 70 nm.[78] Magnetostatic interactions between magnetite NPs reduce the SPM-to-SD transition size in chains of SD grains; at the same time, the SD-to-MD transition size increases as a result of this interaction, which significantly extends the size range of the SD phase.[78] This is due to magnetostatic interaction fields wherein the largest magnetosome crystals observed in living bacteria (250 nm long with an aspect ratio of 0.84)[79] have an SD structure;[80] without magnetostatic interaction, they would be in an MD state.

BMNPs in normal human organs and tissues

BMNPs have been found in various human organs, including heart, liver, spleen,[64,86,87] adrenal glands,[65] ethmoid bone,[88] and brain.[8,20,61,89,90] In terms of phenotypic manifestation, human BMNPs differ in many ways from those observed in MTB. Separate single-crystal BMNPs and BMNP clumps of rather irregular shape have been observed in human tissues. Clumps are arranged in long chains[61,91] associated with the membrane. A chain is several micrometers long and comprises up to 80 NPs.[61] Magnetite clumps in tissues are aggregates of single-crystal particles that have remnant magnetization at 150 K. This excludes magnetic contribution from ferritin (which is superantiferromagnetic and behaves as a paramagnet at this temperature), diamagnetic bulk tissue, and paramagnetic (PM) ions.[19] Unlike MTB, human BMNPs have a wide size range and are observed in all phases of growth. Consequently, SPM and SD phases coexist,[8] and human BMNPs vary in shape, size, and other properties. Also, the number of BMNPs in normal human tissues varies widely. For example, the number of MNPs per gram of tissue in pia and dura ranges from 5 million to 100 million.[61]

In summary, there are similarities between the production of BMNPs in humans and MTB production of magnetite NPs, organized in chains (see Figures 1, 3, and 4) of dozens of NPs, attached to the cell membrane. There are also different features of BMNPs in MTB and humans. BMNPs in humans are not characterized by control of morphology or size and are not surrounded by lipid magnetosome vesicles.

BMNPs in human disease

The problem of the physiological origin of BMNPs gains in importance in light of the discovery of BMNPs in a number of human organs and tissues[61,91] and their observed relation to neurodegenerative disorders,[16,17,19,67] cancer (Figure 3),[20,21] and atherosclerosis (Figure 4).[92] Concentrations of BMNPs in inflammation zones in neurodegenerative diseases[93–97] and cancer[8,20] are higher than those observed in normal tissues.

Therefore, normal iron homeostasis is disrupted in the brain in many neurodegenerative diseases.[20] BMNPs (magnetite and maghemite) are detected in senile plaques and tau filaments in brain tissue affected by neurological and neurodegenerative diseases, such as epilepsy and Alzheimer's disease (AD).[19,66,98] Concentrations of magnetite are significantly higher in samples of AD tissue than in healthy tissue.[19] The total concentration of biogenic magnetite is 15 times greater in the AD brain than controls in some cases.[16] Magnetite NPs are present in amyloid-β (Aβ) plaque cores, and are directly bound into fibrillar Aβ.[99] Magnetite NPs have been found to be directly associated with AD plaques and tangles.[66,89,99,100] In vitro experimental data show that magnetite enhances the toxicity of Aβ.[101]

BMNPs have been detected in various human tumor tissues, including melanoma, breast, ovary, testicle, sarcoma, meningioma, glioblastoma, astrocytoma, glioma, and metastasis.[20] An elevated quantity of BMNPs is observed in tumor samples in comparison with normal ones. For example,

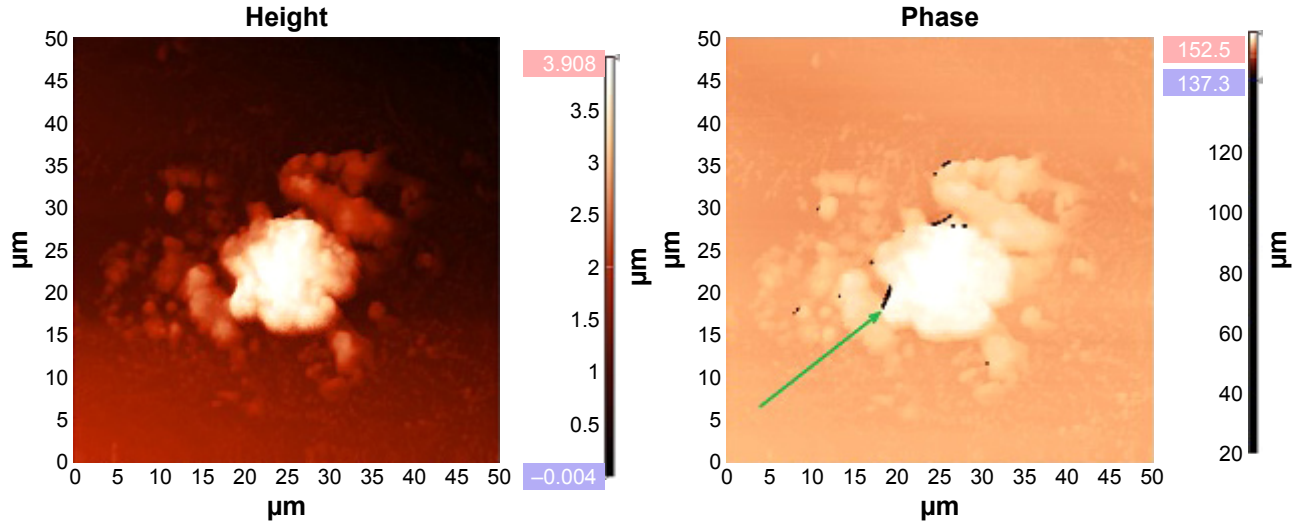

Figure 3 Ehrlich carcinoma cell.
Notes: AFM (left), MFM (right). Data from Chekchun et al.[21] MFM shows BMNPs in the form of dark spots arranged in chains (arrow).
Abbreviations: AFM, atomic force microscopy; MFM, magnetic force microscopy; BMNPs, biogenic magnetic nanoparticles.

human meningioma brain-tumor tissues contain approximately ten times the concentration of BMNPs of nontumor hippocampus.[8]

Magnetic force microscopy (MFM) reveals BMNPs arranged in chains of various lengths up to several microns long (see the MFM images in Figures 3 and 4). Both biogenic and anthropogenic origins of MNPs are found in human tissues.[102,103] The presence of BMNPs can lead to increased accumulation of MNPs, due to magnetic dipole–dipole interaction between biogenic and anthropogenic MNPs. This is important in connection with the influence of polluted urban environments on human health.[102]

Genetic control of biomineralization of BMNPs

Detection of elevated levels of BMNPs in disease raises questions. Is elevated BMNP production the cause or consequence of disease? What genes are controlling this process in humans? In perspective, the answers to these questions would result in new methods of treatment and diagnostics

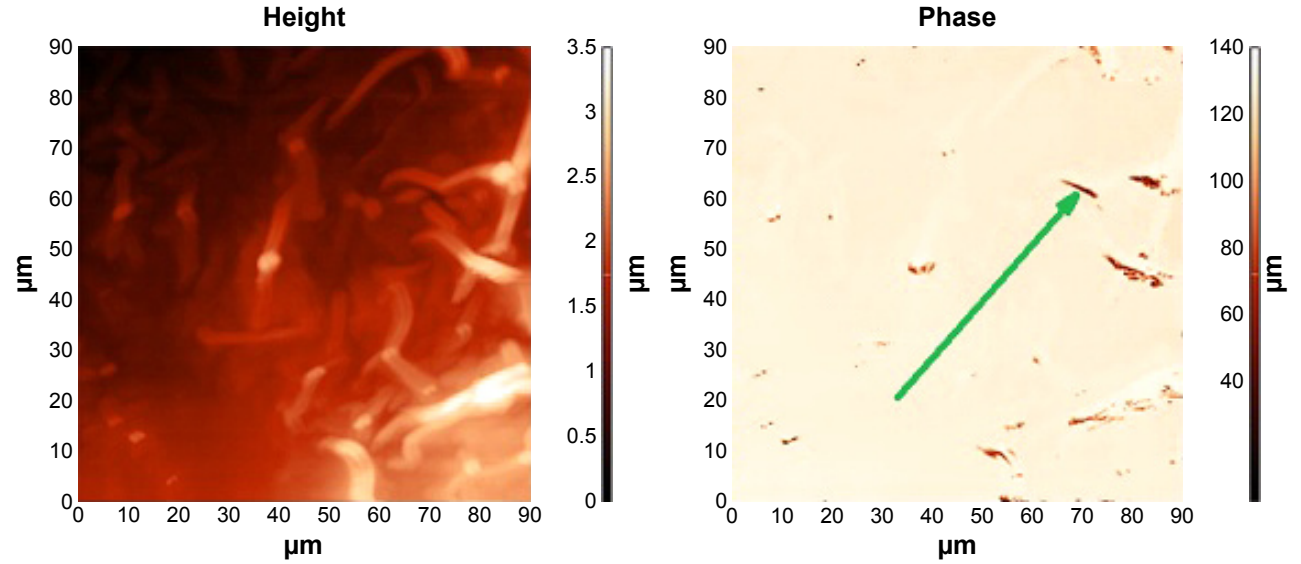

Figure 4 Fragment of an atherosclerotic plaque of mixed composition.
Notes: AFM (left), MFM (right). MFM shows BMNPs in the form of dark spots arranged in chains (arrow). There were no bacteria-like magnetosome BMNPs, but alignment of the BMNPs is visible along the plaque surface. Samples of atherosclerotic vessels were extracted from iliac artery during shunting surgery.
Abbreviations: AFM, atomic force microscopy; MFM, magnetic force microscopy; BMNPs, biogenic magnetic nanoparticles.

of cancer, atherosclerosis, and neurodegenerative disorders, with application of advances in genetic therapy and more sensitive specialized analytical methods. Besides, revealing the genetic mechanisms of biomineralization of BMNPs in bacteria would allow the spread of applications of bacteria with natural ferrimagnetic properties as vectors for magnetic field-assisted drug delivery systems,[104] including non-MTB.[105] For example, recent achievements have demonstrated experimental transfection of human mesenchymal stem cells with the *MMS6* gene of *Magnetospirillum magneticum* AMB1 and bioassimilated synthesis of intracytoplasmic MNPs by mammalian cells.[106]

Biomineralization proteins of MTB

To date, genetic control of the synthesis of BMNPs has only been studied experimentally in MTB,[11–15] where it appears to be strictly regulated by the properties and structural organization of the BMNPs.[11,12] Most of the magnetosome-associated proteins are encoded in the magnetosome island, in MamGFDC, Mms, and MamAB operons.[107] Also, the shape and size of mature magnetite NPs (Figure 1), precisely defined for each strain of MTB, are a manifestation of genes of the magnetosome island.[11,29,30,108]

There are two functional classes of proteins of the MTB magnetosome island (Table 3): proteins indispensable for the process of biomineralization of BMNPs, and other proteins, including regulatory proteins, which exercise strict genetic control of size distribution, species-specific morphologies, and localization of single-crystal magnetite NPs in the cell of a magnetotactic bacterium and proteins with unknown functions or of no effect on BMNP biomineralization.[1,11,12] The loss of the magnetosome island leads to a nonmagnetic phenotype of MTB demonstrating its key role in the biogenesis of BMNPs.[11,97,109–113] Figure 5 shows the participation of proteins of a magnetosome island in the biomineralization of BMNPs in a magnetotactic bacterium. The magnetosome vesicle represents a unique pool providing favorable chemical surroundings for magnetite crystal growth. Black hexagonal symbols represent BMNP crystal growth inside magnetosome vesicles (Figure 5). The magnetosome membrane contains the magnetosome-associated Mam and Mms proteins of the magnetosome island (Figure 5).

The protein MamA (which is known also as Mms24 or Mam22) takes part in the activation of BMNP biomineralization and formation of magnetosome vesicles.[26,110] The proteins MamB and MamM are transporters of Fe^{2+} and other cations, such as Co^{2+}, Zn^{2+}, and Cd^{2+}. The proteins MamB and MamM take part in the formation of BMNP crystals.[11,107,109–113] It has been proved that mutant MTB lacking MamA, MamE, MamO, MamB, MamM, or MamN proteins can form only empty magnetosome vesicles without BMNPs.[11,107,109–113] That is why these proteins are indispensable for the process of biomineralization of BMNPs in MTB. The proteins MamK and MamJ take part in the formation of linear chains of BMNPs.[11,107,109–114] Proteins indispensable for the process of biomineralization of BMNPs have been studied,[26,199,110] and also regulatory proteins of the magnetosome island.[107,109,111,112] Figure 5 depicts the biomineralization of BMNPs in MTB and specifies the localization of biomineralization proteins.

Human homologues of MTB proteins involved in BMNP biomineralization

Comparative genomic studies have been carried out in search of common ways of genetic regulation of BMNP biomineralization in both prokaryotes and eukaryotes, including humans.[23,115] Sequence alignment of human proteins with the magnetosome-island proteins of bacteria *M. gryphiswaldense* have shown significant similarities with proteins indispensable for magnetite biomineralization.[23] Of the 17 regulatory proteins of the magnetosome island, only one, MamK, responsible for the formation of BMNP chains, has a human homologue.[23] This is consistent with the phenotypic manifestations of BMNPs in MTB and in humans. Chains of BMNPs have been observed experimentally in human tissues in MFM studies (Figures 3 and 4).

Table 3 Functional classes of proteins encoded by genes in the magnetosome island[26,30,107,109–113]

Functions of proteins in biomineralization of BMNPs	Proteins of the magnetosome island	References
Proteins indispensable for biomineralization of BMNPs	MamB, MamM, MamA, MamE, MamO, MamN	11, 107, 109–113
Regulatory proteins responsible for		11, 107, 109–113
• vesicle formation	MamQ, MamL	11, 107, 109–113
• magnetosome-chain formation	MamJ, MamK	11, 107, 109–113
• quantity, shape and size of Fe_3O_4 particles	MamF, MamD, MamT, MamP, MamR, MamS, Mms6	30, 11
Proteins with unknown functions or of no effect on BMNP biomineralization	MamH, MamX, MamY, MamZ, MamC, MamG	11, 113

Abbreviation: BMNPs, biogenic magnetic nanoparticles.

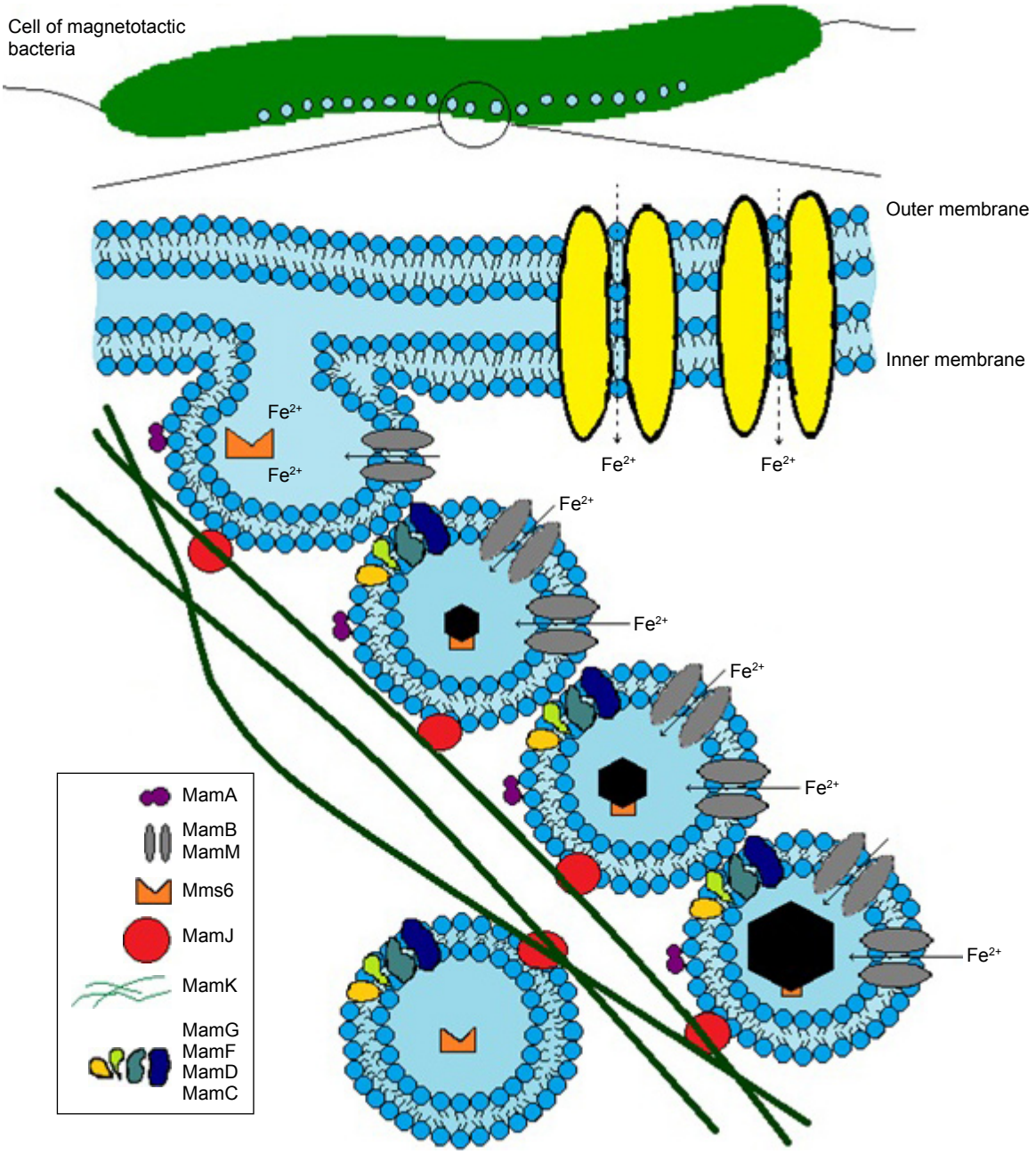

Figure 5 Schematic representation of BMNP biomineralization in magnetotactic bacteria.
Note: Black hexagonal symbols represent magnetic crystal growth inside magnetosome vesicles.
Abbreviation: BMNP, biogenic magnetic nanoparticle.

The absence of human homologues of the other regulatory proteins of the magnetosome island in MTB is in agreement with experimental data,[20,61] indicating the lack of control of the size, form, and quantity of BMNPs and the absence of magnetosome vesicles in human cells.

A common genetic mechanism of BMNP biomineralization, shared by organisms of all three domains of life and based on homologues of MTB proteins indispensable for BMNP biomineralization, has been predicted by comparative genomic methods (Tables 4 and 5).[23,115] Human homologues of MTB proteins indispensable for biomineralization of BMNPs are specified in Table 4. Table 5 provides a functional comparison between MTB proteins indispensable for BMNP biomineralization and their human homologues, based on National Center for Biotechnology Information (NCBI) functional annotation. The Mam proteins and their human homologues are found to have the same known functions and domains.

Table 4 Statistically significant alignment of MTB proteins with human proteins based on BLAST standard parameters[23]

MTB protein	MamA	MamB	MamM	MamN	MamE	MamO
Human homologue	PEX5 proteins	ZnT9 ZnT10	ZnT9 ZnT4	Permease P	HtrA1 HtrA2 HtrA3 HtrA4	HtrA1 HtrA2

Abbreviations: MTB, magnetotactic bacteria; BLAST, Basic Local Alignment Search Tool.

Predicted common genetic mechanism of BMNP biomineralization in prokaryotes, archaea, and eukaryotes

Bioinformatic methods allow comparison of a query protein with a specific set of proteins from a database by sequence alignment of amino acid residues. Statistically significant alignments or matches among the sequences compared are used for finding homologues, ie, proteins descending from a common ancestor. Homologues of proteins necessary for BMNP biomineralization in MTB have been found in nonmagnetotactic organisms with intracellular BMNPs by sequence alignment of Mam proteins with proteins from the NCBI database.[116] This has provided the basis for a prediction of the biomineralization of intracellular BMNPs in eukaryotes, nonmagnetotactic prokaryotes, and archaea. Figure 6 depicts such a prediction with indicated homologues of MTB proteins indispensable for BMNP biomineralization.

It is predicted[23,115] that homologues of indispensable biomineralization proteins of magnetosome islands have analogous functions in control of biomineralization of BMNPs in nonmagnetotactic organisms, including humans (Figure 6, Tables 4 and 5). There is no lipid magnetosome vesicle surrounding BMNPs[68] or homologues of proteins responsible for vesicle formation in humans.[23,115] That is why it is possible that the favorable chemical surroundings for BMNP growth are provided inside the organic matrix or another type of organic material (Figure 6), as is observed in non-MTB with BMNPs.[39]

Not all nonmagnetotactic organisms have a homologue of the MamK protein.[116] This is consistent with the experimental observation of BMNPs not arranged in chains.[39] However, BMNP chains can form even without MamK. Biogenic and artificial magnetite NPs can arrange in chains also as a result of magnetic dipole–dipole interaction (Figure 7).[117,118] Aggregation of BMNPs, based on magnetic forces alone, can allow the formation of less orderly aggregate assemblies from archaea to human cell systems.

The mineral core of ferritin: a precursor of BMNPs?

A protein that supplies iron in cells,[119–121] ferritin has been considered a possible precursor of BMNPs since 1996.[22,122,123] A hypothesis has been proposed that the ferrihydrite core of ferritin can be a precursor of magnetite, by analogy to what is observed in MTB, which in an early growth stage produce

Table 5 Comparative table of functions of MTB proteins and their human homologues[23,116]

MTB protein	MTB-protein functions	Name and functions of human homologue
MamB	Cation (Co^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}) transporter	ZnT9, ZnT10: Zn-cation transporters; changes in these proteins in brain regions are associated with Alzheimer's disease (AD); disturbance of zinc homeostasis plays a role in the pathogenesis of AD
MamE	Serine protease; the PDZ domain of this trypsin-like serine protease is involved in response to heat shock, chaperone function and apoptosis, and may be responsible for substrate recognition and/or binding	HtrA serine proteases, involved in important physiological processes including regulation of mitochondrial homeostasis, apoptosis and transmission of cell signals involved in the development of pathological processes such as cancer and neurodegenerative diseases, including AD
MamA	TPR domain-containing protein; based around a defined consensus sequence and identified in a variety of organisms, including bacteria, cyanobacteria, yeast, and fungi, TPR domains are involved in a variety of functions, which include protein-protein interactions, chaperone functions, the cell cycle, transcription, and protein transport	Pex5: peroxisome receptor, a TPR domain-containing protein; peroxisome is a widespread cell organelle surrounded by a membrane with a large variety of metabolic functions, such as destruction of toxic compounds and construction of the myelin sheath of nerve fibers
MamN	Permease P: the exact function of this protein is unknown, but it is believed to be involved in pH adjustment, together with the ATP-driven proton pump	Human permease P: the exact function of this protein is unknown, but it is believed to be involved in pH adjustment, together with the ATP-driven proton pump
MamO	Serine protease	HtrA2 serine protease
MamM	Cation (Co^{2+}, Zn^{2+}, Cd^{2+}) transporter	ZnT4, ZnT9: Zn-cation transporters

Abbreviations: MTB, magnetotactic bacteria; TPR, tetratricopeptide repeat.

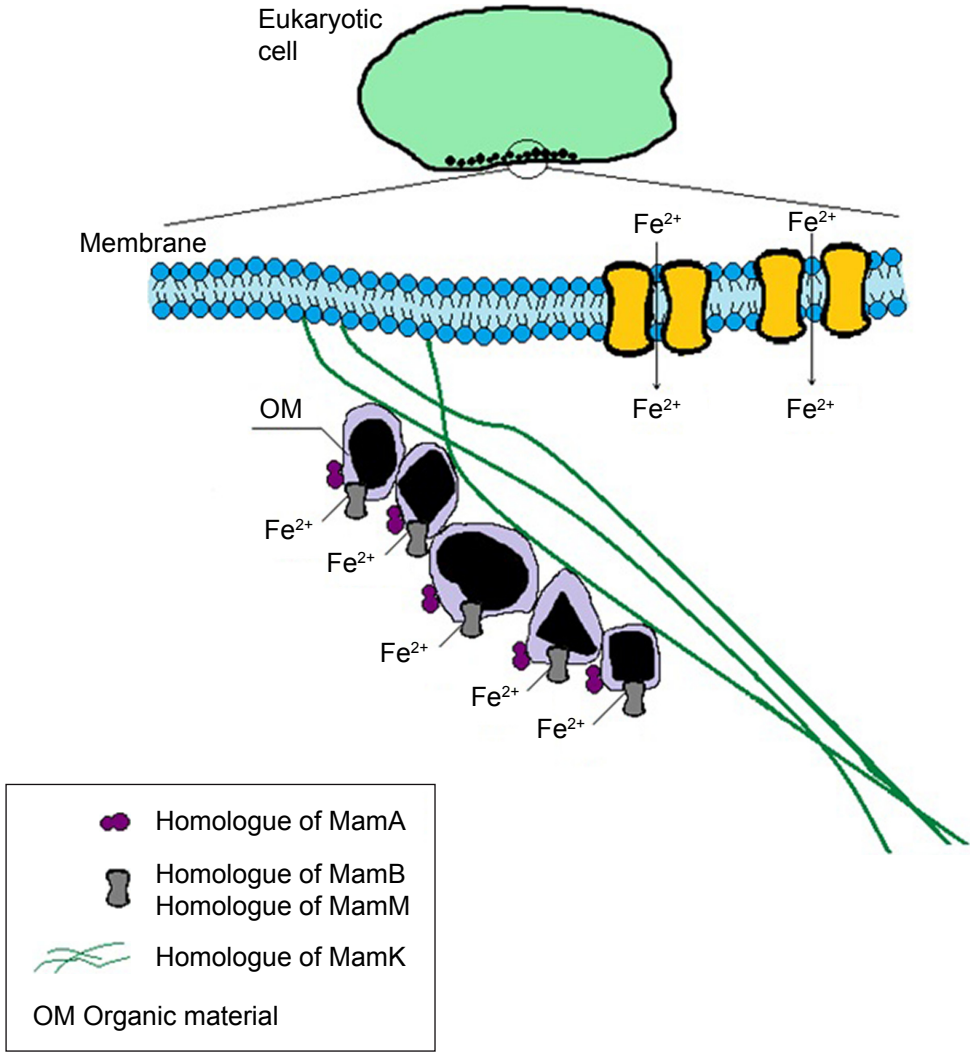

Figure 6 Predicted biomineralization of intracellular BMNPs in eukaryotes, nonmagnetotactic prokaryotes, and archaea.
Note: Black shapes represent the magnetic crystals inside some organic material.
Abbreviation: BMNPs, biogenic magnetic nanoparticles.

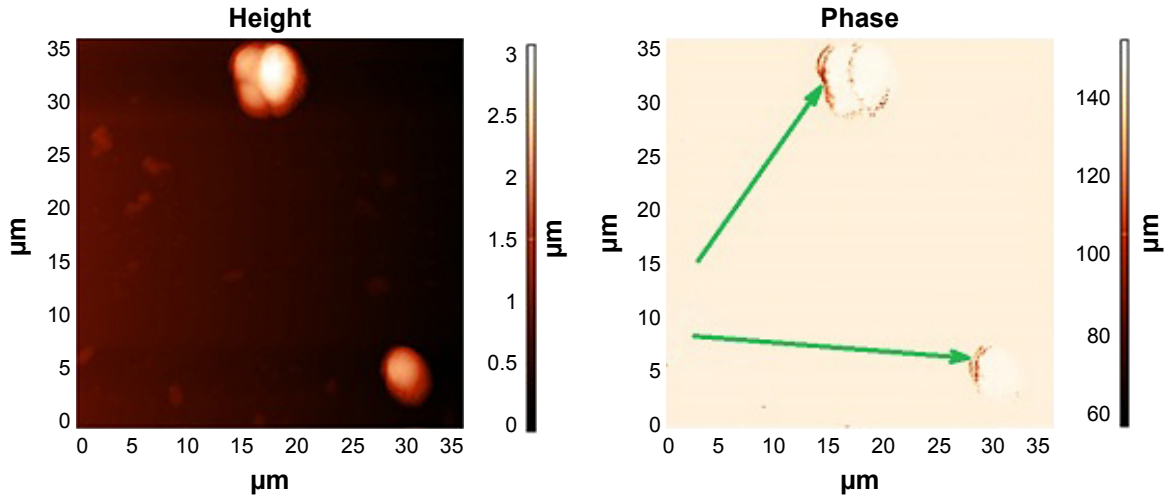

Figure 7 *Saccharomyces cerevisiae* yeast cells with magnetic nanoparticles.
Note: AFM (left) and MFM image (right), showing chains (arrow) of artificial magnetic nanoparticles formed at the biomembranes of the cells, due to magnetic dipole–dipole interaction among the magnetic nanoparticles.
Abbreviations: AFM, atomic force microscopy; MFM, magnetic force microscopy.

noncrystalline ferrihydrite, later converted to magnetite, within the magnetosome vesicle.[22] However, the relation between ferritin and BMNPs seems indirect, involving the protein shell rather than the mineral core of ferritin, as indicated by its role in neurodegeneration, associated with the presence of MNPs in the human brain.[122,124] Though long considered,[22] whether the ferritin molecule is the precursor of BMNPs in human tissues has not been established to date. Also, the role of ferritin in the physiological origin of BMNPs from the point of view of the predicted common genetic mechanism of BMNP biomineralization,[23] as well as the interaction between ferritin and the basic set of proteins indispensable for BMNP biomineralization, remains an open question.

Basic physicochemical characterization of ferritin

Iron is an element of vital importance to nearly all living organisms. At the same time, it is highly toxic in excess. Free Fe^{2+} ions are known to produce highly reactive oxygen species that may cause cell damage. Organisms have developed a way of fast scavenging of excess iron ions by storing them in a safe mineral form inside ferritin molecules. Discovered by Laufberger in 1937,[125] ferritin has been found since in most living organisms, from microorganisms to plants, invertebrates, and vertebrates, particularly mammals. Covering a broad spectrum of its properties and applications, the literature on ferritin is voluminous. We refer the reader to classical[126,127] and recent review papers[128,129] discussing the most important aspects of its physicochemical properties. Herein, we only outline these briefly, along with the methods used for studying the magnetic properties of ferritin.

Ferritins

Ferritin is a hollow spherical protein made up of 24 subunits; iron ions are sequestered in its cavity. The iron core of the protein is described as a mineral with a form similar to that of ferrihydrite, with a stoichiometry of $[FeO(OH)]_8$ $[FeO(H_2PO_4)]$ and different amounts of phosphate.[126,128,129] The empty ferritin shell is known as apoferritin. The protein with iron in the cavity is referred to as holoferritin, or very often simply ferritin.

For decades ferritins, have been considered synonymous with the function of iron storage. The ferritin family includes subfamilies of mammalian, plant, and bacterial ferritins, each composed of 24 subunits. However, in recent years it has become clear that there are also other proteins able to store iron in the form of a mineral core in their central cavity. These include Dps, a subfamily of proteins made up of 12 subunits, often referred to as miniferritins. Another subfamily of protein cages, frataxin is composed of up to 48 subunits. In Table 6, we provide the main information on proteins belonging to the ferritin family. It is worthy of note that the Fe:P ratio varies considerably in native ferritin cores. The Fe:P ratio has an influence on the core morphology; however, no general rules have been observed to date.

The ferritin nanocage has a 432-point symmetry with three fourfold, four threefold and six twofold axes[126,129] (see Figure 8). Dps family members have only 32-point symmetry. The maximal number of iron ions that can be stored in the ferritin cavity is 4,500 (500 in Dps). The actual number of iron ions in natural ferritin depends on the organism and the organ in which it is stored. There are two types of monomers among the 24 subunits that constitute the ferritin molecule: the heavy (~21 kDa) subunit, or H-chain, comprising 178 amino acids, and the light (~19 kDa) subunit, or L-chain, of 171 amino acids.

Only one type of subunit, with a mass of 26.5 kDa, has been identified in the plant ferritin phytoferritin.[131] However, some authors distinguish its three forms with different molecular weight.[131] Some bacteria have a heme group incorporated in their ferritin, which in that case is referred to as bacterioferritin.

The H-chain carries a ferroxidase center, which appears to be essential for iron incorporation, whereas the L-chain

Table 6 Properties of proteins of the ferritin family

Protein	Symmetry	Number of subunits	Outer/inner diameter (nm)	Iron content, atoms	References
Human ferritin	432	24	7–8/12	Up to 4,500	126, 129
Animal ferritin	432	24	8/12	Up to 4,500	128, 130
Bacterial ferritin	432	24	8/12.5	~1,600	128
Bacterioferritin (contains heme)	432	24	8/12.5	Up to 2,700	128
Phytoferritin (plant ferritin)	432	24		~2,000	131
Dps	23	12	5/9	500	132
Frataxin	?	48	?	~2,400	133

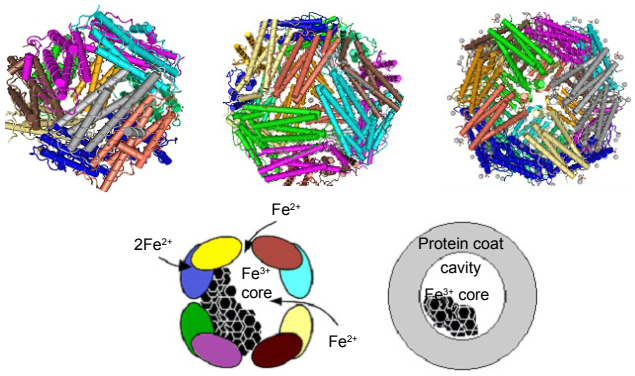

Figure 8 Schematic representation of ferritin molecule with twofold-, threefold-, and fourfold-symmetry axes.
Notes: Dps, PDB – 4DYU (top left); structure of human ferritin L-chain, PDB – 2FG8 (top center); structure of human ferritin L-chain, PDB – 2FFX (top right) (NCBI). The protein-shell diameter is 12 nm, and the core diameter 7–8 nm (right).
Abbreviations: PDB, Protein Data Bank; NCBI, National Center for Biotechnology Information.

facilitates iron mineralization within the cavity. Plant and bacterial ferritins have only a single type of subunit, which probably fulfills both functions. Vertebrate ferritins are heteropolymers that assemble in specific H:L ratios and vary widely with organism and tissue.[126,129] The most often studied – horse-spleen ferritin (HSF) – is composed of ~10% of H-chains and ~90% of L-chains. Ferritins rich in L-chains predominate in iron-storage organs, such as spleen and liver, whereas heart cells and a majority of brain cells tend to contain mostly H-chain-rich ferritins. Apparently, the H:L ratio plays an important role in controlling iron concentration in cells; this has not been fully elucidated to date, but may be related to several pathologies observed in humans.[124,134]

Figure 9A shows transmission electron microscopy (TEM) of well-defined NP crystallites, ie, the core of ferritin of size 3.5–8 nm within holoferritin. The particle-size distribution of ferritin, but also of any MNPs, is very often described by known distribution functions.[135] The log-normal distribution function is the most commonly used,[136] and allows the calculation of average diameter of the particle and standard deviation (Figure 9B).

The ferritin core is antiferromagnetic[137] with a Néel temperature of 240–460 K, but not uniquely determined.[138] The magnetization of the core is about two orders of magnitude lower than that of magnetite[84] (see Table 2). The magnetic moment of ferritin ranges from 100 μ_B to 300 μ_B, while the magnetic moment of magnetite of similar dimensions is of the order of 10^4 μ_B.[139] The superantiferromagnetism of ferritin NPs has been investigated recently by a combination of low-field susceptibility and magnetization measurements, and full-saturation magnetization has proved unattainable even in a magnetic field as high as 55 T.[140,141]

HSF tends to be regarded as a model system, and has been studied by several techniques, specified in Table 7. However, the physicochemical properties of human isoferritins have not been sufficiently studied to date, and require further investigations and correlation with human health data.

Today, ferritin is a powerful clinical tool,[121] but the magnetic structure of its core has not yet been explored by clinicians. It is noteworthy that a number of currently

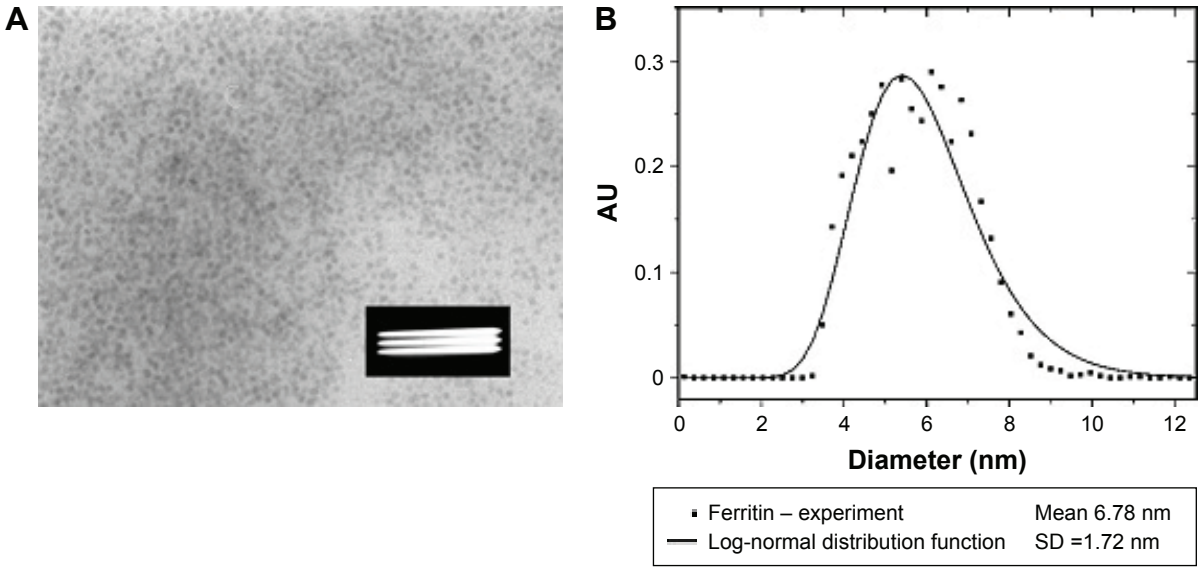

Figure 9 (**A**) Ferritin TEM (HSF), the white stripes inside the black box indicate the scale bar 100 nm; (**B**) particle-size distribution based on TEM.
Abbreviations: TEM, transmission electron microscopy; HSF, horse-spleen ferritin; SD, standard deviation.

Table 7 Methods for study of magnetic properties of biogenic and synthetic ferritin and BMNPs

Method	Properties studied	Resolution	References
Mössbauer spectroscopy	Fe valence	≈0.2 nm	142–145
SQUID magnetometry	Magnetization	~10 nm	19, 146
Transmission electron microscopy	Electron density, phase, and periodicity	≈50 pm	61, 62, 147, 148
Nuclear magnetic resonance	Molecule structure, dynamics, reaction state, and chemical environment	50–100 nm	149
Magnetic force microscopy	Magnetic interactions	10–30 nm	21, 92, 150, 151
X-ray absorption near-edge structure	Valence, interatomic distances, and bond angles	0.1–0.5 nm	152, 153
Small-angle X-ray scattering	Shape, size, characteristic distances of partially ordered materials, pore size	5–25 nm	154, 155
Magneto-optical spectroscopy	Type of mineral	2–30 nm	139, 156–160
Electron energy-loss spectroscopy	Interatomic distances and coordination	~0.1 nm	154
Electron paramagnetic resonance	Valence		161, 162

Abbreviations: BMNPs, biogenic magnetic nanoparticles; SQUID, superconducting quantum-interference device.

available techniques allow the study of the magnetic properties of the core of ferritin of any origin. These include X-ray absorption near-edge structure (XANES) spectroscopy, Mössbauer spectroscopy, MFM, and magneto-optical spectroscopy (see Table 7).

Some of the methods specified in Table 7 can have clinical analytical applications. Magneto-optical spectroscopy seems a very good candidate, as it is not too sophisticated, relatively inexpensive, and can be used for studying liquid and thin-tissue samples. It is important to note that recently a rapid detection method for malaria diagnosis based on a magneto-optical method (Cotton–Mouton effect) was presented and tested.[163,164] Magneto-optical relaxation methods are successfully used in controlling the functionalization of magnetic particles through measurements of size of prepared molecules.[165]

Elevated ferritin levels are associated with inflammatory conditions, including malignancy.[166] In plasma, which normally contains mostly L-chain-rich ferritin, increased concentrations of H-chain-rich ferritin are observed in some pathological conditions.[167] Also, pathological ferritin is observed in a number of human diseases.[133,168,169] The interest in the chemical composition of both physiological and pathological ferritin is stimulated also by the hypothesis that the magnetic core of ferritin and aggregates of pathological ferritin might be a precursor of BMNPs.[62] A large number of papers have been aimed at verification of the idea that biogenic magnetite in humans might originate from ferritin, and the determination of the role of ferritin and BMNPs in the pathogenesis of diseases.[100,122,124,169,170] We would like to point out the environmental pollution by radiofrequency electromagnetic fields used in mobile telephony throughout the world and the long-term exposure of those who use mobile phones. There are very few papers devoted to the possible biological effects of this radiofrequency field studied at the molecular level, though the problem has at least been discussed by Céspedes et al.[171,172] They found that exposure of about 2 hours to a magnetic field of 30 μT at 1 MHz on ferritin have reduced their iron intake rate by about 20%.

Hemosiderin

The literature devoted to hemosiderin is strongly correlated with ferritin; however few studies on hemosiderin alone have been undertaken,[100,173–177] although it is thought that hemosiderin may play an important role directly or indirectly in iron cytotoxicity and thus deserves more intensive study. The hemosiderin aggregates found in diseases might play a similar role as ferritin doses as precursors of BMNPs; however, no direct evidence for this is known.

Water-insoluble tissue iron deposits are known as hemosiderin. Hemosiderin is thought to be a breakdown product of ferritin, and is much less soluble than ferritin. In several iron-overload diseases (eg, thalassemia or hemochromatosis) iron oxyhydroxide particles are mostly found in the form of insoluble aggregates associated with protein residues.[173] Hemosiderin mineral particles vary even more widely in structure than those stored in ferritin.[174] Allen et al identified three main particle structures in hemosiderin: a ferrihydrite-based structure, a highly defective structure based on goethite (α-FeOOH), and a noncrystalline Fe(III) structure.[174] The same authors found that hemosiderin particles generally have larger size distributions than particles in ferritins. As in the case of ferritins, the structural and compositional characteristics of hemosiderin vary with biological source and pathological condition.[174] Miayazaki et al established that denatured H-chain-rich ferritin is a major constituent of hemosiderin in the liver of patients with iron overload.[175]

Mutant ferritins

Genetic engineering has been mostly used for producing ferritin from a specific chain, eg, the H-chain[178] or frog M ferritin.[179] Spectacular results obtained by replacing a particular amino acid in the H- or L-chain shed light on the entry of Fe(II) into the ferritin cavity, its pathway to the center, oxidation, and formation of Fe(III). Detailed information on this procedure can be found in a very recent review by Ebrahimi et al.[128] Some mutations of human ferritin in vivo may be the origin of severe malignancy; this problem is discussed further in a following section.

Synthetic ferritins

As demonstrated by Meldrum et al,[180] apoferritin can be used in vitro as a bioreactor for producing monodisperse metal or metal oxide NPs. In particular, magnetite and/or maghemite have been synthesized in vitro inside apoferritin to produce a novel material known as magnetoferritin. Further development of this biomimetic way of nanosynthesis within the ferritin cavity[181,182] has allowed the production of ferritin with various cores, as illustrated in Figure 10. In general, HSF is used as the starting material for preparation of apoferritin, which is used as a nanoreactor. In special cases, genetically modified apoferritin is also used. Homochains, ie, only L-chains or H-chains, were synthesized to follow iron entry and its mineralization process in ferritin.[128] H-chain magnetoferritin was used for enhanced magnetic resonance imaging (MRI).[178] Worthy of note are also other considered approaches based on the disassembly of the apoferritin shell and its reassembly in the presence of the species to be encapsulated.[183–185] Besides the possible applications of synthetic ferritin in electronics[186] and biomedicine,[119,120] the interest in this unique material has been stimulated also by its role as the artificial modeling object for the development of methods for the determination and study of the physical and chemical properties of the hypothetical precursor of BMNPs.[139,160]

The magnetic core of mutant ferritin as a precursor of BMNPs

Pathological ferritin is observed in a number of diseases, including neuroferritinopathy (NF), a rare genetic disorder resulting directly from a known mutation in the gene encoding the ferritin light polypeptide (L-subunit).[134,170] A slowly progressive adult-onset disease, NF is characterized by the aggregation of ferritin clusters in the brain and other organs.[187] It has been shown to provide direct evidence that changes in the ferritin structure resulting in inefficient iron storage can lead to neurodegeneration, with damage to neural cells probably caused by an excess of labile iron, rather than by iron or ferritin aggregates.[168] Oxidative stress injury may be caused by labile iron available for the Fenton reaction.

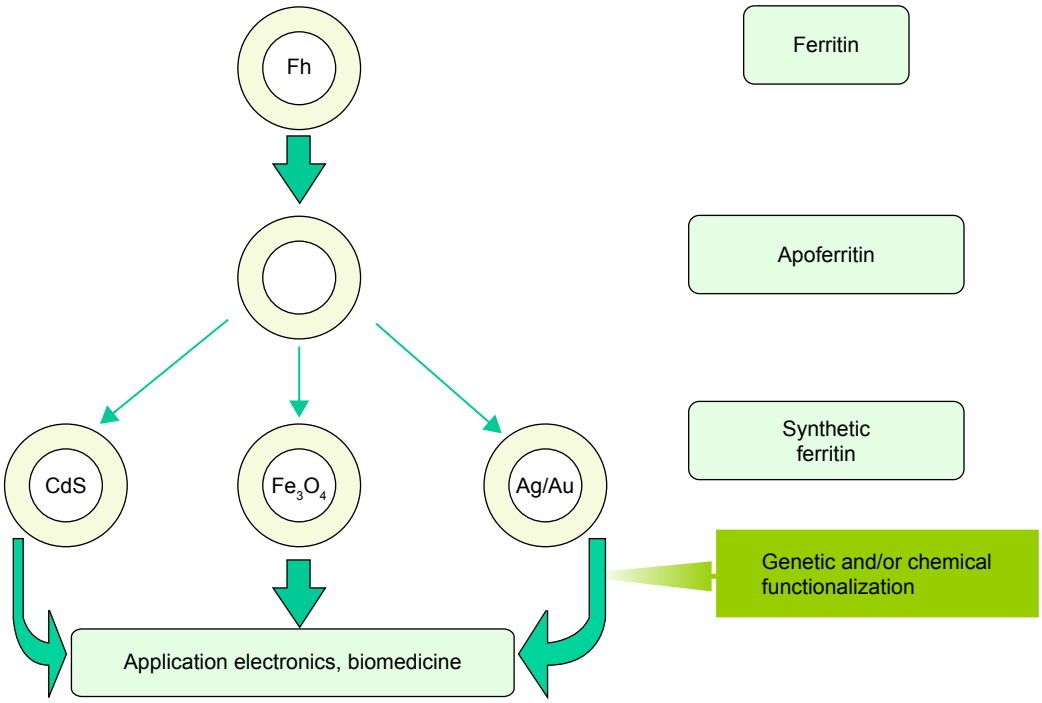

Figure 10 Schematic representation of synthetic pathway.
Note: Using apoferritin in vitro as a bioreactor for producing monodisperse metal (eg, Ag or Au), semiconductor (eg, CdS), or metal oxide (eg, Fe_3O_4) particles for applications in electronics or biomedicine.
Abbreviation: Fh, ferrihydrite.

This may be related to a decreased ability of ferritin to retain iron within its core.[124,169] Iron leakage from ferritin is observed also in Parkinson's disease. However, in this condition there is a pathological decrease in the concentration of ferritin L-subunits, while in NF a genetically induced mutation in the L-subunit of ferritin results in its loss of function.[124] Oxidative stress is considered one of the pathways leading to neuronal cell death in neurodegenerative diseases. A number of studies have aimed to assess the possible role of iron in this process, but no consensus has been reached. We refer the reader to recent papers of Collingwood et al[188,189] for details.

As mentioned earlier, a number of authors have considered the biomineralization of the ferrihydrite core of ferritin a possible pathway for the formation of larger magnetite particles.[19,62,76,148,190–192] The structure of nanocrystals in the cores of physiological horse spleen, human liver, and human brain ferritin and pathological human brain ferritin of patients with progressive supranuclear palsy and AD has been studied by electron nanodiffraction and high-resolution TEM.[62] A polyphase structure of the ferritin core has been postulated, but not unequivocally confirmed to date.[147,193] There are significant differences in the mineral composition between physiological and pathological ferritins. Although both physiological and pathological ferritin cores have a polyphase composition, hexagonal ferric iron oxide (ferrihydrite) predominates in physiological ferritin cores, while the major phases in AD brain ferritin cores are two cubic mixed ferric–ferrous iron oxides (magnetite and wüstite).[62,100,148]

HSFs from which iron had been gradually removed, yielding samples containing 200, 500, 1,200, and 2,200 iron atoms, were studied by TEM, XANES spectroscopy, electron energy-loss spectroscopy, small-angle X-ray scattering, and superconducting quantum-interference device (SQUID) magnetometry.[154] The relative amount of magnetite in ferritin containing 200–2,200 iron atoms rose steadily from approximately 20% to approximately 70%, whereas that of ferrihydrite fell from approximately 60% to approximately 20%. These results indicate a ferrihydrite–magnetite core–shell structure.[154]

However, these data may be questionable, as the mineral ferrihydrite is electron beam-sensitive and will undergo internal atomic rearrangements when exposed to the electron beam in TEM and scanning TEM studies, or studied by other techniques using electron beams.[147,193] Results obtained by nuclear magnetic resonance (NMR) relaxometry indicate that the proportion of iron contained in brain ferritin in the form of well-crystallized magnetite, rather than ferrihydrite, must be $<1\%$,[149] much less than the reported percentages in the dozens of particles of a "magnetite-like" phase found in TEM studies of similar samples.[62,154] Consequently, the magnetization of this "magnetite-like" phase must be very low compared with that of magnetite.[149] Also, recent magneto-optical and NMR studies of reconstructed and reduced HSF in aqueous solution, presented at the Tenth International Conference on the Scientific and Clinical Applications of Magnetic Carriers, indicate that high-magnetization minerals, such as magnetite or maghemite, are not present in the core of such ferritins.[194]

Search for magnetoferritin in normal organs containing BMNPs

The hypothesis of the presence of a magnetically strong phase in pathological ferritin has inspired a number of experimental studies in which magnetoferritin, synthetic ferritin with a magnetic core, has been produced and investigated. However, to our best knowledge, the presence of magnetoferritin in specific human organs, serum, or cerebrospinal fluid has not been reported to date.

Various MRI methods for the estimation of iron levels in the human brain[195–200] are the most promising in vivo techniques. Also, SQUID susceptometry is being developed for the assessment of iron content in human tissues.[201] Of particular interest is the search for methods for the detection of magnetite in ferritin both in vitro and in vivo. Koralewski et al proposed a magneto-optical method based on the measurement of magnetic linear birefringence (MLB; Cotton–Mouton effect) followed by that of magnetic circular birefringence dispersion (Faraday rotation dispersion, or magnetic optical rotatory dispersion [MORD]) for the discrimination of the core mineral in magnetoferritin or any other MNP.[139,157–160] The method is depicted in Figure 11. First, MLB is measured, which allows the classification of unknown samples to a magnetically strong material, eg, magnetite or maghemite, or a magnetically weak one, eg, ferrihydrite or akaganeite (see Table 2). MLB dependence on magnetic field is very characteristic for such classes of materials, as is shown in Figure 11. For magnetically strong materials, we observe saturation of MLB, but for magnetically weak materials, typical parabolic dependence on H is observed, ie, $\Delta n \sim H^2$. Next, MORD measurements should be performed to obtain spectra of the studied sample. Features of MORD spectra are quite different for Fe^{3+} or Fe^{2+} ions present in studied magnetic materials (see Figure 11), so information on the oxidation state of Fe will be acquired. Taking into account results from both methods, discrimination of minerals for particular MNPs may be obtained.

Koralewski et al studied the MLB of biogenic HSF and synthetic magnetoferritin.[139,160] Direct observation

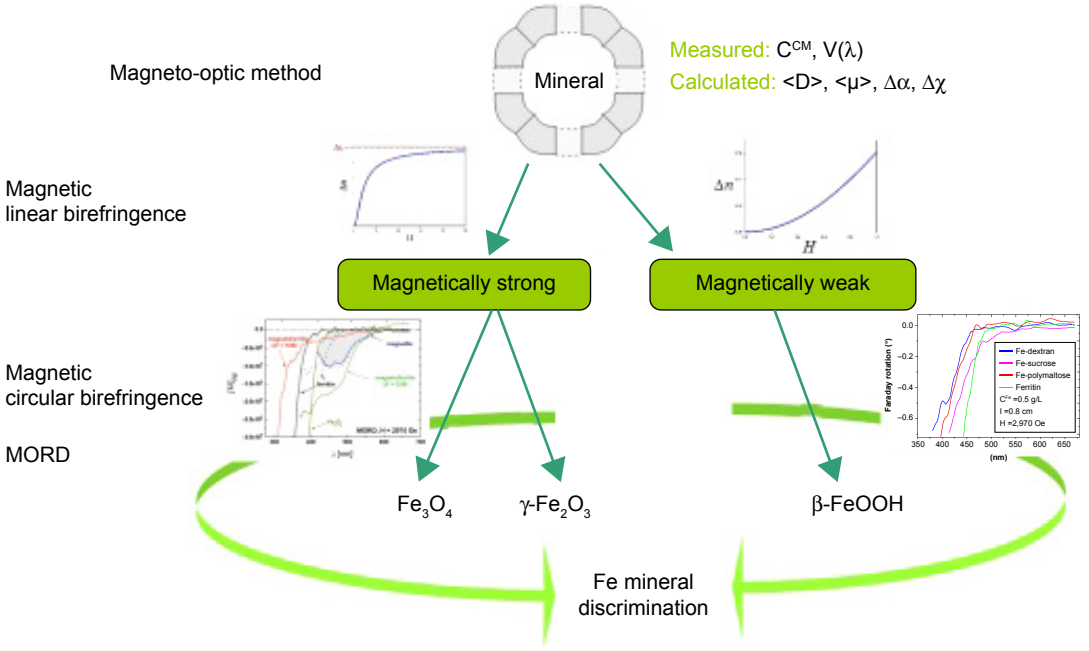

Figure 11 Schematic representation of discrimination.
Notes: Based on differences in magnetic linear birefringence and MORD spectra between ferrite (magnetically strong) materials, such as magnetite/maghemite, and antiferromagnetic (magnetically weak) materials, such as ferrihydrite or akaganeite. For details of magnetically strong MORD data, see Figure 13 and Koralewski et al.[159] Magnetically weak MORD data were obtained for akaganeite-type materials, the same as were studied in Koralewski et al.[160]
Abbreviations: MORD, magnetic optical rotatory dispersion; C^{CM}, Cotton-Mouton constant; V, Verdet constant; D, particle diameter.

in a relatively low magnetic field has shown a saturation effect in artificial magnetoferritin, but not in HSF.[139,158,160] As may be seen in Figure 12, distinguishing between magnetically strong and weak materials is obvious; however, discrimination between magnetite or maghemite cores of magnetoferritin is not achieved with this single method.

Further information on the magnetic core and oxidation state of Fe can be acquired from Faraday-effect dispersion studies.[159] Characteristic bands of 450–478 nm are associated with magnetite NPs and magnetoferritin with a magnetite core. Observed in the visible spectrum, this feature is directly related to Fe^{2+} ions, which indicate the presence of magnetite in the studied suspension. It should be noted that Fe^{2+} ion is by definition absent in maghemite. The lack of these bands indicates a mineral other than magnetite (see Figure 13).[159] The characteristic band intensity may be correlated with the amount of magnetite in the studied suspension. In Figure 13, magnetoferritin with low iron content (loading factor 1,250; the same material presented in Figure 12 showing saturation of MLB) shows a very low intensity in the region of Fe^{2+} ion bands. This means that the core of this magnetoferritin consists mainly of maghemite, with a very small amount of magnetite, in contrast to highly loaded magnetoferritin (loading factor 3,250), in which magnetite is the major component of the core.

Among the methods indicated in Table 7, Raman spectroscopy is also a very promising tool for discrimination

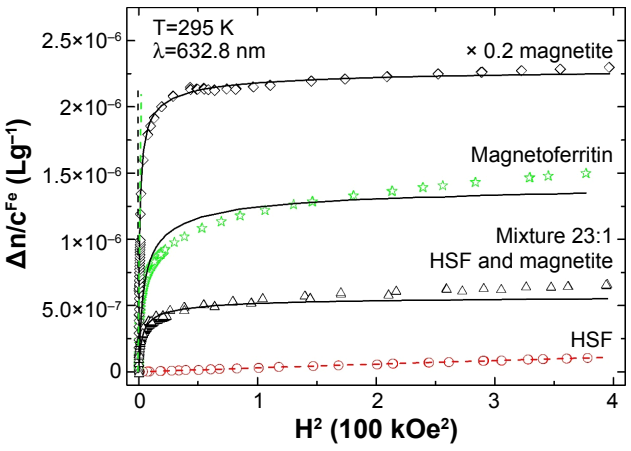

Figure 12 Reduced linear magnetic birefringence.
Notes: HSF, synthetic magnetoferritin (loading factor 1,250), magnetite, and a mixture of HSF and magnetite (Fe weight proportion 23:1) versus the square of the applied magnetic field – H^2. Dashed line indicates the low-field region in which the Cotton–Mouton (C^{CM}) constant was determined (ie, $\Delta n = C^{CM} \lambda H^2$, where λ is light wavelength and H magnetic field intensity); solid line represents the best fit for the Langevin function. Reprinted from *J Magn Magn Mater*. Vol 323. Koralewski M, Pochylski M, Mitroova Z, Timko M, Kopcansky P, Melnikova L. Magnetic birefringence of natural and synthetic ferritin. Pages 2413–2417. Copyright 2011, with permission from Elsevier.[139]
Abbreviation: HSF, horse-spleen ferritin.

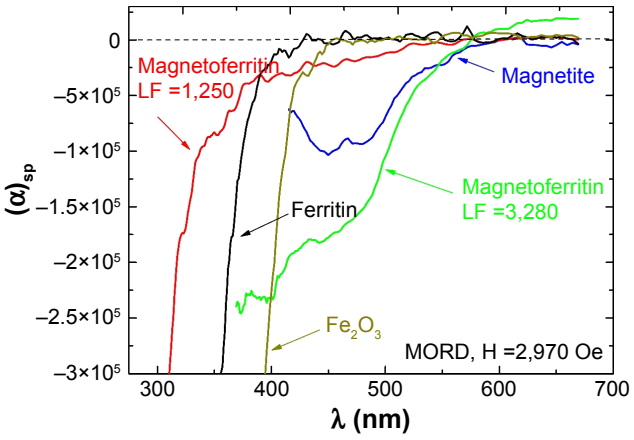

Figure 13 Wavelength dependence.
Notes: Faraday rotation (MORD) for HSF, synthetic magnetoferritin with different loading factors (loading factor 1,250 and 3,280), Fe_2O_3, and magnetite suspensions. Reprinted from Koralewski M, Kłos JW, Baranowski M, et al. The Faraday effect of natural and artificial ferritins. *Nanotechnology*. 2012;23:355704.[159] Copyright 2012. IOP Publishing Ltd.
Abbreviations: MORD, magnetic optical rotatory dispersion; HSF, horse-spleen ferritin; LF, loading factor.

among different iron minerals.[202] Both solutions and tissue samples have been studied by this technique; we refer the reader to the latest review papers[203,204] for details of these studies in biological materials. Also, the recently developed MFM may be very useful in clinical analysis of biomaterials (see Figures 3 and 4).[21,92,150,151]

Correlation between BMNP and ferritin distribution in human tissues

Several studies have been carried out to investigate the possible correlation between the levels of ferritin and BMNPs for the purpose of elucidating the role of ferritin in the process of BMNP biomineralization. However, elevated BMNP levels, associated with various diseases, are not necessarily correlated with increased levels of iron-storage or -transport proteins (ferritin or transferrin, respectively).[20,166] Magnetic materials in various human tumor tissues, including melanoma, breast, ovarian and testicle tumors, sarcoma, meningioma, glioblastoma, astrocytoma, glioma, and metastasis, were first detected by Kobayashi et al in a study using SQUID magnetometry.[20] However, it was impossible to demonstrate a covariance between ferritin and magnetite in that study. Investigations by magnetic methods reported by Brem et al[8] showed that the concentration of ferrimagnetic particles in human meningioma brain-tumor tissues was an order of magnitude higher than in nontumor hippocampus. In a comparative study of ferritin and magnetite distributions in the human brain, it has been established that magnetite is distributed homogeneously throughout the whole brain, except for the meninges, but ferritin is not.[90] These results suggest that magnetite in the human brain and tumor tissues does not originate from ferritin;[20] however, further experimental documentation is necessary to confirm this conclusion.

Comparison between size distributions of clumps of biogenic magnetite and ferritin aggregates

Measurements of the size distribution of BMNPs and aggregates of pathological ferritin do not confirm the hypothesis that ferritin might be a precursor of BMNPs either.[170,205] Biogenic magnetite observed in brain tissues[97,192,206,207] has a wide particle-size range, including both SPM and larger magnetite particles (clump magnetite) with a size of 10–200 nm. Larger particles were observed in tissue extracts; optical microscopy studies revealed 5–10 μm clusters of finer opaque particles in tissue slices.[205] The magnetite-clump level measured in NF tissue was 57 and 128 ng/g wet tissue, higher than that normally measured in age/sex-matched freeze-dried control tissues from the same region of the brain (12–27 ng/g wet tissue).[170] The observed nontrivial magnetization corresponds to clumps of magnetite with a coercivity larger than 200 Oe, which is consistent with the results of isothermal remnant-magnetization measurements, indicative of magnetite clumps.[170] Also coercivity data reported by Hautot et al[170] and TEM imaging of magnetic extracts from hippocampal tissue[205] indicate the presence of larger clumps of magnetite particles. Moreover, the ferrihydrite core of ferritin is superantiferromagnetic,[137] and the saturation magnetization of ferritin proves unattainable, even in a field as strong as 550 kOe.[140,141] Therefore, direct formation of BMNPs from the ferrihydrite core of ferritin is impossible. Also the origin of large clumps of magnetite crystals (BMNPs) remains unclear, according to Hautot et al,[170] because of the inconsistency in size distribution and magnetic properties between clumps of biogenic magnetite and ferritin aggregates.

Biological formation of BMNPs in vitro

There are a number of papers on the influence of MTB proteins involved in BMNP biomineralization on the formation of magnetite nanocrystals in vitro.[208,209] For example, the magnetosome-membrane protein Mms6 has allowed the artificial control of the morphology, crystallinity, and magnetism of nanocrystals in a manner observed in MTB.[209–211] To investigate the conditions of biological formation of magnetite nanocrystals, Prozorov et al precipitated iron oxide in an aqueous viscous Pluronic solution of Fe(II) and Fe(III) by increasing the pH in the presence of various proteins.[208] A protein isolated from magnetosome membranes mediated

the formation of 30 nm-large magnetite crystals with good crystallinity; NPs formed within ferritin under the same conditions were much smaller and largely amorphous[208] (NP growth within the ferritin core is limited by the protein shell; see Figure 8). Nanocrystals formed in the presence of ferritin do not have uniform sizes and shapes, in contrast to those produced in the presence of the biomineralization protein Mms6.[208] A protein assisting magnetite production, MamP has been established recently[212] as an iron oxidase contributing to the formation of Fe(III) ferrihydrite. As such, this protein will be the next candidate for in vitro testing.

Genetic analysis of role of ferritin in BMNP biomineralization

The elucidation of the physiological origin of BMNPs in eukaryotes, including humans, is still more complex because of the difficulties in the detection of BMNPs in human tissues. Finding magnetite in tissue is a nontrivial problem, due to its low concentrations, of the order of dozens of ng/g tissue. A powerful tool in this field is provided by bioinformatic methods based on comparative genomics. These bioinformatic methods are complementary to physical methods. The sophisticated physical methods for BMNP detection (Table 7) do not always allow the distinction of BMNPs from artificial MNPs in human tissues in contact with the environment. Also, by using only physical methods, it is often difficult to distinguish extracellular biomineralization of MNPs by microorganisms from their biosorption from the environment.[116]

As we have mentioned, the genetic mechanism of BMNP biomineralization is predicted to be based on homologues of MTB magnetosome-island proteins indispensable for the biomineralization of BMNPs in MTB.[23,213,214] However, the question remains open as to whether ferritin also, together with homologues of MTB magnetosome-island proteins, is involved in the metabolic pathway of BMNP biomineralization. An answer has been proposed[214] on the basis of comparative genomic studies. To this end, ferritin-encoding genes were searched for full genomes of MTB.[108,113,215–218] Gorobets et al[214] demonstrated that the magnetotactic bacterium *Magnetococcus marinus* MC1 had no genes encoding ferritin or ferritin-like proteins in their full genomes.

Research[214] has led to the conclusion that the presence of ferritin in cells of MTB is not necessary for the biomineralization of BMNPs, that ferrihydrite in ferritin is not a precursor of biogenic magnetite in MTB, and that prokaryotes and eukaryotes have a common genetic mechanism of biomineralization of intracellular BMNPs.[23,213,214] In general, ferrihydrite in the ferritin core is not a precursor of BMNPs in humans or other multicellular organisms. As mentioned, this has been confirmed by an experimental study of conditions of magnetite biomineralization in vitro.[208]

These findings of bioinformatic studies are in accordance with the aforementioned experimental data on the lack of correlation between BMNP and ferritin distributions in human tissues, and the inconsistency in size distribution between clumps of biogenic magnetite and ferritin aggregates. In this context, the bioinformatic analysis in the paper[214] proves that the biomineralization of BMNPs is in general a process independent of iron storage in the core of ferritin and ferritin-like proteins. However, in our opinion, an excess of labile iron related to the decreased ability of ferritin to retain iron within its core in pathological conditions[123,169] may represent an additional iron supply for BMNP biomineralization. Besides, the biomineralization of BMNPs can protect tissues against oxidative stress, since iron in magnetite is bound irreversibly and cannot be released for the Fenton reaction.[219] In this regard, iron storage in organisms can be classified as either reversible (in iron-storage proteins) or irreversible (in BMNPs).

Metals accumulated in AD and other neurodegenerative disorders are known to include (besides iron) such elements as copper or zinc.[220,221] The accumulation of copper and zinc can be explained by a common genetic mechanism of BMNP biomineralization, since the proteins indispensable for BMNP biomineralization include divalent cation (Zn^{+2}, Cu^{+2}, Cd^{+2}, Ni^{+2}, and Fe^{+2}) transporters. Therefore, Co, Ni, Zn, Cu, Mn, and Cd can be incorporated in the magnetite structure[211,222] and bound irreversibly in BMNP biomineralization. On the other hand, purified ferritin cages in vitro can incorporate a variety of metal ions (Fe, Au, Pd, Rh, Pt, Ni, Cr, Cd, Ti, Tb, Co, Cu, and Zn), most likely through a hydrophilic threefold ion channel.[183,223,224] Therefore, both ferritin and BMNPs might contribute to the excess of zinc and copper in neurodegenerative disorders.[225]

Conclusion and prospects

In this review, we have outlined the research efforts toward understanding the biomineralization of BMNPs and especially their role in human health and disease. In general, three basic steps can be distinguished in BMNP biomineralization in organisms of all three domains (prokaryotes, archaea, and eukaryotes, including humans): 1) formation of a specific organic material, organic matrix, or vesicle to prepare a chemical medium favorable for BMNP biomineralization; 2) formation of a transient iron mineral; and

3) conversion of the transient iron-mineral precursor into the target BMNP mineral.

Each of these steps requires the participation of a set of specific proteins. The formation of an organic matrix or other organic surroundings of BMNPs involves proteins that are not homologues of those controlling the formation of vesicles in MTB.[23,115] Steps 2 and 3 are predicted to be controlled by homologues of MTB biomineralization proteins.[23,115]

Ferrihydrite is the most probable transient mineral and precursor of biogenic magnetite.[9,214] However, the accumulation of iron in BMNP biomineralization and the accumulation of iron in the ferrihydrite core of ferritin are independent processes in general.[9,214] The role of ferritin in BMNP biomineralization remains an open question. In diseases and mutations, an increase in labile iron due to the reduced ability of ferritin to retain iron within its core can influence the process of biomineralization of BMNPs. There are two modes of iron storage in living organisms: reversible storage in iron-storage proteins, and irreversible storage in BMNPs, in which iron is bound in magnetite or other chemically resistant iron oxides and cannot be released. Since ferrites represent the most magnetically sensitive compounds of biogenic origin and elevated BMNP levels are related to a number of human diseases, such as cancer, neurodegenerative disorders, or atherosclerosis, the study of the influence of magnetic fields on the expression of genes encoding biomineralization proteins[226,227] is of key importance in the investigation of the influence of magnetic fields on living organisms.

The discovery of BMNPs in organisms of all three domains – prokaryotes, archaea, and eukaryotes – and the observed peculiarities of their formation in health and disease have prompted the investigation of their metabolic functions. Controlled application of weak static magnetic fields may cause rotation of SD magnetite, which may result in the opening of ionic membrane channels, modulation of the transmembrane potential, and/or generation of action potentials in neurons.[48,228] Simulations performed by Jandacka et al[229] show that SPM ferritin molecules cannot be deformed or rotated in weak geomagnetic fields, and thus cannot be involved in magnetoreception by deformation. Furthermore, there is an alternative hypothesis that ferritin molecules in the avian ear may function as intracellular electromagnetic oscillators, generating additional electrical fields with an amplitude of ~0.1 pV in receptor cells and consequently auditory neurons.[229] However, we think that a voltage of 0.1 pV is too low to produce any significant biological effect, since the working membrane voltages are of the order of dozens of millivolts. There is also a hypothesis that BMNP chains represent nanoscale high-gradient magnetic separators of cluster components (eg, vesicles, granules, cells) in organisms.[229–231]

We hope that further development of physical methods for the discrimination of the core minerals in ferritin in physiological fluids and/or tissue will provide powerful tools to fight neurodegenerative disorders. In this regard, we think that the magnetism of the ferritin core may be a useful prognostic indicator, especially in some neurodegenerative diseases. Better understanding of core mineral content and its composition and also tissue–organ distribution of ferritin will certainly help in clarifying the etiology of several diseases. This calls for an intensification of research into the magnetic properties of ferritin from different organs (see Figure 8) from healthy and pathological human subjects. The mapping of ferritin and BMNP in different organs and especially the brain would be very important, and not only from the clinical analytical point of view. Such studies may shed new light on long-term memory in which it is believed magnetite can be involved.[232,233] Recent studies by the Kirschvink group[234] on possible human magnetic sensing await further proof, and many questions remain unanswered.

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Disclosure

The authors report no conflicts of interest in this work.

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