Electron Tunneling in Ferritin and Associated Biosystems

Ismael Diez Perez, Sierin Lim, Christian A. Nijhuis, Olivier Pluchery, and Christopher J. Rourk, *Member, IEEE*

***Abstract*—Ferritin is a 12 nanometer (nm) diameter iron storage protein complex that is found in most plants and animals. A substantial body of evidence has established that electrons can tunnel through and between ferritin protein nanoparticles and that it exhibits Coulomb blockade behavior, which is also seen in quantum dots and nanoparticles. This evidence can be used to understand the behavior of these particles for use in nanoelectronic devices, for biomedical applications and for investigation of quantum biological phenomena. Ferritin also has magnetic properties that make it useful for applications such as memristors and as a contrast agent for magnetic resonance imaging. This article provides a short overview of this evidence, as well as evidence of ferritin structures *in vivo* and of tunneling in those structures, with an emphasis on ferritin structures in *substantia nigra pars compacta* (SNc) neurons. Potential biomedical applications that could utilize these ferritin protein nanoparticles are also discussed.**

***Index Terms*—Ferritin, electron tunneling, nanoparticle, conductive atomic force microscopy, substantia nigra pars compacta.**

I. Introduction

To a solid state semiconductor scientist or engineer, ferritin may seem like an unlikely candidate to exhibit electron tunneling and Coulomb blockade behavior, but that behavior has been extensively documented and can likely be used for bioelectronics and biomedical applications. Ferritin is a protein complex formed from 24 protein subunits that self-assemble into a spherical shell. It contains molecular machinery that allows it to receive iron in the water-soluble ferrous (Fe^{2+}) oxidation state and to oxidize it to the water-insoluble ferric (Fe^{3+}) oxidation state, which is then stored primarily as the mineral ferrihydrite. Under the right conditions, ferritin can also release the stored iron by reducing it from the Fe^{3+} oxidation state back to the Fe^{2+} oxidation state. The released iron can react with hydrogen peroxide to generate reactive oxygen species (ROS) by a process known as Fenton's reaction. It is understood by cellular biologists that cellular processes associated with ferritin are due to either the release of iron and associated increase in ROS generation, or the storage of iron and reduction in ROS generation [1]. Rather than viewing ferritin as a biological material and iron storage protein, an alternative way would be to view it as a nanomachine that has numerous biological functions in both plants and animals, and in prokaryotes and eukaryotes.

This article will discuss the unusual electrical characteristics that could make ferritin a good/interesting candidate for use as a quantum biological agent in a number of different applications. A brief overview of the structure and physical properties of ferritin will be provided, followed by a discussion of the electron tunneling properties and magnetic properties of ferritin that have been observed and documented to date. Ferritin structures that have been observed in cells and tissues will then be discussed, and some potential applications of the unusual electron tunneling properties of ferritin *in vivo* and areas for further research are identified.

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II. Overview of Ferritin: Structure and Physical Properties

Structure of ferritin: Ferritin refers to a number of different proteins that have biological origins tracing back more than 1 billion years. These proteins have a three dimensional shape that is critical to their function, and are conglomerates of identical or highly similar subunits that act as building blocks for a hollow protein shell that is roughly spherical in shape. The proteins form a molecular cage for the storage of iron. Ferritin is part of a super family of 11,500 related proteins [1].

Three protein subunits have been identified to date that can form ferritin in humans: heavy chain, light chain and mitochondrial [2]. However, the genetic structure of these protein subunits (which are formed from different combinations of monomers/residues and ligands) and the way in which they function can vary from species to species, such as in bioluminescent worms [3], plants [4] and bacteria [5], [6]. While the different types of ferritin generally self-assemble to form iron-storing spherical protein complexes, their chemical and physical properties can vary. Each ferritin is unique. Ferritins that have been isolated and studied include those that are derived from horse spleen, human, bacteria, and archaea. Ferritin with no iron stored is referred to as apoferritin, and ferritin that contains stored iron is referred to as holoferritin.

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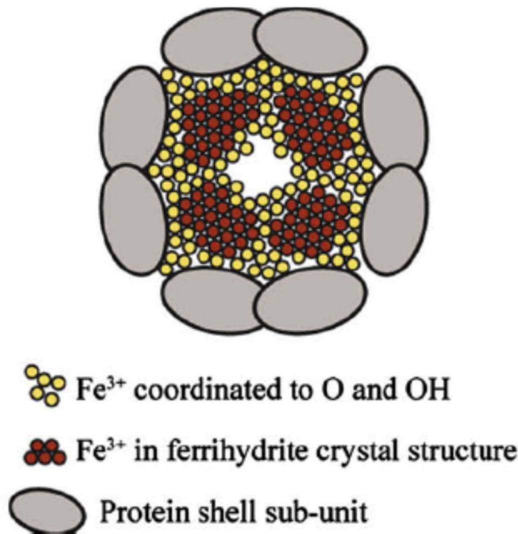

Fig. 1. Stylized diagram of protein sub-units and core material structures of ferritin. From [9].

Iron uptake and release mechanisms by ferritins: Ferritin serves as iron storage and distribution in the body of mammalians, as well as other species. The iron content from ferritin that has been harvested from organisms is primarily ferrihydrite, but the manner in which ferrous iron is received and stored in ferric form in ferrihydrite structures and then released again when needed results in complex mechanisms within the core that change as a function of iron loading and the cellular environment [7], [8], [9], [10]. The ferritin 24 subunit protein shell has channels where ferrous iron enters the core, and other channels where it leaves (not explicitly shown). As the ferrous iron is oxidized into ferric iron compounds such as ferrihydrite, magnetite and hematite by the protein structures (which essentially function as nanomachinery, as discussed), it forms precursors that accumulate and surround separate crystalline core structures [9], [11].

Electrical considerations on ferritins: It has been shown that ferritin can store electrons for at least up to 3 hours when loaded with electrons that are implanted from an electron beam or activated from the protein shell by UV light [12], and can store a large number of electrons that reduce the stored Fe^{3+} ions to Fe^{2+} ions within the protein shell with a low rate of release of Fe^{2+} from the core in the absence of a chelator [10]. It has also been observed that even when the number of stored electrons is equal to the number of Fe^{3+} ions in the core, the amount of iron released is less than 20%, in the absence of a chelator. These observations establish that electrons are not easily conducted through the protein shell, and that chemical processes involving the ferritin protein subunits or tunneling is associated with electron movement into and out of the core. It has also been shown through experiments and molecular dynamics modelling that storage and release of iron from the core can be a function of the pH of the surrounding fluid in which the ferritin is contained [13]. The structure of the core materials changes as the number of stored electrons increases, and also as a function of electron energy and dose [7], [8], [9].

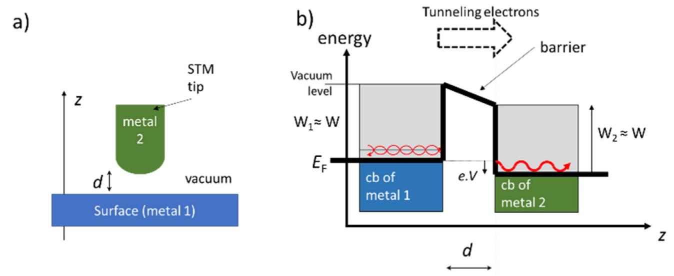

Fig. 2. Principle of the tunneling effect. a) Two metallic conductors such as an STM tip and a surface are placed at a distance d from each other in vacuum. b) Energy diagram: due to quantum tunneling, the electron can cross the barrier of height W when a potential difference V is applied, even is its energy is lower than the barrier.

III. Electron Tunneling Properties of Ferritin

The efficiency of electron transport (ET) over long distances in biological systems can be remarkably high and underlies many processes including enzymatic catalysis or photosynthesis. The mechanism of charge transport depends on the specific molecular structures, how strongly the molecules couples to other molecules or electrodes, tunneling barrier height, electron-vibration coupling, and other factors [7].

Electron tunneling is a well-known mechanism of electron transport in solid-state physics where the charge carrier succeeds in crossing an energetic barrier although this barrier is higher than the energy of the charge carrier. Before discussing this phenomenon in biological media, it is important to recall some key physical parameters of electron tunneling. Electron tunneling is the central phenomenon of Scanning Tunneling Microscopy (STM) and occurs when a metallic tip (metal 2) is approached in the close vicinity of a surface (metal 1) as shown in Fig. 2(a). The distance between the two metals is noted d. Free electrons in metal 1 have an energy close to their Fermi energy E_F. They are situated in the conduction band (cb) of the metal and are represented by a wave in a quantum physics approach as depicted in Fig. 2(b).

For pure tunneling, the energies for the incoming and tunneled electron are the same, what changes is the probability (the amplitude of the wave function). Energy will change if an inelastic process occurs during the electron transport process, in which case the electron will exchange energy and the final energy of the transmitted electron will then be different. Inelastic processes can be referred to as sequential tunneling or hopping. The term "tunneling" may be used for a pure elastic quantum mechanical tunneling when electron do not interact with the medium.

Referring to Fig. 2(b), in order to extract such electrons to the vacuum (*i.e.*, outside of metal 1), they need to receive an energy W_1, which is the work function of metal 1. These electrons can be collected by the metal 2 and they will recover an energy W_2. Here, we assume that $W_1 \approx W_2$ for the sake of simplification. This value is noted W. Fig. 2(b) illustrates the energy barrier of height W that electrons need to cross. The tunneling effect is a quantum physics phenomenon that states that even if the electrons have an energy smaller than W, a fraction of them might cross this barrier and give raise

to a current in accordance with equation (1):

$$J_{tunnel} = J_0 \exp\left(-2d\sqrt{2mW/\hbar^2}\right) \quad (1)$$

Here, m is the mass of the electron, $\hbar$ is the reduced Planck constant and J_0 a proportionality constant. Equation (1) shows several important features of tunneling effect. First, the current quickly decreases with the distance d between the two conductors. Since typical values of the work function of metals are $W = 4$ eV, it is easy to calculate that the tunneling current is divided by 10 when the distance increases by just 0.11 nm. Actually, when performing STM on metals, the tip-surface distance is in the order of magnitude of 0.3 nm away from the surface (it is noted that STM can also be performed in a liquid environments (even a polar liquid like water), which may be more suitable for testing ferritin, and that the distances are higher, typically with STM junctions of 1.5-2 nm). Therefore, a distance of $\sim$0.5 nm represents the typical length scale of tunneling phenomena in vacuum. The tunneling distance is far larger in a biomolecular system.

A second important consequence from Equation (1) is that the tunneling rate increases when the barrier height W decreases. This is the case when the electrons tunnel through the lowest unoccupied molecular orbital (LUMO) of a biomolecule instead of vacuum. Finally, Equation (1) also shows that the tunneling current is independent of the temperature, which is an important method for asserting this way of charge transport.

Tunneling was proposed as a charge transport (CT) mechanism across the protein shell of ferritin as early as 1988 [14], and much later confirmed in other protein structures [15]. Experimental evidence of quantum tunneling associated with ferritin was obtained as early as 1992 [16]. The earliest test to provide an indication of electron tunneling associated with ferritin through the use of conductive atomic force microscopy (c-AFM) may have been reported in 2005 [17]. In that set of experiments, the metallic tip of the AFM, was used to measure current as a function of applied voltage through individual ferritin cores that were deposited on a gold substrate. Current measured through holoferritins was 13 times larger than the one measured through apoferritins. The conclusion that electron tunneling could be occurring was based on the fit of the current-voltage measurements to the Fowler-Nordheim theory, a model of tunneling associated through a rounded triangular barrier created at the surface of an electron conductor. While these tests ruled out adiabatic, ballistic and conductive electron transport as the primary mechanism by which electrons move through ferritin, they did not study the effect of temperature variations that could be used to determine whether the electron tunneling was coherent or incoherent (also referred to as incoherent hopping). Nevertheless, these tests showed that tunneling was dominant even through distances as large as 9.5 nm which was the thickness of the ferritin measured with AFM [17]. It is noted that other AFM-based techniques, such as electrostatic Force Microscopy (EFM), Kelvin Probe Force Microscopy (KPFM), Piezoresponse Force Microscopy (PFM) and Scanning ElectroChemical Microscopy (SECM) have been used to investigate other nanoscale electrical properties of

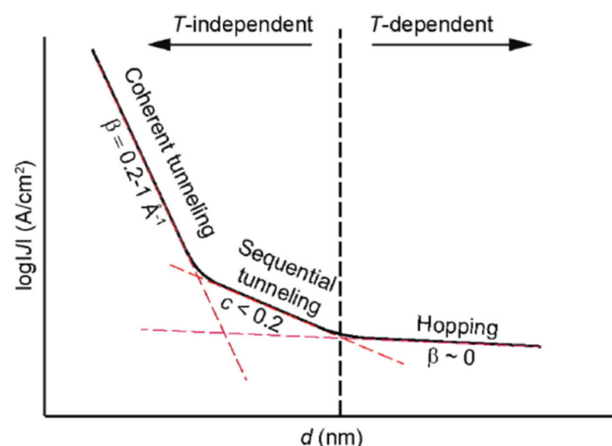

Fig. 3. Schematic representation of the tunneling regimes through a molecular bridge connected to metallic electrode. (Reproduced with permission from [7]).

biostructures such as DNA and bacteria [18], and experiments could also be designed using these techniques to look for ET mechanisms. Quantum biological electron transfer mechanisms such as tunneling and hopping have been observed in many other biological structures, such as microbial nanowires [19] and encapsulin [20].

Long range tunneling in molecular and biomolecular electronics occurs through three families of processes as explained in [7] and summarized in Fig. 3. In this figure, d is the distance that electrons need to cross between two electrodes through a biomolecule or an assembly of biomolecules. Coherent tunneling occurs when the *molecular bridge* is short (< 4 nm). It sharply depends on the distance following the classical tunneling relationship:

$$J = J_0 \exp(-\beta \mathrm{d}) \quad (2)$$

Here, β is large with values of 0.2 - 1.0 Å^{-1}.This is called the ***coherent tunneling*** because the wave function of the electron retains its phase through the molecular bridge. However, when this latter increases, the various collisions undergone by the electrons lead to an incoherent tunneling or ***sequential tunneling***. In this regime the current follows the relationship:

$$J = J_0 \exp(-\mathrm{cd}) \quad (3)$$

where the decay constant c is smaller than β ($c < 0.2$ Å^{-1}). These two regime do not exhibit any dependence with the temperature.

Finally, when the molecular bridge becomes larger than $\sim$15 nm the temporary trapping of the electrons inside intermediates states leads to thermally activated processes (activation energy E_a) and a weaker dependency with the distance d ($\beta \sim 0$). In this case, the current follow the relationship:

$$J = J_0 \exp(-E_a/\mathrm{kT}) \quad (4)$$

Kumar et al. and his group studied how ferritin exhibits long range tunneling as a function of iron loading and temperature [7]. It was shown that tunneling over distances as

great as 8 nm between electrodes may occur. With holoferritin and iron loading between 1200 and 4800 iron atoms per ferritin, the CT is dominated by sequential tunneling. When the molecular bridge is constituted with one monolayer of apoferritin, the CT however is controlled by hopping and strongly temperature dependent [7], [21]. Tests on ferritin and other proteins using other junction configurations have also been conducted [22]. Because these tests and the other tests discussed below measured current between two electrodes that were both in contact with the ferritin particle, it was possible to gain a more thorough understanding of the electron transport mechanisms associated with ferritin, but a determination of whether tunneling between an electrode and a ferritin particle that was separated by a distance was not possible.

Electrode-biomolecule contact: In molecular electronics, it is well known that CT is strongly affected by the contact between the electrode and the molecule [23]. This effect was also investigated with biomolecules, using monolayers of ferritin on bilayer graphene (BLG). The use of graphene allowed electrostatic adjustment of the Fermi level of the electrode and tuning of the contact from Schottky-type behavior to ohmic behavior [24]. It was determined that in this configuration, electrons would migrate from the BLG into the ferritin, resulting in an induced doping in the BLG. It was concluded that the BLG has a vanishing density of states toward its intrinsic Fermi level ("Dirac point"), which increases away from the Fermi level, in contrast to ferritin junctions with metal electrodes. The amount of charge carriers in the BLG was found to be sensitive to temperature and electrostatic charging (induced doping). The temperature dependence of the electron transport through the contact was found to be within the coherent tunneling regime due to excitation of hot carriers. Ferritin-graphene structures have also been used to fabricate a stable p-n junction [25]. These experiments demonstrated the importance of understanding the impact of the contact material and other environmental factors when studying electron tunneling associated with ferritin.

Evidence of a tunneling mechanism associated with ferritin that was hypothesized to possibly be magnon-assisted has also been reported [26]. Large values of tunnel magnetoresistance were observed for junctions based on ferritins immobilized between Ni and EGaIn electrodes. The study concluded that ferrihydrite nanoparticles (NPs) in the ferritin core that contain magnetite and maghemite defined the tunnel barrier, and that the ferritin magnetically decoupled the NPs from a ferromagnetic (FM) electrode and stabilized the NPs. The data also indicated that ferritin acts as a spin filter, and has the potential for use in biomolecular tunnel junctions of nanoscale spintronic devices.

The electron spin characteristics of ferritin have also been observed using nanometer-sized diamonds containing nitrogen-vacancy defect centers (NV) [27]. Ferritin induced magnetic noise as a function of the inner paramagnetic iron acts as a contrast mechanism, where a reduction of both coherence and relaxation time was observed due to the presence of ferritin on the surface of the nanodiamonds. These tests provide additional empirical evidence of electron spin states in

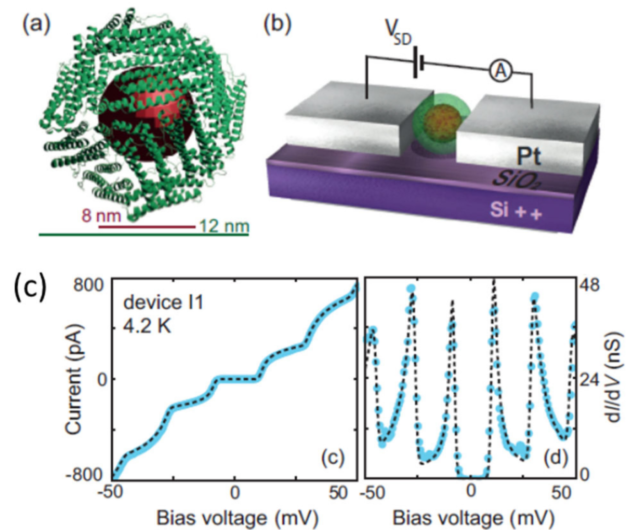

Fig. 4. a) Ferritin protein depicted with its iron core (metallic island) and the protein cage (insulating tunnel barrier). b) The ferritin is placed between source and drain electrode at 5 K and when a bias V_{SD} is applied the current is controlled by Coulomb blockade. c) The electrical current through the device exhibits steps (left panel) and the current derivative shows regular peaks which is a clear indication of single electron charge transport controlled by Coulomb blockade. Reproduced from [30].

the ferritin core due to ferrihydrite NPs that contain magnetite and maghemite.

Double barrier tunnel junctions: As explained before, holoferritin can be viewed as a thin protein cage that is insulating and a ferrihydrite core. The protein provides an insulating barrier whereas the iron core is the so-called conductive *island* (see Fig. 4(a)). This system is a double tunnel barrier junction that is known to exhibit Coulomb blockade behavior at low temperature [28], [29], [30]. In the Coulomb blockade regime, electrons are allowed to cross the metallic *island* one by one, or two by two, *etc.* as a function of the applied potential between drain and source, V_{SD} (see Fig. 4(b))

The group of Labra-Muñoz et al. have demonstrated such single electron tunneling behavior through individual ferritin particles at 4 K, and demonstrated behavior consistent with the formation of a Coulomb blockade as shown in Fig. 4(c) [30]. Single-electron devices based on horse-spleen ferritin particles were tested at low temperatures, and the current/voltage characteristics were stable enough to enable the acquisition of reproducible data that established the Coulomb blockade as the main transport mechanism through the ferritin particles, similar to fabricated nanoparticles. The ability to realize single-electron charge transport in ferritin establishes a route for further characterization of its magnetic properties at the single-particle level, with prospects for electronic and medical applications.

In addition to studies of the electron tunneling properties and behavior of individual ferritin cores, electron transport in quasi-ordered ferritin structures has also been studied. They allow fabricating larger molecular bridge and further testing the long distance electron tunneling between two electrodes. Multilayer ferritin arrays have been demonstrated between two electrodes separated by a distance of 40 microns, with current

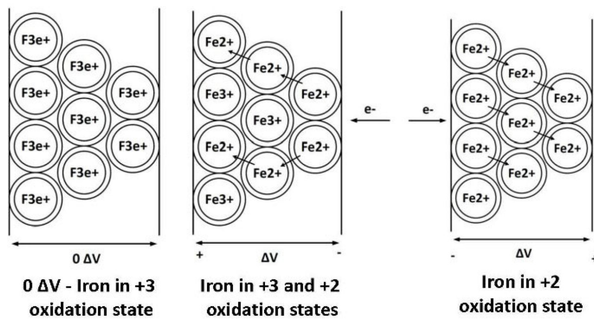

Fig. 5. Coulomb blockade formation in ferritin structures.

of 0.3 microamperes measured at 3 volts [31]. This separation distance is equivalent to sequential tunneling though approximately 3300 ferritin particles. The disordered multilayer ferritin arrays were formed using a layer-by-layer fabrication technique that provided sufficient ordering in each layer to support electron tunneling, consistent with models of electron tunneling through disordered quantum dot layers [32]. Because ferritin is a nanoparticle, precise placement of ferritin cores in devices is difficult, and the layer-by-layer process used in the tests demonstrated that it was potentially viable for device design and manufacture. Observations of similar electron tunneling effects in ferritin layers have also been reported [33], [34].

The layer-by-layer fabrication process was subsequently used to manufacture four terminal devices with interdigitated and parallel electrode design configurations and different separation distances, to perform a parametric study of electron transport as a function of the number of layers and electrode separation distance, and also to determine whether a switching mechanism was present in such multilayer ferritin structures [35]. A maximum of 3 microamperes of current was measured at 3 volts in one of the devices with an electrode separation distance of 80 microns. This separation distance is equivalent to sequential tunneling though approximately 6600 ferritin particles. In these tests, it was observed that the yield of devices that were capable of supporting electron tunneling using the layer-by-layer deposition process was approximately 25% and highly variable, with 75% of the manufactured devices producing no measurable current between electrodes. These results further indicate that long-distance electron tunneling associated with ferritin results from its quantum dot-like properties in devices where a sufficient level of order within each layer and between layers was obtained, and not from classical conduction. A switching function was also observed for some devices, which was consistent with Mott insulator behavior resulting from Coulomb blockade formation. The switching function was not observed in every device that was capable of supporting long-distance electron tunneling, and was hypothesized to result from structural disorder arising from the fabrication process, see Fig. 5. These results suggest that devices with controllable forward and reverse current-voltage characteristics could be designed using controlled placement of ferritin particles between electrodes.

Small angle neutron scattering (SANS) of self-assembled monolayer arrays of ferritin cores on a silicon substrate and encapsulated in a silica matrix has also been observed [36]. The protein shell was removed for monolayer arrays by heating after the layers were formed, which resulted in a separation of at least 4 nm between cores. Measurable SANS is also a characteristic of quantum dot systems [37], but the resultant devices were not tested for electron tunneling.

This body of work has thus established that ferritin can store electrons and use a tunneling mechanism that may be magnon-assisted to enable coherent and incoherent electron tunneling in configurations that include molecular junctions, ferritin-metal junctions and three dimensional ferritin structures having at least planar dimensional order. Ferritin thus has potential for use in a wide range of nanoscale, mesoscale and larger circuits, depending on the specific device configuration and design, similar to quantum dots.

IV. Magnetic Properties of Ferritin

As discussed, electron tunneling associated with ferritin may be due at least in part to the presence of magnetite microdomains within the core and magnons associated with electron transport through the surrounding ferrihydrite crystalline structures. These magnetite microdomains also create magnetic properties that can potentially be used for nanoscale circuits or other applications.

For example, ferritin-based memristor devices have been reported [38]. These devices used on-wire lithography to create a 12 nm gap that was filled with up to 700 ferritin particles. Subsequent tests that provided evidence of room-temperature hysteresis of ferritin [39] suggest that ferroelectric effects may be associated with this observed memristive behavior [40]. One potential advantage of using ferritin for such applications is that it is formed from self-assembling proteins and can be easier to fabricate than other nanodevices. The memristive behavior of ferritin has also been observed to vary as a function of iron loading [41].

Ferritin can also be used as a T2 contrast agent for magnetic resonance imaging (MRI) [42], [43]. Different types of ferritin (such as genetically-modified ferritin from *Archaeoglobus fulgidus* (AfFtnAA), a bacteria-like single-celled organism), and different iron loading conditions (such as in an anaerobic environment) can significantly increase the amount of magnetite and maghemite formation in the core of the ferritin particles, which not only improves its performance as an MRI contrast agent, but which could also improve its magnetic and electron tunneling properties for other applications [39].

V. Ferritin Structures In Vivo

Evidence also exists that biological structures evolved to utilize the electron tunneling properties of ferritin, and that they could possibly be used to create electrical interfaces with biological systems and tissues. This evidence has been difficult to establish because ferritin is a nanoparticle and was not readily observable in tissues prior to the commercial development of electron microscopy in 1938. In addition, very few studies have been conducted to determine whether these ferritin structures are capable of routing energy that uses quantum mechanical effects such as electron tunneling, in a

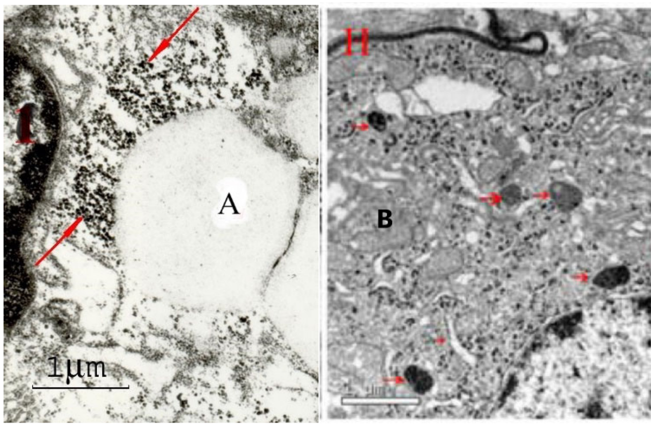

Fig. 6. Comparison of ferritin structures in a) placental macrophages and b) in glial cells.

manner similar to that photosynthetic biosystems [44]. This section will review the evidence that has been obtained to date, and proposes a number of hypotheses of areas where future research could be conducted to identify potential applications involving the electron tunneling properties of ferritin.

A. Macrophages

Even after ferritin was observed using electron microscopy, evidence that suggested electron tunneling is associated with ferritin was not obtained until 2004, when increased self-aligned magnetic ordering of ferritin structures in placental macrophages was observed using SANS [45]. As can be seen in Fig. 6(a), the ferritin in the electron microscope images of placental macrophage cells is visible as black, electron-dense dots, and forms quasi-ordered three dimensional structures. The increased magnetic ordering of the ferritin that naturally occurred in these fixed tissues, as indicated by SANS, was substantially greater than the magnetic ordering of the ferritin after it was removed from the tissues and tested. Similar magnetic ordering has been observed in self-assembled ordered monolayers of ferritin cores [36] and also in quantum dot solids [37]. It has not yet been investigated whether these structures have the capability to support long distance electron tunneling at room temperature under ambient conditions in the same manner as quantum dot arrays. In placental macrophages, the electron transfer function may be used by those cells to provide electrons to neutralize ROS and free radicals associated with infections inside of the placenta. In this regard, it is noted that macrophages form part of the magnetosensory mechanism of migratory birds [74], and are also associated with providing ferritin to cancer cells [75]. At present, it is unknown whether the electron transport properties of ferritin in macrophages could help to explain migratory behavior in animals or provide additional treatment approaches for cancer.

B. Amoeba

It is hypothesized that ferritin iron loading may be used in biological systems as a data storage mechanism. For example, amoeba use ferritin for iron storage [46], and also exhibit learning behavior that can be modelled using a memristive model [47]. Complex hybrid computing processes in other single-celled organisms, such as for flagella control, have previously been identified [48]. In view of the experimentally-observed memristive behavior of ferritin as a function of iron loading, it is possible that biological systems such as those that control the behavior of single-celled or larger organisms have evolved to utilize that capability of ferritin, and further investigation would seem to be warranted.

C. Cochlea

Ferritin has been found in high concentrations in a subtype of intermediate cells of the *stria vascularis* of the cochlea, in the vicinity of melanin [49], [50]. Because ferritin contains iron in the Fe^{3+} oxidation state, it may have electrical characteristics similar to a P-type semiconductor material. Melanin is a pi-conjugated polymer and has characteristics of an N-type semiconductor material. The *stria vascularis* has been characterized as a "battery" [51], and it is hypothesized that the observed potential is associated with the junction potential created at the interface between the ferritin and melanin, in response to electrons that migrate from the melanin into the ferritin and holes that migrate from the ferritin into the melanin, similar to charge migration observed at ferritin-BLG junctions. Melanin also exhibits strong electron-phonon coupling and sound absorption properties [52], so it is further hypothesized here that melanin also modulates the junction potential as a function of the sound energy received, which could help to protect the cochlea from damage. However, further study is needed to understand how ferritin and melanin might be associated with cochlear function.

D. Neurons

Evidence of ferritin structures in electron microscope images of glial cells of the substantia nigra pars compacta (SNc) that are similar to the ferritin structures from placental macrophages that were tested with SANS is shown below in Fig. 6(b) [53]. In this regard, it is noted that glial cells and macrophages are similar cell types. It is also noted that [53] does not identify the electron dense structures as ferritin, but there is substantial similarity between those and the electron dense structures in the electron microscope images from Mykhaylyk that were positively identified as ferritin. The spacing of the electron dense dots in Xiong appears to be greater than that observed by Mykhaylyk, with distances of perhaps 10-20 nm between some particles, and none of the tests on ferritin in solid state configurations have been capable of measuring electron tunneling between ferritin cores or ferritin and an electrode that are separated by distances of more than approximately 4 nm. As such, the ability of ferritin to support electron tunneling over such distances has not yet been corroborated in solid state experiments. Electron microscope imaging evidence of ferritin structures in catecholaminergic neurons in layers of iron outside neuromelanin organelles (NMOs) [54] and particle-induced X-ray emission evidence of iron in regions between SNc dopamine neurons [55] has also been obtained. Charge migration between the layers of ferritin outside of NMOs and the neuromelanin inside of the

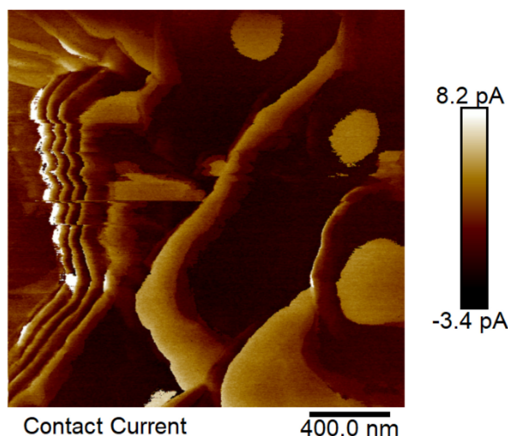

Fig. 7. Conductive atomic force microscopy image of tunneling currents in substantia nigra pars compacta neuron from ferritin layers outside of neuromelanin organelles.

NMOs could condition the ferritin to have a higher loading of electrons, to make it more sensitive to electron tunneling from nearby neurons as part of a hypothesized inter-neuron signaling mechanism [56].

Based on that hypothesis, conductive AFM was performed on fixed human SNc tissue. Current measurements consistent with widespread electron tunneling were obtained, and at higher resolution, the tunneling currents corresponded to layers of ferritin outside of NMOs in that tissue, as well as the NMOs themselves [57]. An example of these tunneling currents can be seen in Fig. 7, which maps 250,000 electron separate tunneling measurements that were measured using an AFM probe operating at a mechanical oscillation frequency of approximately 100 Hz. These measurements suggest a frequency-related electron tunneling response for the different structures in these tissues, but additional research in this area is needed. It is also noted that the ferritin layer structures are consistent with those observed using electron microscopy by Sulzer, and that the probe tip of the conductive AFM equipment may have been able to make direct contact with those ferritin structures, but would have been separated from the NMOs by a tissue layer of at least several nanometers and possibly more.

E. Mitochondria

Ferritin is also present in mitochondria at different levels in different tissues. For example, mitochondrial ferritin is present in higher concentrations in certain tissue (e.g., brain, heart, kidney) than others (e.g., liver, esophagus) [58]. In addition, it has been observed that *cristae* in mitochondria accumulate protons [59], which suggests a functional relationship with electrons stored in mitochondrial ferritin, although that has not yet been investigated. It has been observed that the protons stored in mitochondrial *cristae* have a capacitive function [60].

F. Inflammation

Ferritin is overexpressed in tissues in response to inflammation, which results from ROS and free radicals, and catalyzes neutralization of ROS by antioxidants [61], even when the ferritin core is filled with platinum nanoparticles [62]. While it has not been shown that electron tunneling from ferritin is the mechanism associated with this catalytic function, it should be possible to test for electron tunneling using QD fluorophores that have been conjugated with ferritin antibodies [63]. Given that storage and release of iron by ferritin is generally not associated with inflammation and antioxidant function, which occurs in the absence of significant concentrations of cytosolic iron, it is hypothesized here that electron tunneling associated with ferritin could be involved, as that would not only allow the ferritin to store excess electrons that are received from antioxidants until they are needed to neutralize free radicals, but would also increase the effective area over which the electrons would be available to interact with the free radicals, compared to electrons that are still physically associated with antioxidants.

G. Retina

Substantial concentrations of ferritin have been identified in the retinal pigment epithelium, inner segments of the rod and cone cells, and the outer plexiform layer of the retina, adjacent to pigments that include melanin and rhodopsin [64], [65]. It has been observed that pigment-protein complexes are used in photosynthetic biosystems to route energy [44]. As such, it is hypothesized here that ferritin may form pigment-protein complexes in combination with the pigments in these cells, and may help to direct energy flow in the retina. Ferritin in the retina could also be associated with protective storage of electrons from long-lived triplet electron chemical complexes, which have been observed to be capable of persisting for hours in association with UV exposure of melanin in skin cells and subsequent DNA damage that can result in skin cancer [76].

H. Other Tissues

Evidence of ferritin structures like the ones found in placental macrophages, the cochlea and catecholaminergic neurons does not appear to have been specifically sought yet in other tissues, but those structures may be found in a number of tissues that have high concentrations of ferritin. Ferritin has been identified in heart, liver, spleen and bone marrow tissue as well as erythrocytes, leucocytes and platelets [66], and may form closely packed structures with increased ordering in one or more dimensions, similar to placental macrophages.

VI. Applications for Electron Tunneling in Ferritin Structures In Vivo

A number of biomedical applications for ferritin have been proposed. These include biomolecular electronics [67], theranostics [68], nanomechanical sensors [69], [70] and bio-nanotechnology [71]. The identification of electron tunneling in ferritin structures in fixed brain tissue and the possible frequency-specific electron tunneling characteristics of those ferritin structures and other associated biostructures may open the path to using such structures to detect electrical activity associated with the structures and to functionally interface with them.

For example, a neural probe for deep brain stimulation (DBS) that has been discussed in the literature has an electrode size of 16 microns and spacing of 74 microns [72], which would allow it to be used for detecting signals in the ferritin structures of the SNc and possibly to provide stimulation to SNc neurons through those structures. It is hypothesized here that this mechanism could also be used to increase the accuracy for DBS probe placement by greater than one order of magnitude, as such placement accuracy is presently approximately 1 millimeter.

DBS-compatible probes are also used for other applications, such as to stimulate the vagal nerve [73]. It is further hypothesized here that other ferritin structures, such as those in placental macrophage cells, could potentially be monitored and interacted with using those probes, such as to detect activity in placental macrophages associated with infection without penetration of the placenta to access amniotic fluid and to help neutralize ROS and free radicals arising from such infections.

The identification of the function of ferritin and melanin in the *stria vascularis*, ferritin in the retina and the relationship between macrophages, cancer cells and ferritin may also have biomedical applications, once they are more fully understood.

Other applications will likely become apparent with the identification of ferritin structures *in vivo* and their associated function. QD fluorophores or other new diagnostic techniques could provide an easier way to investigate living tissues instead of electron microscopy.

VII. Conclusion

Electron tunneling associated with ferritin makes it a quantum biological agent that has potential applications in a number of areas. While iron release and the associated Fenton reaction are often assumed to be the mechanism associated with cellular processes that involve ferritin, that assumption may be due to a lack of familiarity with electron tunneling in ferritin by researchers in that area. Further research is needed to develop a better understanding of both where electron tunneling associated with ferritin may be occurring *in vivo* and how that physical mechanism could be used to treat diseases and disorders.

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