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Magnetoferritin: A Novel Magnetic Protein Cage Nanocarrier

Sumedha Bobade*, K. Vijayarani, K.G. Tirumurugaan, A. Thangavelu, S. Vairamuthu and G. Kalaiselvi

Department of Animal Biotechnology, Madras Veterinary College, TANUVAS, Chennai (Tamilnadu), India

**Corresponding author*

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A B S T R A C T

Nanotechnology is the rapidly expanding field and nanoparticles are omnipresent. Biological nanoparticles are assembled from molecules or atoms synthesized in a biological system. They include magnetosomes, lipoproteins, viruses, exosomes and ferritins.. A typical instance of a protein cage possessing this native biological function is ferritin. This engineered ferritin, which has the same architecture as natural H-ferritin, is termed magnetoferritin. The iron storage protein ferritin consists of a spherical polypeptide shell (apoferritin) and accommodates various metal ions. During the last two decades, the manipulation of protein cages for the encapsulation of single inorganic nanoparticles into their core to design novel hybrid bioinspired nanoparticles Such hybrid nanoparticles represent an opportunity for advanced nanotechnology applications in the nanodevices, disease diagnosis and therapy, drug delivery, vaccine development and bioassay.

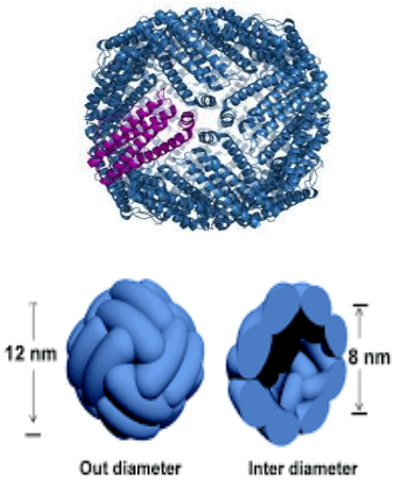
Introduction

Nanoparticles are the spearheads of the rapidly expanding field of nanotechnology. Among all classes of biological nanoparticles ferritins, an ubiquitous iron storage and transport proteins found in most living organisms, eubacteria, archea, plants and animals except yeast. Ferritin was discovered in 1937 by Laufberger, as a novel protein structure for storing and transporting iron molecules isolated it from horse spleen. The FRT superfamily can be divided into three subfamilies: the classical FRTs; the bacterioferritins (BFRs); and the DNA-binding proteins from starved cells (DPSs). Ferritins have been classified as maxiferritins and miniferritins. The maxiferritins, 12 nm in diameter with 8 nm diameter cavities, formed from 24 subunits (MW ≈ 480 kDa); and miniferritins, also called DNA protection during starvation proteins, 8 nm in diameter with 5 nm diameter cavities, formed from 12 subunits (MW ≈ 240 kDa).

The classic ferritin (Ftn), found in eukaryotes and some bacteria, is a four-helix bundle protein of around 200 amino acids. Some bacteria and archaea possess bacterioferritin (Bfr), The mini-ferritin, DNA-binding Protein

from Starved cells (DPS), was initially discovered in *Escherichia coli* cells during the stationary phase and is found in many bacteria and some archaea and its primary role is to protect the bacterial chromosome from oxidative damage (He and Wright, 2015).Ferritin is a large protein of 450 kDa composed of 24 subunits that self-assemble into a spherical complex cage-like structure. One molecule of ferritin stores up to 4,500 iron atoms.

Fig.1 Structure of Ferritin



The emergence of nanotechnology, ferritin nanoparticle has been biomimetically synthesized using H-chain ferritin as a template, which self-assembles to form a 24-subunit cage-like nanostructure, with an internal iron oxide core (Fig. 1). This engineered ferritin, has same architecture as natural H-ferritin, is termed magnetoferritin. The structural and biochemical properties of ferritin protein are used for tailoring it to a wide range of applications, from the synthesis of nanoparticles to the design of vaccines in biomedicine (He and Wright, 2015).

Appoferritin

The iron storage protein ferritin consists of a spherical polypeptide shell (apoferritin) surrounding a 6-nanometer inorganic core of the hydrated iron oxide ferrihydrite ($5Fe_2O3$-$9H_20$). The incorporation of magnetite into the apoferritin has been conducted to manufacture magnetoferritin. The magnetic property of magenetoferritin, which contains magnetite (Fe_3O_4) instead of the hydrated iron oxide, has been implied to have potential in biomedical and industrial applications, such as an information storage device and for biomedical imaging. The structure of apoferritin is remarkably stable and robust, and it is able to withstand biologically extreme temperatures (up to 70°C) and a wide pH range (pH 2.0–10.0) for an appreciable period of time without significant disruption of their quaternary structure.

Application

Ferritin is itself a catalytic bionanoparticle and nanocarrier, a safer choice, when engineered or appropriately distributed in a biological system.

Drug delivery

Mosca *et al.*, (2017) studied the ability of ferritin to bind and deliver metals and metal-based drugs to human neuroblastoma SH-SY5Y cells. They used heavy chain (H) ferritin-based metal-containing nanocarriers used for the delivery of toxic molecules to brain cells, Iron-containing nanocarriers have a proliferative effect and ferritins can be used for the delivery of toxic molecules to brain tumors. Liang *et al.*, 2014, developed a natural H-ferritin (HFn) nanocarrier that delivered the therapeutic drug doxorubicin (Dox) to tumor cells and significantly inhibited tumor growth with excellent biocompatibility and safety profiles in murine cancer models.

Bioassay

Fan *et al.*, 2018 developed a novel platform and named fenobody by substituting the fifth

helix of ferritin with the nanobody, in which a nanobody developed against H5N1 The fenobody system presents a suitable platform for various large-scale biotechnological processes and should greatly facilitate the application of nanobody technology in these areas.

Genetically functionalized ferritin nanoparticles with a high-affinity protein binder can be utilized as a signal generator in a variety of immunoassays and imaging. The repebody-functionalized ferritin nanoparticles can be effectively used for sensitive and specific immunoassays and imaging in many areas (Kim *et al.,* 2017).

Uchida *et al.,* 2006 synthesized an iron oxide (magnetite) nanoparticle within the interior cavity of a genetically engineered human H-chain ferritin (HFn) capable to serve as a multifunctional nanoscale container for simultaneous iron oxide loading and cell-specific targeting.

Charlton *et al.,* 2016, Ferritin is a naturally occurring iron storage protein, proposed as a clinically relevant nanoparticle with applications as a diagnostic and therapeutic agent. Cationic ferritin is a targeted, injectable contrast agent to measure kidney microstructure with MRI.

Vaccine development

Fusion of eight influenza hemagglutinin (HA) trimers or engineered HA stem antigens to *Helicobacter pylori* ferritin greatly improved NAb responses against influenza in animals (Kanekiyo *et al.,* 2013). Human ferritin heavy-chain nanoparticle (hFTH) is genetically engineered to present tumor receptor-binding peptides (antibody and/or RGD-derived cyclic peptides, named 4CRGD) on its surface. The specific interactions between receptors on tumor cells and receptor-binding peptides on engineered hFTH is critical in active tumor cell targeting (Kwon *et al.,* 2016)

Wang *et al.,* 2017 confirmed that the ferritin nanoparticle is a robust platform to present antigenic peptides and ideal system for rational design of immunogens. The feasibility was investigated using the *Helicobacter pylori* ferritin (Hpf) nanoparticle to present rationally designed gonorrhea vaccines

Ferritin, an iron-containing natural protein nanoparticle, was applied as a biomaterial to improve the self-renewal and differentiation of NSCs and neural progenitor cells (NPCs). This can be applied in neural tissue engineering and cell therapy for neurodegenerative diseases (Lee *et al.,* 2018)..

Cancer therapy

Hwang *et al.,* 2013, genetically modify apoferritin and generate a universal interface system with high targeting efficiency, in detection of a pancreatic cancer biomarker and used to demonstrate its potential in the facile exchange of nanoprobe components.

In Mouse model study, Human ferritin nanoparticle (HFn) conjugated Arg–Gly–Asp (RGD) enhanced near-infrared fluorescence imaging (Kitagawa *et al.,* 2012) and MRI imaging (Kitagawa *et al.,* 2016) of AAAs in the and II-infused Apo E−/− mouse model.

Iron deficiency is a worldwide nutritional disorder. Iron enriched yeasts and cereals are alternative strategies to diminish iron deficiency. The yeast *Saccharomyces cerevisiae* lacks ferritin and uses vacuoles as iron storage organelles. The soybean ferritin expression influenced yeast iron metabolism, confirming that yeasts that express soybean seed ferritin could be explored as a novel

strategy to increase dietary iron absorption (Rosa *et al.,* 2016).

Nano actuation

Nano actuation is actuation of a specific action using a nanoscale object with or without the input of an external force acting on it. The ferritin nanoparticles dissipate heat when exposed to AC magnetic field which triggered calcium ion influx facilitated by TRPV1 activation. Calcium ion influx initiated transgene expression of insulin. Insulin in turn lowered blood glucose level. This nano actuation application has significant therapeutic benefits (Stanley and Sarah, 2015).

Purification of water

The quality of natural protein ferritin that can store metal (hydr)oxide nanoparticles of tunable size in its cavity and bind oxyanions can be used in water purification by applying nanotechnology (Hiemstra and Zhao 2016).

In conclusion, the Magnetoferritin can be genetically engineered and chemically addressed to alter their functionalities for future therapeutic applications. This newly emerging biological approach will open up a new path to the fabrication of functional nanostructures based on Magnetoferritin NPs and protein nanocages as nanocarrier. The use of ferritin derivatives has potential to transform the diagnosis and treatment of tumours *in situ*.

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