A Versatile Protein Scaffold for Biotherapeutics is Ferritin

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Abstract

In almost all animals, there is an endogenous protein called the ferritin nanocage. The hollow spherical structure's capacity to naturally store iron ions has been used in a variety of bio-therapeutic research projects. The nanosized ferritin particles show controlled/ sustained release pharmacokinetics and have outstanding biosafety characteristics. Additionally, the huge surface-to-volume ratio and the behaviour of the 24 monomer subunits breaking down and reassembling into a sphere allow for a variety of chemical and genetic alterations on the ferritin surface and inner cage. Here, we offer a critical analysis of ferritin and its uses. We offer an (i) overview of the use of ferritin in imaging and diagnosis for biomedical reasons, (ii) explore ferritin-based vaccinations, and (iii) examine ferritin-based agents now in clinical trials. We also introduce the application of ferritin in drug delivery. Ferritin is a versatile protein scaffold that exhibits enormous potential for drug development across a variety of categories, despite the fact that no pharmaceuticals based on it are currently approved, and ferritin-based medications have just recently begun phase I clinical trials. Researchers looking into ferritin and other protein-based biotherapeutics can profit and be interested right away from this rich shortlist of recent advancements.

Keywords: Biotherapeutic • Ferritin • Scaffold • Drug

Introduction

The use of protein nanocarriers has significantly advanced both illness diagnosis and treatment. Their excellent qualities allow for a variety of alterations, such as surface functionalization, and they enable the quick dispersion of loaded pharmaceuticals because of their nanoscale size range. Additionally, protein nanocarriers have enhanced the pharmacokinetic characteristics and targeted distribution of therapeutic cargo. Additionally, because they leave the bloodstream somewhat slowly, controlled/sustained drug release is possible at specific locations. Diverse protein nanocarrier types have been highlighted for their inherent biodegradability and simplicity of genetic alteration in comparison to other forms of nanocarriers because of these benefits. Ferritin nanocages are highlighted in this review. Almost all living things include ferritin, which helps maintain the balance of iron in the body by storing and releasing iron ions. The nanosized ferritin particles show controlled/sustained release pharmacokinetics and have outstanding biosafety characteristics. Additionally, the huge surface-to-volume ratio and the ability of the 24 monomer subunits to disassemble and reassemble into a sphere allow for a variety of chemical and genetic alterations to the ferritin surface and inner cage. Researchers working on biotherapeutics have used its naturally occurring hollow spherical structure to store iron ions in a variety of ways.

Chemotherapeutic agents, genes, fluorescent compounds, and different peptides that have been exhibited on ferritin's surface are a few examples of medications and substances that have been loaded onto it. All delivery vehicles must continually work to improve the effectiveness of their medication loading, although different attempts have been made to load different, poorly soluble medicines into ferritin. Additionally, a distinguishing characteristic of ferritin in comparison to other particles is that the threefold symmetry axis of the ferritin structure has also permitted antigenic presentation in its proper conformation. The effectiveness of ferritin in numerous medical domains is summarised in this review. The main objective is to summarise the most intriguing recent and ongoing uses of ferritin in nanomedicine. Here, we provide a comprehensive assessment of ferritin and its uses, including (i) the therapeutic use of ferritin, (ii) its use in imaging and diagnosis, (iii) the use of ferritin-based vaccines in immunotherapy, and (iv) ongoing and upcoming clinical trials of ferritin-based medicines. Researchers looking into ferritin and other protein-based biotherapeutics can gain immediate benefit from and be interested in this summary of current advancements.

Ferritins in biotherapeutics

Ferritin's hollow spherical core enables the loading of a variety of goods. Usually, the nanocage's disintegration and reassembly are mediated by pH or the mineral pores on the surface. The targeted delivery of chemotherapeutic drugs to tumours employing ferritin as a delivery vehicle has been the subject of numerous studies, mostly in anticancer therapy. *In vitro* and *in vivo* tumour growth suppression, better pharmacokinetic profiles, and fewer side effects were observed in the majority of these trials when compared to the free medication. The development of ferritin nanocages for application in medication delivery for cancer therapy has advanced significantly. In many mouse cancer models, doxorubicin-loaded ferritins have successfully inhibited tumour growth. In one instance, Transferrin Receptor 1 (TfR1)-overexpressing tumour cells targeted and internalised Dox-loaded ferritin to produce 10-fold greater intracellular amounts of doxorubicin than free doxorubicin. Additionally, in *in vivo* models, the paclitaxel encapsulation demonstrated strong induction of apoptosis in MDA-MB-231 breast cancer cells. This is an illustration of the delivery of an insoluble medication via ferritin, with the targeted treatment of tumour cells reducing the side effects of the chemotherapeutic agent. Gemcitabine was also loaded onto ferritin and delivered in conjunction with photothermal therapy, demonstrating the efficacy of this adjuvant treatment for breast cancer animals. Ferritin also successfully delivered cisplatin, which increased the therapeutic index of antiblastic therapy in an advanced, refractory melanoma animal. With some promising in vivo outcomes so far, ferritin's targeted delivery of chemotherapeutic drugs to cancer cells has improved therapeutic benefits for a variety of cancer types.

This has made it possible to use a variety of methods to display different immune-stimulating peptides on the ferritin surface for the creation of efficient immunotherapeutic drugs. This distinguishing feature of ferritin nanocages enables the one-step modification and distribution of a variety of peptides. For instance, the surface of ferritin's trimeric peptide display configuration enables the best delivery of TRAIL peptides. This apoptosis-inducing signal has been successfully delivered to ferritin nanocages' surface more than once. Through the constant proliferation of antitumour T cells, which was made possible by this study's attempt to stimulate the presentation of cancer cell neoantigens to the host immune system, an extremely intriguing and potent treatment strategy was produced. In addition to the experiments listed above, there are other intriguing ways to use ferritin. For instance, one study suggested co-administrating chemotherapy with thrombolytic ferritin that expresses multivalent clot-targeting peptides and fibrin degradation enzymes.

Similar to this, a study16 employed Thrombin Receptor Agonist Peptide (TRAP) and PC-Gla to treat acute inflammatory sepsis in vivo mice models.

Another intriguing study used doxorubicin-loaded ferritin to show the phagocytosis-inducing peptide SIRP in order to produce an intrinsic vaccination effect. The simultaneous infusion of SIRP and doxorubicin, an Immunogenic Cell Death (ICD) inducer, achieved substantial tumour growth inhibition in a melanoma model and even against tumour rechallenge in a colon cancer model. This was made possible by the cross-priming of effector CD8+ T cells.

Ferritins in imaging and diagnosis

To create diagnostic agents for different imaging techniques, ferritin nanocages have been easily changed. When peptides on the ferritin surface are being targeted as disease indicators, fluorescent molecules can be added or loaded as cargo. The developed ferritin-based agents are listed below, and this would allow multimodal imaging approaches for ferritin-based agents with improved diagnostic accuracy. For the multimodal imaging of malignancies, magneto-ferritin probes with iron oxide and 125I radionuclides on the ferritin surface were created. In addition, Huang et al. created a high imaging contrast near-infrared dye IR820-loaded ferritin for fluorescence and photoacoustic photothermal therapy. Gadolinium-loaded ferritin was created for contrast MRI in a different work by Crich et al., enabling the imaging of tumoral endothelial cells. A work by Lin et al., which created hybrid ferritin probes for tumour cell-targeted Near-Infrared Fluorescence (NIRF) imaging, is another illustration. Similar to this, Sitia et al. produced Indocyanine Green (ICG)-loaded ferritin for tumour-specific imaging that showed therapeutic value for fluorescence imaging-guided cancer surgery. In order to image *in vivo* inflammation, fluorescent Cy5.5 was also loaded onto magnetic ferritin and targeted vascular macrophages. These illustrations demonstrate that ferritin is a versatile platform with the ability to target particular cells and indicators.

Ferritin-based vaccines in immunotherapy

Due to their effectiveness and safety, ferritin-based vaccinations have generated a lot of interest. Conventional vaccinations made from inactivated viruses or other organisms have the potential to cause reversion, therefore efforts to create more immunogenic but secure vaccines are ongoing. Numerous advantageous characteristics of antigen display on the ferritin surface include monodispersity, the ferritin nanocage's temperature and pH stability, and the uniform presentation of 24 epitopes. Additionally, it has been demonstrated that particle-mediated transport of peptides results in a more powerful stimulation than soluble peptides. Due to the size of ferritin nanocages, Dendritic Cells (DCs) may easily take them up and move them to the lymph node to boost cellular and humoral immune responses. Ferritin-based vaccinations have shown very effectively and can be used not just for infectious diseases but also for cancer vaccines and vaccines for autoimmune diseases because of their multiple benefits. Representative ferritin-based vaccines have entered phase I clinical trials and target influenza, SARS-CoV-2, and Epstein-Barr viruses. Ferritin-based vaccines have demonstrated biocompatibility while remaining immunogenic with no obvious side effects. The difficult aspects of developing a ferritin-based vaccination, however, are the heterogeneity of nanoparticles, improper antigen folding, and intersubunit interactions that interfere with antigens. The self-assembled expression and purification of ferritin-based vaccines still require careful tuning because antigens are encoded onto the ferritin protein scaffold. The list below includes the ferritin nanocage clinical studies that have been chosen for the next vaccine.

Ferritins in clinical trials

Ferritin-based vaccines are still in the early phases of clinical studies. One illustration is the work of Kanekiyo, which involved fusing trimeric Hemagglutinin (HA) to ferritin's 3-fold axis to produce the appearance of eight trimeric viral spikes. In comparison to an inactivated vaccine, the ferritin-HA had a robust immunological effect (10-fold greater antibody titers).

Conclusion

The field of illness detection and treatment development benefits greatly from protein nanocarriers, and there is no question that current methods used in a variety of biotherapeutic, immunotherapeutic, and vaccination categories will be beneficial therapeutically. Excellent biocompatibility and biodegradability, as well as a wide range of customization options, characterise ferritin. Ferritin's subunit structure enables the uniform display of 24 peptides on its surface, which can be accomplished through direct chemical conjugation or one-step genetic alteration. In addition, the particle-mediated distribution of peptides is known to trigger immunomodulatory reactions, which is another well-known feature in peptide delivery. Additionally, the hollow cage structure enables the mineralization through surface pores or disassembly/reassembly of many hazardous or weakly soluble medicines. A complete, multifunctional protein scaffold is ferritin. The creation of vaccines is ferritin nanocages' main area of advantage in nanomedicine. Three influenza vaccines have started phase I clinical testing, and one of them has shown promising results. Due to the effectiveness of ferritin-based vaccinations, efforts have been made to create alternative ferritin-based vaccines in clinical trials. The detection, prevention, and treatment of diseases all show considerable promise for ferritin.

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