Biomimetics Builds Better Nanoparticles for Biomedicine

Dr. Changqian Cao

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Dr. Changqian Cao uses biomimetic approaches to synthesize high-quality magnetic nanoparticles. Here he discusses his development of a novel magnetic nanoparticle with enhanced capability for detecting early stage tumours.

To begin, could you describe your research background and how you became interested in studying magnetic nanoparticles?
I came into contact with the magnetic nanoparticles when I became a graduate student of professor Yongxin Pan. Professor Pan is a pioneer involved in the research of biogeomagnetism. When I first came into his laboratory, he told me some stories related to geomagnetism and magnetic nanoparticles that I have never seen. For example, many organisms such as magnetotactic bacteria, pigeons, bees, salmon etc. could use the Earth's geomagnetic field for navigation. There were also many magnetic nanoparticles (magnetite, Fe3O4) found in these organisms. These biological magnetic nanoparticles are characterized by narrow size distribution, distinct crystal morphorlogy, and chemical purity. My initial idea for synthesizing magnetic nanoparticles in a biomimetic way was inspired both by biomineralization of magnetic nanoparticles in organisms and the current requirement for high-quality magnetic nanoparticles in biomedicine.

How are microscopic or pre-angiogenic tumours currently detected in the clinic? What limitations do these technologies have?
Pre-angiogenic tumors could not be detected in the clinic until now. This is because the primary tumors at an early stage usually exhibit very small size (microscopic level), no angiogenesis, they have biological barriers, and express low level of tumor-associated antigen. Current clinical imaging techniques still cannot sensitively and specifically detect them. Nuclear imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and computed tomography (CT) show a high sensitivity, but they have problems of ionizing radiation, low resolution and anatomic localization of the small tumor lesion. MRI is a very promising clinical tool to diagnose tumors thanks to its higher resolution, noninvasive nature and tomographic abilities, but its applications have been limited by intrinsic low sensitivity and non-specificity.

What advantages do magnetoferritin nanoparticles offer over current in vivo tumour detection methods?

The magnetoferritin nanoparticles show two advantages over current in vivo tumor detection methods. First, magnetoferritin nanoparticles exhibit much higher relaxivity compared with current clinical Gd-based or iron oxide-based magnetic resonance contrast agents, which will significantly enhance the sensitivity of MRI. Second, magnetoferritin nanoparticles have intrinsic tumor targeting ability with no need of conventional surface coating and targeted ligand modification. The magnetoferritin nanoparticles can specifically bind to the transferrin receptor 1 (TfR1) overexpressed on cancer cells. When these nanoparticles were intravenously injected, they could intrinsically cross serial biological barriers (endothelium, epithelium and blood-brain barrier), specifically target to tumor cells and enhance MRI of microscopic (<1-2 mm) breast and brain tumors in vivo.

Did you run into any challenges from conception to synthesis of the magnetoferritin nanoparticles?
I have spent nearly three years from conception to successful synthesis of high-quality magnetoferritin nanoparticles because the synthesis is really tricky. Ferritin shell should be expressed and purified with intact structure and biomineralization ability. The synthesis condition should be strictly controlled. Otherwise, it is very easy to form aggregated magnetic nanoparticles outside of protein shell. Fortunately, we successfully explored a simple process for synthesizing magnetoferritin nanoparticles in these three years, which guarantee our further investigation of their practical application in biomedicine.

You found that a larger M-HFn core size enhanced its performance in MRI and immunoassays. How else might you enhance M-HFn functionality?
Magnetoferritin nanoparticles have three distinct interfaces for modification to enhance their functionality: the interior, the exterior, and the interface between subunits. We can enhance their functionality through not only controlling the size and structure of interior core, but also modifying the exterior and the interface though chemical conjugation or genetic engineering. For example, we are now conjugating the exterior of the protein cage with polyethylene glycol (PEG) and we find that circulation time in blood and relaxivity are significantly enhanced.

Are there any limitations or barriers to using this technology in the clinic? How long do you anticipate before this technology is implemented in clinic?
Our recently developed magnetoferritin enhanced MRI technology shows high promise for in vivo detection of cancer at the earliest stage. However, we still need a long time to extensively study phamacokinetics, nano-toxicity and to perform clinical trials of magnetoferritin nanoparticles. Usually, drug development is a very complicated process that takes an average of 10-15 years from the time it is discovered to when it is available for treating patients. But if we find any company who is interested in developing this technology, it will be a brilliant future for this technology implemented in clinic.

Biomimetic Magnetic Nanoparticles Enable the Detection of Microscopic Tumours

Early detection is key for treating most cancers. Now, research by Dr. Changqian Cao and colleagues has led to the development of a novel magnetic nanoparticle capable of detecting microscopic tumours with high sensitivity and specificity.

CHALLENGES IN EARLY TUMOUR DETECTION

Without a blood supply tumours cannot grow beyond a couple of millimeters. To sustain their growth, tumours stimulate the formation of new blood vessels, a process known as angiogenesis. If tumours can be detected and treated before they undergo angiogenesis then cancer progression and metastasis can be prevented. But detecting pre-angiogenic tumours is challenging. In addition to their small size, they do not produce significant amounts of tumour-associated antigens, biomarkers that could be used to detect the cancer or target drugs to the site of the tumour. Pre-angiogenic tumours may also possess biological barriers that prevent efficient drug delivery. While currently used nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are very sensitive, their resolution is poor and they require the use of ionizing radiation. As such, there is a significant need for new technologies capable of sensitively, specifically, and safely detecting and treating early-stage tumours.
Magnetic resonance imaging (MRI) is an attractive tool for tumour detection because it has higher resolution than nuclear imaging techniques and does not require the use radiation. However MRI is limited in its sensitivity and specificity and thus is not suitable as a standalone technology for detecting microscopic tumours. To enhance the sensitivity of MRI magnetic nanoparticles have been used as a contrast agent. With further functionalization magnetic nanoparticles are capable of specifically being targeted to cancer cells for imaging or drug delivery. One of the major challenges of developing magnetic nanoparticles is their synthesis. For biomedical applications, magnetic nanoparticles need specific properties that can be difficult to control through physical and chemical synthesis. To address this problem Dr. Changqian Cao, Associate Professor at the Institute of Geology and Geophysics, Chinese Academy of Sciences, and colleagues have taken a lesson from nature, enabling the synthesis of high-quality magnetic nanoparticles with intrinsic tumour-targeting ability.

BIOMIMETIC SYNTHESIS – BORROWING FROM NATURE

Ferrimagnetic iron oxide nanoparticles are widespread in nature, used by many animals and bacteria for navigation using the Earth's magnetic field. These biological nanoparticles exhibit properties that are highly desirable for biomedical applications including uniform size, shape and chemical purity. However, attempts to synthesize such magnetic nanoparticles by chemical and physical means have failed to achieve the same elegant precision as nature. As an alternative approach, Dr. Cao, in collaboration with Professors Weifeng Liu and Guanjun Chen from Shandong University, used the ubiquitous iron-storage protein ferritin as a biotemplate for the synthesis of a novel magnetic nanoparticle.
Nearly all organisms, including humans, synthesize ferritin for the storage of free iron. It is comprised of 24 subunits that form a spherical protein shell with an outer diameter of 12 nm and an inner cavity of 8 nm where the iron is stored as ferrihydrite. The ferritin synthesized by Dr. Cao and colleagues, known as magnetoferritin, contains a magnetic iron oxide core that can be used as an MRI contrast agent. In the past, other groups have used demetalized ferritin purified from horse spleens to form magnetoferritin, but these nanoparticles suffered from aggregation and nonuniform shape and size. The approach taken by Dr. Cao and colleagues is unique in that they used genetically engineered, recombinant human heavy-chain ferritin as a biotemplate for the formation of magnetoferritin. This resulted in monodispersed nanoparticles with uniform shape, size and high crystallinity. In addition to their high-quality structure, Dr. Cao found that biomimetically-synthesized magnetoferritin has several other advantages over traditionally synthesized magnetic nanoparticles.

IMPROVED TUMOUR TARGETING AND DETECTION

Ferritin-based nanoparticles are highly amenable to biomedical applications because they are made from a molecule that is naturally produced by human cells. This means that unlike chemically synthesized magnetic nanoparticals, which require special coating to make them biocompatible, magnetoferritin is inherently nontoxic to cells. Another advantage of using magnetoferritin for tumour detection is that it requires no modification to be targeted to cancer cells. It was recently shown that cancer cells overexpress a receptor for ferritin known as transferrin (TfR1). Dr. Cao showed that magnetoferritin specifically binds to TfR1 on cancer cells and that this interaction was sufficient to target the molecule to tumours in vivo. This was true even in the case of microscopic tumours and brain tumours, indicating that magnetoferritin is capable of crossing biological barriers, a limit of many imaging and therapeutic agents. In addition to showing high specificity towards tumour cells, magnetoferritin also displays high sensitivity. Compared to current clinical MRI contrast agents, magnetoferritin has greatly increased relaxivity, thereby improving the detection limit of MRI. Indeed, Dr. Cao showed that magnetoferritin could be used to detect tumours as small as 1 mm by MRI.
As with any new biomedical tool, it will be some time before magnetoferritin sees the clinic, but the initial work conducted by Dr. Cao and colleagues indicates that magnetoferritin holds great potential for improving the detection and treatment of tumours. In the meantime, Dr. Cao and others are investigating other uses for magnetoferritin, including targeted drug delivery, treatment of hyperthermia, magnetic separation and biosensor applications.

Researcher Profile

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Dr. Changqian Cao is an associate professor at the Institute of Geology and Geophysics, Chinese Academy of Sciences. He received his B.Sc. in Veterinary Medicine from Shenyang Agricultural University and his Ph.D. in Geobiology from the Institute of Geology and Geophysics, Chinese Academy of Sciences. In 2011 he received the honour of Excellent Doctor of Chinese Academy of Sciences. His research focuses on genetic engineering of biomineralization for the biomimetic synthesis of magnetic nanoparticles with highly desirable properties as well as their use in nanomedicine and nanodevices.

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