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学 位 （ 博 士 ） 論 文 要 旨
(Doctoral thesis abstract)

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論文題目 Title	Coordination-Assembled Nanomedicine Based on Reactive Oxygen Species (ROS) for Anti-Inflammatory and Anti-Tumor Therapy				

論文要旨（和文要旨(2000 字程度)または英文要旨(500words)）
※欧文・和文どちらでもよい。但し、和文の場合は英訳を付すこと。
Write a summary in Japanese (2000 characters) or in English (500words).
If the abstract is written in Japanese, needed to translate into English.

The physiological actions and features of ROS at the lesion site have been deemed as a therapeutic target. Increasing number of special nanomaterials as nanomedicines for dealing with different diseases. Notedly, thanks to all-in-one development of ROS biology, ROS chemistry and ROS nanotechnology, ROS-regulating nanomaterials have made greater medical advances. However, many intractable problems need to be overcame, which are worth to ameliorate for leap-forward development of ROS-related therapeutics. In this work, the areas we strive to improve are as follows:

The biocompatibility and safety of materials is the most important issue, which determines whether it can be used for biological research and clinical transformation in the future. Although many inorganic nanomaterials have exhibited good properties of antioxidant and ROS generation, the metabolic mechanisms and potential toxicity of inorganic nanomaterials remained controversial. Because peptides and proteins have many favorable advantages, including nonimmunogenicity, high biocompatibility, tissue permeability, clear metabolic mechanisms. Especially, programmability brings greater hope for precision medicine. Therefore, peptides and proteins derived from biological systems should be strived to develop, such as antioxidative and immune proteins, peptides and enzymes. Nevertheless, peptides and proteins easily suffer from enzyme hydrolysis, causing low bioavailability. In addition, many small-molecule bioactive compounds, such as flavonoid and curcumin, have drawn wide attention for antioxidant and anti-inflammatory effects for disease treatment. However, their bioapplication and clinical translation are restricted owing to low bioavailability and poor water solubility. To solve these problems, different nanocarriers are developed, including polymer, liposome and inorganic nanomaterials. But further induced side effects, for example systemic toxicity, immune response, and other shortcomings, such as low loading efficiency, complex process, also seriously restrict bioapplication and clinical transformation.

Assembly nanotechnology is gradually developed by the self-assembly phenomenon derived from natural phenomena. Assembly nanotechnology has received wide attention. Firstly, assembly nanotechnology is simple manufacturing process. Secondly, assembly nanotechnology possesses multiple noncovalent coordination and noncovalent interactions for fabricating nanomedicines, achieving robust construct for long blood circulation and susceptible response to environmental variations for targeted burst release. Thirdly, assembly nanotechnology possesses high encapsulation efficiency that is ascribe to directly assemble building blocks.

Inspired by these, antioxidant nanoparticles are prepared by co-assembly of flavonoid Myricetin (Myr) and glutathione (GSH) in the presence of Zn^{2+}. As-obtained nanoparticles not only overcome the disadvantages of Myr and GSH for improving their bioavailability, but also possess sustainable ROS scavenging activity for protecting cells from ROS damage.

Casein phosphopeptides (CPP) and Genipin are combined to covalently assemble robust GCPP nanoparticles. Covalent-assembled GCPP nanoparticles with antioxidant activity are fabricated for IBD treatment via oral administration. As-prepared GCPP nanoparticles possess stable nanostructure in harsh pH/enzymatic conditions, which cannot be destructed by oral delivery for achieving high bioavailability of peptides Moreover, GCPP nanoparticles present favorable therapeutic effect, which attributes to properties of controlled antioxidation to sustainably scavenging ROS and nano size preferentially accumulated at the inflamed colon site and remarkable advantage of promoted crypt regeneration. As-made GCPP nanoparticles have been spotlighted as a potential antioxidant agent to treat ROS-related inflammation diseases.

Supramolecular photosensitizer nanorods have been constructed by coassembly based on the combination of ovalbumin (OVA), Zn^{2+} and pheophorbide a, (PheoA) Co-assembled OVA-Zn^{2+}-PheoA nanorods exhibit high encapsulation efficiency compared with loading strategy. Owing to the dynamic flexibility of noncovalent interactions, as-prepared nanorods can respond to acid pH in tumor cells for the controlled release of monomeric photosensitizer and corresponding generation of ROS, thus enhancing *in vitro* PDT. During *in vivo* experiment, nanorods can selectively accumulate in tumors and further diagnose tumor site for antitumor treatment.

（英訳）※和文要旨の場合(300 words)

If the abstract is written in Japanese, needed to translate into English. (300 words)

Reactive oxygen species (ROS) play a double-edged-sword role on various physiological functions. The low or normal level of ROS can participate in the regulation of redox homeostasis, immune function and associated cell signaling. Nevertheless, the high level of ROS can induce cellular dysfunction and increase risk of chronic diseases and carcinogenesis. Therefore, excessive generation of ROS in lesion site has been a new target for treating diseases. Recently, nanomaterials-regulated *in vivo* ROS have received increasing attention, which dynamically guide process of ROS in biological milieu. This a new-generation therapeutic methodology ascribes to advances of ROS science, including ROS chemistry, ROS biology ROS nanotechnology. Especially, the advance of ROS nanotechnology promotes to fabricate various nanomaterials with ROS-regulating properties. Covalent and coordination assembly approaches as important nanotechnologies perform many remarkable advantages, such as high drug-loading ratio and simple manufacturing process. In our work, we design three peptide-protein based nanomedicines through assembled nanotechnology. As-prepared peptide-protein based nanomedicines not only improve their bioavailability, but also exert curative effect at the lesion site. Nanomedicines are further employed for antioxidant, anti-inflammatory and anti-tumor by scavenging or generating ROS, achieving satisfyingly therapeutic outcomes. To our expect, our researches have laid a certain foundation for the development of peptide-protein based nanomedicines, even clinical applications in the future.