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Biomimetic Nanozymes for Toxicity Control

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Abstract. Biomimetic nanozymes are a class of artificial enzyme mimetics that integrate the intrinsic properties of nanomaterials, such as small particle size and large specific surface area, with the catalytic mechanisms of natural enzymes. They exhibit high catalytic activity, excellent stability, and tunable enzymatic performance, serving as stable and efficient alternatives to natural enzymes. This article reviews the application potential of biomimetic nanozymes in advanced drug delivery systems (DDS), with particular emphasis on their roles in overcoming the limitations of current intelligent DDS by enabling stimulus-responsive drug release. This includes responses to endogenous stimuli like pH (targeting the acidic tumor microenvironment), temperature, and glucose (for insulin regulation), as well as exogenous triggers such as light, electrical, and magnetic fields. In comparison with conventional drug delivery systems, these third-generation biomimetic nanozyme platforms enable precise targeting, on-demand release, reduced toxic and adverse effects, and enhanced therapeutic efficacy. Although challenges remain in terms of biocompatibility, biodegradability, response sensitivity and specificity, as well as clinical translation including large-scale manufacturing, biomimetic nanozymes demonstrate broad prospects in personalized therapy, closed-loop drug delivery systems, and toxicity monitoring.

Keywords: biomimetic nanozymes, controlled drug release, stimulus-responsive delivery systems, targeted therapy, intelligent nanomaterials

1. Introduction

A drug delivery system (DDS) is a technical system that uses engineering methods or drug preparation ways to control the spread of drugs in different body parts, at different times and in different amounts in a full way [1]. It aims to send a proper amount of a drug to the right body part at the right time. It also makes the drug release as people plan in advance. In this way, it can make the treatment work better, cut down the bad reactions the drug may cause, and make the drug be used more effectively on the whole. Common ways of drug delivery usually have many limits. These limits include low bioavailability of drugs, short drug half-life, obvious side effects and poor patient cooperation with the treatment. To deal with these difficult problems, drug delivery systems have changed a lot. They are no longer just a general conceptual system, but have become a more careful and smart form that focuses on controlling drug release in a planned way. Controlled drug release means giving drugs to the body through special technologies. These technologies can make drugs release at a set speed, at a fixed body part and within a certain time. Such systems can reach

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the zero-order release kinetics [2]. They also allow drugs to release at specific parts or be triggered to release by certain outside things. What's more, they can reduce the total amount of drugs used and how often patients take drugs. They can make the treatment effect as good as possible and reduce the side effects to the least degree. In the past, people divide controlled drug release systems into different types according to the features of their matrix [3]. The types are diffusion-controlled, dissolution-controlled, osmotic pressure–controlled and ion exchange–controlled modes. These system designs are usually based on the thought that the inside environment of the human body is relatively ideal and unchanging. This basic thought brings some natural limits to the systems. For example, these systems often only release drugs in one direction and lack flexibility in use. Their drug release condition may be easily affected by the body's physiological state. They are not good at targeting the right body parts, which may lead to toxic side effects in the whole body. They may fail to get over the complex biological barriers in the human body, and it is also hard to stop the treatment early when needed. Because of these bad points, biomimetic nanozymes are better than common enzyme mimetics in many ways. They have stronger catalytic activity and better stability, and people can control their enzymatic activity more easily. When biomimetic nanozymes are used in the controlled drug release, they are expected to make drugs be given to the body when needed and target the right parts accurately. Scientists can build responsive mechanisms based on the body's own physiological and biochemical environment and also the outside stimulus. These mechanisms can help people control the drug release from a distance in a more accurate way. This method makes the treatment efficiency much higher and cuts down the bad effects of drugs. It also provides a good system for personalized treatment for different patients. So, this application has both practical and theoretical meaning for medical research.

The basic goals of sustained- and controlled-release nanomedicines are clear. They are to make the treatment more effective and safe, cut down the cost of medical care, and make patients more willing to cooperate with the treatment. So, the technologies of controlled drug release need to keep developing all the time. The first generation of drug delivery systems has typical forms like oral sustained-release tablets and transdermal preparations [3]. These systems usually depend on diffusion, dissolution, osmotic or ion exchange to work. The second generation of drug delivery systems has examples such as microspheres and liposomes. It uses biodegradable polymers and protein/peptide delivery technologies, and it is the start of nanocarrier basic forms. Now the drug delivery field has developed into the third generation. This generation includes targeted nanoparticles, intelligent hydrogels and photothermal-triggered systems, and these systems can realize precise-targeted nanotherapeutics. Though the field has kept making progress, the intelligent DDS technologies used now still face many big challenges. We can sum up the main difficult problems in two main aspects. For the exogenous stimuli like light, heat and magnetic fields, there are many limits [4]. These limits are not enough depth of tissue penetration, complex equipment needed for use, poor portability and high cost of use. For the endogenous stimuli such as pH, enzymes and reactive oxygen species (ROS), the limits are low sensitivity in response and not enough specificity in action. Biomimetic nanozymes combine the natural advantages of nanomaterials with the enzymatic kinetics and structural features of natural enzymes. The advantages of nanomaterials include small particle size, large specific surface area and high surface atom proportion. By this combination, biomimetic nanozymes can copy the biological catalytic behavior of natural enzymes. Compared with traditional enzyme mimetics, biomimetic nanozymes have better catalytic activity, better stability and higher sensitivity. These advantages make them very suitable for working in the complex physiological environments of the human body. They can also deal with the above-mentioned limits in a good way.

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1.1. Nanozymes as stable and efficient alternatives to natural enzymes

Biological enzymes are protein or RNA molecules made by living cells. They can identify specific substrates and have extremely high catalytic efficiency. They are very important for the normal physiological activities of the human body, and they are also widely used in the fields of biomedicine and industrial production. But natural enzymes usually have poor stability in severe conditions. For example, they work in high temperatures or strong acid and strong alkali environments, and this will make their catalytic effect worse [5]. So people need to create new substances that are stable and have high activity to take the place of natural enzymes. Nanozymes have a lot of obvious advantages. These advantages include good reproducibility, easy preparation, high catalytic efficiency, adjustable catalytic activity and good compatibility with living organisms. Compared with common enzyme mimetics, nanozymes have better catalytic activity and stability. They also have a stronger ability to adapt to complex physiological environments in the body, and this fully shows that they have great potential to be reliable substitutes for natural enzymes.

1.2. Controlled drug release based on biomimetic nanozymes: synergistic regulation by endogenous and exogenous stimuli

When biomimetic nanozymes are used in the controlled drug release of medicines, they can bring high catalytic efficiency. And their enzymatic activity is also flexible and easy to adjust at the same time. But if people want to make the most of their potential in drug delivery work, it is really necessary to control their catalytic activity in a precise way. The ways to regulate their catalytic activity can be roughly divided into two main types, which are endogenous and exogenous factors. Endogenous regulation usually makes use of different stimuli, such as pH value, temperature, enzymes and glucose. Exogenous regulation, on the other hand, includes stimuli like light, electricity and magnetism [5]. Besides, people can combine endogenous and exogenous stimuli to carry out synergistic modulation of the activity. This kind of combined regulation method can provide a more precise and flexible strategy for the controlled drug release of drugs. It also opens up new paths for the development of intelligent therapeutic systems in the medical field.

2. Modulation of biomimetic nanozymes through endogenous factors

2.1. Ph-responsive biomimetic nanozymes for controlled drug delivery

pH has a key influence on drug delivery that is mediated by biomimetic nanozymes, and this influence is mainly shown in the precise control of where drugs are released in the body. The pH value of normal body tissues is about 7.4. But pathological tissues like tumors get their energy mainly through glycolysis, and this process will produce a large number of metabolic byproducts such as lactic acid. So the microenvironment of tumors has a lower pH value than normal tissues. It is usually in a weakly acidic state, and the pH value is about in the range of 4.5 to 6.5. Researchers made use of this pH difference to create an intelligent drug delivery system based on nanozymes [6]. This system has a pH "on/off" switch function, and it can make drugs be released in a targeted way at the damaged parts of the body. In the design of this system, they used a metal-organic framework (MOF) that has a porous structure. Inside this structure, succinylated β-lactoglobulin and catalase are fixed together through supramolecular assembly, and this is how the whole delivery system is built. In a neutral environment, β-lactoglobulin has the property of permeability. This allows catalase to get in and catalyze hydrogen peroxide (H_2O_2), and this reaction can drive the whole delivery

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system to move forward. But in a weakly acidic environment, β-lactoglobulin will have a reversible gelation reaction, and this reaction will block the small pores of the MOF structure. Because of this, the catalase that is wrapped inside can no longer react with its substrate. This leads to the loss of power for the system and makes it stop moving, so the system can stay at the damaged lesion sites all the time. When the system is loaded with an anticancer drug, it will move much faster in the tumor microenvironment because of the acidic pH there. This faster movement can make part of the anticancer drug be released from the system. After that, the tiny particles of the system will be taken in by the cells, and they will stay in the acidic compartments inside the cells, where the pH value is between 6.3 and 4.7. Finally, these particles will break down and release all the anticancer drug completely. This whole process realizes the programmed release of the drug, and it can greatly inhibit the survival activity of HeLa cancer cells in the in vitro experiments. The researchers used the MTT assay to test the cell viability after 48 hours of the experiment. The test results showed a clear dose-dependent cytotoxic effect: the higher the concentration of the system particles is, the stronger the cytotoxic effect will be. In another related study, other researchers developed a drug delivery system that can move in a vertical direction [7]. In a neutral pH environment, gas bubbles will stick to the hydrophobic poly(2-diisopropylamino) ethyl methacrylate (PDPA) material. This makes the whole delivery system float up in the environment. But in an acidic environment, the PDPA material will turn into a hydrophilic one, oxygen (O_2) will be released from the system at the same time, and the system will sink down as a result. This special change makes the system realize the vertical transport of drugs in the body.

2.2. Temperature-responsive biomimetic nanozymes for controlled drug release

Temperature affects biomimetic nanozyme-mediated drug delivery mainly by enabling targeted delivery and raising local drug concentration [8]. Ruan et al. created a temperature-responsive drug delivery system that targets mitochondria, aiming to reverse lung tumor's resistance to doxorubicin (DOX). This system is also a type of biomimetic nanozyme, with a poly(N-isopropylacrylamide) (PNIPAM) carrier as its core part. Mitochondria have a relatively high-temperature environment, and mild local thermal stimulation makes the PNIPAM carrier release the loaded drug. In this way, the effect of DOX is greatly improved, and more DOX gathers in mitochondria. At the same time, the level of intracellular ATP drops, which stops the work of ATP-dependent drug efflux pumps. This leads to higher drug concentration inside cells and stronger cytotoxic effect. This method not only delivers drugs to the target position accurately but also successfully reverses the drug resistance of tumor cells.

2.3. Glucose-responsive biomimetic nanozymes for controlled drug release

Glucose-responsive biomimetic nanozyme drug delivery systems are mainly used to control insulin release (Fig. 1) [9]. Omid Veiseh et al. incorporated glucose oxidase (GOx) into nanocarriers based on microgels. When the surrounding glucose concentration rises, GOx catalyzes the oxidation of glucose to generate gluconic acid, causing a local drop in pH. pH-sensitive nanocarrier materials like chitosan and poly (lactic-co-glycolic acid) (PLGA) change their structure and swell in response to this pH decrease, which then triggers insulin release. This mechanism closely imitates the physiological way healthy pancreatic β-cells secrete insulin, allowing for rational and responsive control of insulin delivery. In their experiments, they combined GOx with chitosan microgels to build a glucose-responsive insulin delivery system. In diabetic mouse models, a single injection regulated blood glucose for 10 to 295 days. These results indicate that glucose-responsive

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biomimetic nanozyme delivery systems have the potential to create an integrated "sensing–response" closed-loop insulin delivery platform. While glucose-responsive nanozyme-based systems show great promise for regulating insulin release, key challenges in enzyme stability, response kinetics and material safety still need to be solved before they can be used in clinical practice.

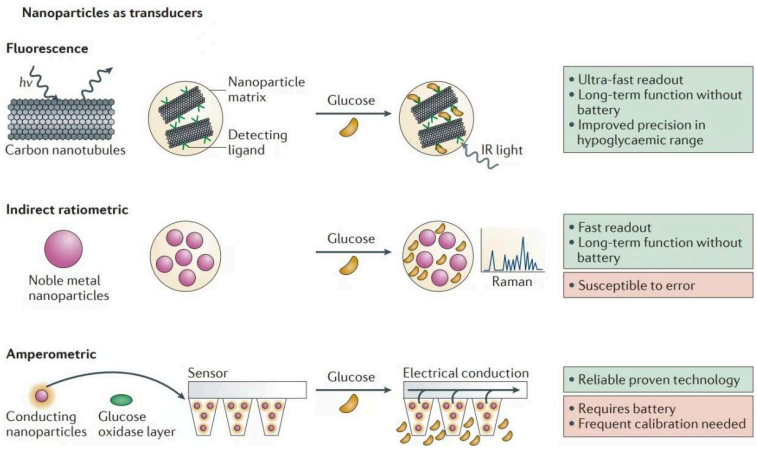

Figure 1. Glucose-detecting molecules can be coupled to nanoparticles engineered as transducers with unique optical or electrical properties, as well as the ability to generate surface plasmon resonance. The strengths (green boxes) and weaknesses (red boxes) associated with each technology are indicated. ConA, concanavalin A; hν, excitation light; IR, infrared; PBA, phenylboronic acid [9]

3. Modulation of biomimetic nanozymes through exogenous factors

3.1. Light-responsive biomimetic nanozymes for controlled drug release

Light-responsive nanozyme-based drug delivery systems have a key advantage: a high level of controllability. Hong Ji and his team linked a cartilage-targeting peptide (WYRGRL) to Au@Pt nanospheres (MB) to create targeted photothermal nanozymes (TPMB). When irradiated with an 808 nm laser at 0.5 $W \cdot cm^{-2}$, the Au core raised the local temperature by 10–15 °C in just 30 seconds. This local photothermal effect boosted cartilage targeting and therapeutic effect notably, and also lowered the required drug dosage. Besides, activation by near-infrared (NIR) light strengthened the photothermal effect of TPMB, which greatly enhanced its catalytic production of reactive oxygen species (ROS) and further promoted collagen deposition and cartilage repair. This method solved the problems of poor targeting, high demands for effective drug concentration and potential toxicity effectively. Experimental data showed that Au@Pt-F127 nanocomposites loaded with fibroblast growth factor 18 (FGF18) saw their cumulative drug release rate jump from 22% to 78% after 3 minutes of NIR irradiation. When laser exposure stopped, the release rate dropped to below 10% within 24 hours, which cut down off-target toxicity significantly. By combining catalytic activity with NIR responsiveness, nanozymes allow the building of an integrated "photothermal–catalytic–drug release" platform, and this platform has become a new way for the precise treatment of diseases like arthritis. Although these light-responsive nanozyme systems have great potential, they are still limited by shallow tissue penetration depth, unstable photothermal conversion efficiency and worries about long-term biocompatibility. Future research should focus on developing nanozymes that react to longer-wavelength irradiation, so as to realize more precise and deeper tissue drug delivery [10].

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3.2. Electrical-responsive biomimetic nanozymes for controlled drug release

Electrically responsive nanozyme drug delivery systems have a very key benefit, which is that they are easy to operate and can be controlled quickly. The catalytic activity that traditional nanozymes have is mainly determined by their own structural features, but the tumor microenvironment is usually complex and uneven, and this condition often restricts their catalytic efficiency. Zhong Zhang and other researchers did related research, and they put forward lattice expansion as a method to adjust the electronic structure of nanozymes. This method can greatly improve the catalytic effects of nanozymes and also make them more sensitive to electrical stimulation. Take ruthenium-based nanozymes (RuX) as a typical example: when these nanozymes are calcined at the temperature of 1000 °C, they will have a 5.99% lattice expansion, and this change can make them have stronger multi-enzyme-like activities (Fig. 2). When these RuX nanozymes are placed in the self-driven electric field from a triboelectric nanogenerator (TENG), they can produce reactive oxygen species (ROS) efficiently and also destroy tumor cells effectively. This research method combines structural engineering with external electrical stimulation together, and it can realize the double improvement of nanozyme performance in this way. Researchers can control the catalytic activity of nanozymes accurately in different time and space by changing the strength, frequency and lasting time of the applied electric field. This kind of precise control can adjust the speed of ROS generation and the dynamic process of drug release, and finally it can help to carry out therapeutic intervention according to actual needs [11]. Electrical regulation has more advantages than the traditional stimulation ways like light, heat and magnetic fields. For instance, it can penetrate deeper into human tissues, the related devices are easy to carry, and it can work well with wearable technologies. Right now, this regulation method is especially fit for carrying out remote intervention treatment on deep-seated tumors in the human body. In the coming time, if people combine electrically responsive nanozymes with biosensors or closed-loop control systems, it may push the development of personalized tumor therapy further. And this combination can make tumor treatment more efficient, safer and easier to control in the end.

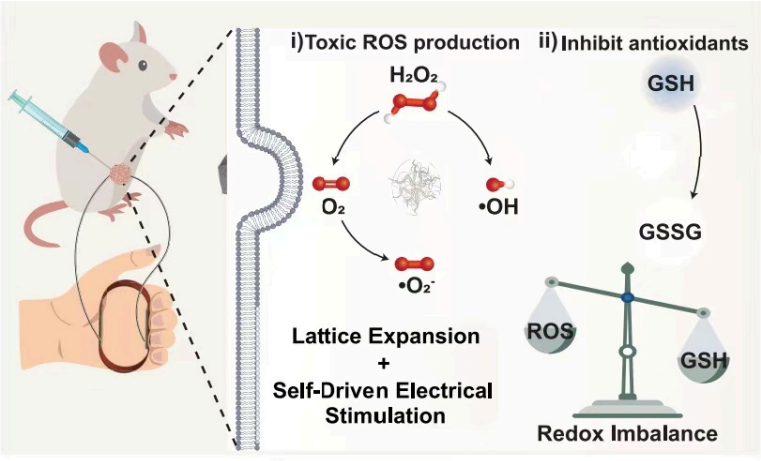

Figure 2. Schematic illustration of ROS production for enhanced oxidative stress in tumors by Ru nanozymes (RuX) under self-driven electrical stimulation generated by a triboelectric nanogenerator [11]

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3.3. Magnetic-responsive biomimetic nanozymes for controlled drug release

Magnetic-responsive nanozyme drug delivery systems have two prominent features: self-sustained catalytic activation and wide adaptability as a platform. We can add magnetic responsiveness to the systems and at the same time make them have a high ability to load drugs and an easy way to modify surfaces. This can be done by combining magnetic nanoparticles like superparamagnetic iron oxide nanoparticles (SPIONs) with mesoporous silica to build core–shell structures. Lin and other researchers put catalytic enzymes directly into the carrier matrix, and they used magnetically induced localized nanoheating to start enzymatic cleavage reactions (Fig. 3). Researches have proved that when the materials are exposed to an alternating magnetic field (AMF), the magnetic core will produce localized thermal effects, and these effects can help control drug release accurately in different time and space. The research group led by Lin designed a special delivery system with ultralarge-pore mesoporous silica nanoparticles as the main part. In this system, the anticancer peptide melittin and porcine liver esterase (PLE) are linked by ester bonds, and a thermosensitive azo-chitosan oligosaccharide partition is set between them. Besides, the entrances of the pores are closed with a β-cyclodextrin (β-CD)/polyethylene glycol (PEG) supramolecular gate. When there is no external AMF, the partition stops the enzyme and substrate from touching each other, so the drug leaks in a nearly unnoticeable amount. When an AMF is applied, the SPION core will generate local heat inside the pores, and the temperature rise is over 20 °C. This heat can break the azo bonds and take the partition apart. After that, PLE can quickly break down the ester bonds. As a result, about 70% of melittin can be released in 30 minutes, and the tumor growth can be inhibited by up to 80%. It is worth noting that the temperature of the bulk solution only goes up by less than 7 °C, and this small temperature change makes the systemic toxicity drop down a lot. This method makes smart use of nanoscale magnetothermal effects instead of macroscopic hyperthermia, so it can stop normal tissues from being damaged by heat. What's more, it solves the problems of traditional magnetically controlled release systems that only depend on physical desorption to work. It offers a practical method to deliver highly toxic biomacromolecules such as melittin, bacterial toxins and ribonucleases in a precise and controllable way [12]. These research results show that nanozyme–magnetic field synergistic platforms have a very broad development future in tumor immunotherapy and the targeted delivery of drugs to deep tissues in the body.

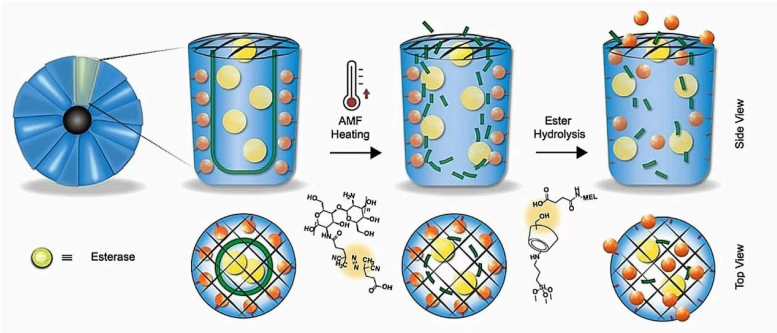

Figure 3. Schematic illustration of peptide drug encapsulation and AMF-triggered release from the pores of a core–shell large-pore mesoporous silica nanoparticle (side and top views) [12]

4. Conclusion and prospects

Biomimetic nanozymes are a new type of artificial enzymes. They combine the inherent characteristics of nanomaterials with the catalytic functions of natural enzymes, and they have

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shown obvious advantages over traditional drug delivery methods in the field of controlled drug release. This review has summed up the latest research progress of biomimetic nanozyme-based systems that can react to both endogenous and exogenous stimuli. For endogenous stimuli, the systems that are responsive to pH, temperature and glucose can identify pathological microenvironments accurately and realize programmed drug release. For exogenous regulation, the platforms that can respond to light, electricity and magnetic fields create new therapeutic models, and these models are marked by spatiotemporal controllability and on-demand intervention. Even though there have been such research advances, turning biomimetic nanozymes from laboratory research into clinical applications still faces several key challenges. First of all, we have to deal with the problems related to biosafety, especially the poor biodegradability of some polymeric carriers. Secondly, it is necessary to improve the response sensitivity and specificity of the systems. This can make sure that controlled drug delivery systems keep accurate and reliable in complex physiological environments and when facing various interfering stimuli. Thirdly, large-scale production and quality control bring practical difficulties to the development. Raising the consistency between different production batches, cutting down production costs and improving the overall production efficiency are all vital for the successful industrialization of these systems. We expect that with the continuous innovation across different disciplines, these challenges will be solved step by step. The further development and maturation of biomimetic nanozyme technologies will offer great support to the progress of oncology and immunotherapy research, and it will finally help develop more precise, efficient and safer therapeutic strategies for related diseases.

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