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REVIEW

Supramolecular Nanozymes Based on Self-Assembly of Biomolecule for Cancer Therapy

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Abstract: Natural enzyme systems possess extraordinary functions and characteristics, making them highly appealing for use in eco-friendly technologies and innovative cancer treatments. However, their inherent instability and structural complexity often limit their practical applications, leading to the exploration of biomolecular nanozyme alternatives. Supramolecular nanozymes, constructed using self-assembly techniques and various non-covalent interactions, have emerged as a promising solution. Amino acids, peptides, and protein motifs offer flexible building blocks for constructing these nanozymes. Importantly, the well-defined structural regulation mechanisms of biomolecular nanozymes, along with their unique properties as fundamental biological modules in living systems—such as selectivity, permeability, retention, and biocompatibility—present new opportunities for cancer therapy. This review highlights recent advances in supramolecular self-assembled nanozymes, including peroxidases, oxidases, catalases, superoxide dismutases, and other nanozyme systems, as building blocks for tumor therapy. Additionally, it discusses precise functional modulation through supramolecular non-covalent interactions and their therapeutic applications in targeting the tumor microenvironment. These studies provide valuable insights that may inspire the design of novel supramolecular nanozymes with enhanced catalytic selectivity, biocompatibility, and tumor-killing efficacy.

Keywords: supramolecular nanozymes, self-assembly, biomolecular, tumor therapy

Introduction

Catalytic therapy has garnered significant attention in cancer treatment due to its high specificity and efficiency. Enzymatic reactions, known for their ecological efficiency, have been extensively studied across various fields such as agriculture, chemical industries, food production, and medicine.[1] Traditional nanozymes are generally composed of inorganic nanomaterials (such as metal nanoparticles, metal oxides, etc)., and their catalytic activity comes from the physical and chemical properties of the nanomaterials themselves. The function is usually relatively simple, and the catalytic efficiency is low and the selectivity is poor. Compared to traditional nanozymes, biosupramolecular nanozymes are usually assembled by supramolecular interaction between nanomaterials and organic molecules. This structure allows the nanozymes to exhibit activity similar to that of natural enzymes, as they can mimic the active site of the enzyme through these organic molecules. Supramolecular nanozymes can show versatility and can catalyze many different types of chemical reactions, and its catalytic activity and selectivity can be adjusted by changing the assembled organic molecules. In addition, supramolecular nanozymes generally have better biocompatibility and tunability.[2,3] Meanwhile, natural enzymes face several limitations, including limited availability, poor stability, and high cost, which restrict their practical application in sustainable and repeatable processes. To overcome these challenges, biosupramolecular nanozymes have been developed through self-assembly strategies involving various non-covalent interactions, exhibiting catalytic properties similar to those of natural enzymes.[4]

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Biosupramolecular nanozymes consists of amino acids or short peptides, peptides and their derivatives are simple but essential components of life, and they show good biocompatibility and excellent properties in constructing supramolecular enzymes.[5] Biosupramolecular nanozymes exhibits excellent in vivo cycling stability due to its stable structure and resistance to protease degradation, and takes advantage of the tumor microenvironment (such as low pH, high levels of reactive oxygen species and local hypoxia) to activate its catalytic activity to play a role. By adjusting the structure of biosupramolecular nanozymes (such as size, shape, composition control, surface modification, etc). or changing the catalytic environment (such as pH, temperature, ionic strength, etc)., a variety of biocatalytic functions can be demonstrated.[6,7] In addition, the half-life of nanozymes can be adjusted through different strategies to meet different treatment needs. Therefore, biosupramolecular nanozymes hold great significance in cancer therapy. Unlike natural enzymes, biomolecular nanozymes offer enhanced enzyme activity, stability, and controllability. They also provide additional advantages such as resistance to protease degradation, drug delivery capabilities, molecular targeting functions, synergistic therapeutic effects, and responsiveness to the tumor microenvironment. In cancer treatment, it is therefore essential to develop biomolecule-based nanozymes that can function within tumor cells, demonstrate excellent tumor site enrichment, and possess unique biocompatibility, predictability, adaptability, and safety.[8,9] The supramolecular self-assembly of biomolecular nanozyme systems plays a pivotal role in forming ordered functional molecular sequences or unit structures within these systems.[10] As a result, supramolecular nanozymes represent a highly promising alternative to natural enzymes for a variety of applications, including cancer therapy.

Compared to inorganic nanoparticles (NPs) or metalloid materials, amino acids and their derivatives serve as simple yet vital biological building blocks. In particular, the 20 common amino acids, along with the rare amino acids selenocysteine and pyrrolysine, provide a vast molecular space, with small structural variations that allow for the assembly of ordered tissue structures.[11] The diverse functional groups present in amino acids provide both structural simplicity and flexibility, making them ideal for self-assembly and as carriers in various applications. Peptides, as fundamental motifs of natural proteins, offer a wide range of possibilities for creating biomimetic nanozymes specifically tailored for cancer treatment. The well-defined structural regulation of peptide-based nanozymes, along with their inherent biological characteristics as elemental biological modules in living systems—such as selectivity and autocatalysis—create additional opportunities for regulating cancer therapy.

Supramolecular nanozymes also be designed to target cancer cells. First, most solid tumors have unique pathophysiological features not found in normal tissues or organs, such as extensive angiogenesis, vascular structural defects, and increased production of a large number of permeable mediators. Therefore, passive targeting of solid tumors is largely dependent on penetration and retention (EPR) effects.[12] Second, ligand-mediated active targeting is achieved by linking specific ligands/antibodies to supramolecular nanozymes. Such as: specific receptors on the surface of tumor cell membrane, lysosomal targeting, mitochondrial membrane potential targeting, etc.[13] Third, polypeptide-modified liposomes, such as RGD targeting peptides, deliver supramolecular nanozymes to tumor cells or tumor microenvironment by binding to tumor cells or tumor microenvironment factors.[14]

The reason why catalytic therapy has attracted attention is mainly due to the following aspects: 1. Nanozymes have attracted attention due to their high catalytic activity, low cost, mild reaction conditions, good stability, and suitability for mass production, making them potential replacements for natural enzymes. These characteristics make nanozymes have great potential in catalytic therapy.[15] 2. Nanozymes can trigger enzymatic reactions in the tumor microenvironment, achieving good substrate specificity and low side effects.[16] 3. Inspired by the multi-enzyme cascade reactions in the human immune system, researchers have developed nanozymes that simulate this mechanism to enhance the effect of tumor treatment. 4. The biocompatibility and in vivo clearance ability of nanozymes are good. Catalytic therapy has attracted widespread attention due to its innovation, effectiveness, and potential clinical application prospects in tumor treatment.[15] With the further development of research, this field is expected to provide more treatment strategies and methods for tumor treatment. This review will classify and discuss the latest progress in supramolecular self-assembly nanozymes for tumor treatment according to peroxidase, oxidase, hydrogen peroxide, superoxide dismutase, and other nanozymes systems (Figure 1).

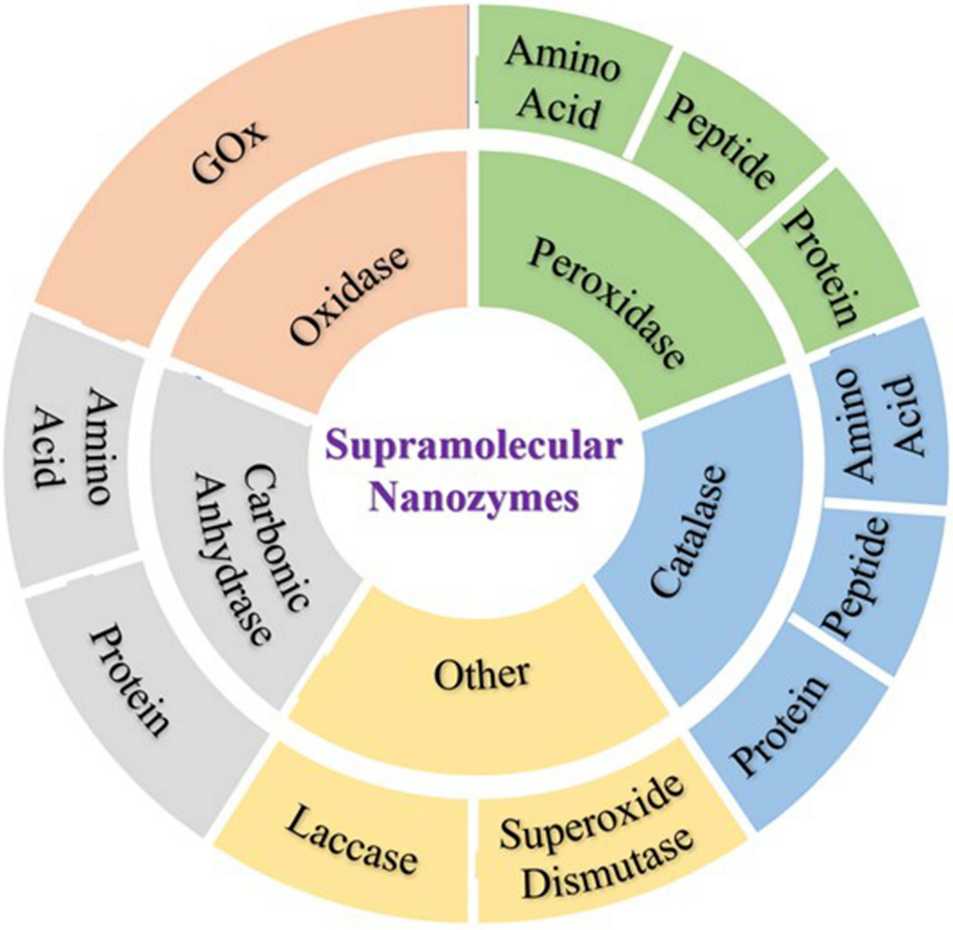

Figure 1 Classification of supramolecular nanozymes based on biomolecular self-assembly.

Peroxidase (POD)

Amino Acid-Based Mimics

Supramolecular nanozymes can target the tumor microenvironment to produce therapeutic effects on cancer cells, such as ROS generation, pH modulation, or nutrient depletion. High concentration of ROS can trigger apoptosis process, induce DNA and liposome damage by affecting mitochondrial function and activating caspase cascade, leading to apoptosis.[17] The acid-alkalinity of cancer cells is an important factor in their growth and survival. Cancer cells produce a large amount of ATP and lactic acid through a metabolic pathway called "Warburg effect", and the accumulation of lactic acid continues to stimulate T cell receptors, and T cells will enter a state of dysfunction and promote tumor immune escape.[18] The main treatment of tumor starvation is to prevent tumor angiogenesis, block tumor blood vessels, oxygen and blood supply, inhibit tumor cell metabolism, and thus inhibit the proliferation and growth of tumor cells.[19]

Nanozymes with POD or oxidase-like activity can effectively facilitate apoptosis in cancer cells through converting H_2O_2 into toxic reactive oxygen species (ROS).[20] Based on the simulated catalytic properties of POD, polyvalent metal ions, and Fenton-like reactions, researchers have developed nanoenzymes with multi-modal anti-tumor therapeutic effects. For instance, Ling et al designed MoO_{3-x} nanozymes based on the valence changes between Mo^{5+} and Mo^{6+}, which exhibited structure-dependent enzymatic activity for cascade catalytic tumor therapy.[21] Nanomaterials containing polyvalent metallic elements (eg, Fe^{2+}/Fe^{3+},[22] Cu^{+}/Cu^{2+},[23] Co^{2+}/Co^{3+},[24] $Mo^{4+}/Mo^{5+}/Mo^{6+}$,[25] $Sn^{2+}/Sn4+$[26]) can function as nanozymes by generating ROS, thereby inducing apoptosis through their catalytic properties. For example, Ma et al developed self-assembled Cu-amino acid sulfhydryl NPs (Cu-Cys NPs) for in situ chemodynamic therapy (CDT) of glutathione-activated and H_2O_2-enhanced drug-resistant breast cancer (Figure 2).[27] Despite these advancements, the

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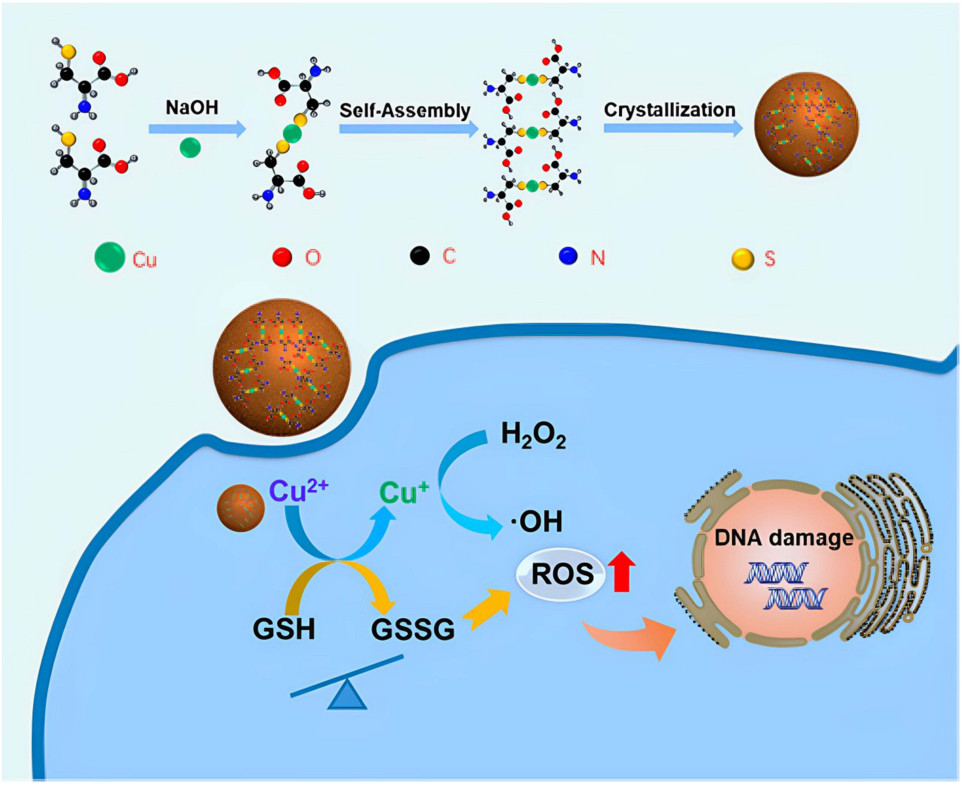

Figure 2 Exploiting the tumor microenvironment through Fenton and Fenton-like reactions.
Note: Reprinted from Ma B, Wang S, Liu F. Self-assembled copper–amino acid nanoparticles for in situ glutathione "AND" H2O2 sequentially triggered chemodynamic therapy. *J Am Chem Soc*. 2018;141(2):849–857. Copyright (2019) American Chemical Society.[27]

application of inorganic nanozymes, such as metal ion-based systems, in cancer therapy faces challenges related to biocompatibility. In recent years, the use of self-assembled biomolecular nanozymes for cancer therapy has gained increasing attention. A notable example involves the incorporation of a zinc(II) phthalocyanine-based photosensitizer (ZnPc) and the hypoxia-inducible factor 1 (HIF-1) inhibitor acriflavine (ACF) into the Fe^{3+}-promoted self-assembly of Fmoc-protected cysteine (Fmoc-Cys). This process produced nanovesicles, Fmoc-Cys/Fe@Pc and Fmoc-Cys/Fe@Pc/ACF, which can be disassembled intracellularly.[28] These synthesized nanosystems exhibited good stability and biocompatibility under physiological conditions. They also demonstrated high potency in photodynamic therapy (PDT) by disrupting the tumor microenvironment, with photocytotoxicity unaffected by oxygen levels. The synergistic therapeutic effects led to powerful and efficient inhibition of tumor cells in vitro and tumor growth in mice, even under hypoxic conditions. This novel concept of supramolecular nanozymes, constructed from simple biomolecules and metal ions, offers a promising and versatile approach for the treatment of hypoxic tumors.

Biomolecular supramolecular nanozymes constructed through the self-assembly of amino acid ligands exhibit potent anti-tumor effects, offering a new approach for cancer therapy. Inspired by oxidase, Zhang et al developed amino acid-based nanozymes via the supramolecular self-assembly of simple biomolecules, combining amino acids, chemotherapy motifs, and metal ions. These nanozymes exhibited uniform size distribution, well-defined nanosphere structures, and high chemical drug content.[29] Similarly, Song et al designed a homogeneous supramolecular nanozyme via amino acid coordination self-assembly and multiple non-covalent interactions. This system leveraged the tumor microenvironment, combining CDT, starvation therapy, and chemotherapy to achieve synergistic anti-tumor effects through cascade catalysis (Figure 3).[30] By collaborating with biological small molecules or therapeutic drugs, these tumor-specific biomimetic nanozymes achieve advanced catalytic therapeutic effects, paving the way for the development of catalytic biomolecular nanozymes with potent anti-cancer capabilities.

Among various amino acids, histidine stands out due to its amphiphilic nature and excellent active sites, making it an effective general base catalyst and nucleophile for initiating hydrolysis reactions. Histidine not only serves as a ligand

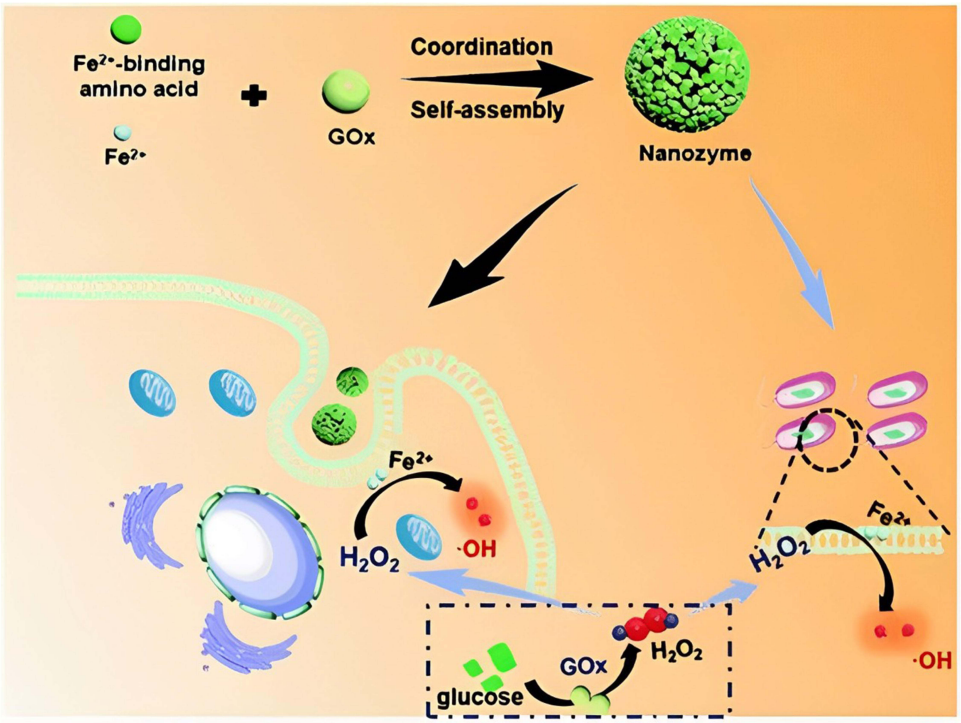

Figure 3 Schematic illustration of ferrous ion-driven coordination self-assembly of supramolecular nanozymes using GOx and amino acids as metal-binding motifs, along with their mechanistic actions for anticancer therapy.
Note: Reprinted from Song E, Li Y, Chen L. An amino acid-based supramolecular nanozyme by coordination self-assembly for cascade catalysis and enhanced chemodynamic therapy towards biomedical applications. *Nanoscale Adv.* 2021;3(22):6482–6489. Creative Commons.[30]

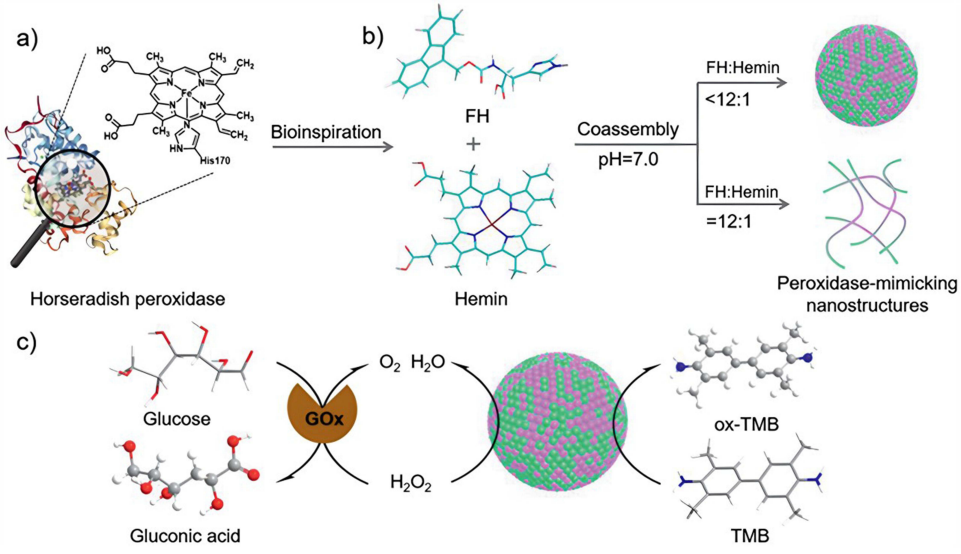

Figure 4 Schematic illustration of biomimetic nanozymes for glucose detection. (**a**) The catalytic active site in natural HRP (PDB: 1W4W). (**b**) Construction of biomimetic nanozymes through the co-assembly of FH and hemin. (**c**) The cascade reaction for glucose sensing using the nanozymes as catalytic agents.
Note: Reprinted from Geng R, Chang R, Zou Q, Shen G, Jiao T, Yan X. Biomimetic nanozymes based on coassembly of amino acid and hemin for catalytic oxidation and sensing of biomolecules. *Small.* 2021;17(19):2008114. © 2021 Wiley-VCH GmbH.[31]

binding site but also engages in oxidation reactions. Drawing inspiration from the supramolecular structure of horseradish POD, Geng et al co-assembled amphiphilic amino acids (Fmoc-histidine, FH) and hemin derivatives to construct nanomodules (Figure 4).[31] The resulting FH/hemin components possess tunable nanostructures and morphologies, which can be manipulated by adjusting the molar ratio between FH and hemin. This provides a simple and effective strategy for optimizing catalytic activity. Moreover, the FH/hemin component has been successfully used as a nanozyme, establishing

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a fast and sensitive platform for glucose detection. In medical applications, elevated histidine levels enhance the metabolism of tetrahydrofolate, which is targeted by anti-tumor drugs. Thus, combining histidine with anti-tumor agents, such as methotrexate, significantly enhances their anti-cancer efficacy. Additionally, spherical nanostructures can be formed by coordinating amphiphilic aspartic acid with GOx via Cu ion coordination and multi-component self-assembly. By encapsulating the prodrugs doxorubicin (DOX) and theophylline within ROS-cleavable thioketone linkers, researchers developed Fmoc-D/Cu/G@C nanospheres. These nanospheres demonstrate strong anti-tumor activity and high stability under physiological conditions, promoting prolonged blood circulation and increased tumor accumulation.[32]

In recent years, research has shown that the high proliferation and overexpression of ROS in pancreatic cancer can increase the uptake of cysteine (Cys) to sustain REDOX balance, identifying Cys as a potential therapeutic target. In 2024, Chen et al introduced polyvinylpyrrolidone-modified CuO nanoparticles (PVP@CuO NPs) as a novel strategy to disrupt REDOX homeostasis by depleting cysteine. These PVP@CuO NPs not only reduce cysteine levels and generate H_2O_2 but also mimic peroxidase-like activity, efficiently converting H_2O_2 into hydroxyl radicals (•OH). Additionally, cysteine depletion consumes NADPH and promotes thioredoxin (TXN) synthesis, ultimately initiating ferroptosis. This significant REDOX imbalance, combined with the release of large amounts of Cu^{2+} ions, further induces pyroptosis, enabling a highly effective Cys-targeted therapy for pancreatic cancer.[33]

Peptide Scaffolded Mimics

Peptides are abundant in living organisms and serve as fundamental building blocks for life processes and biomaterial development. They play essential roles in regulating bodily functions. In recent decades, peptides have been utilized in targeted cancer therapies, the synthesis of key medications for treating diabetic osteoporosis, and the clinical application of hormone mimics for injections. As a result, peptide-based drugs have become integral to the advancement of the biomedical field. However, the increased use of peptide drugs faces challenges due to their poor stability, high cytotoxicity, and short half-life, creating significant bottlenecks in their development. Self-assembled peptides are composed of one or more peptide molecules that spontaneously or voluntarily aggregate through intermolecular interactions to form nanostructured assemblies.[34] Peptide self-assembly systems are currently being widely used in various fields: (1) Peptide materials are applied as nanofibrils (for cell interactions, tissue engineering scaffolds, etc)., gels (for tissue reconstruction, scaffolds, etc)., NPs (for drug delivery, bioimaging, biosensing, etc)., and nanotubes (for transmembrane conduits, scaffolds, etc). in bioinspired nanotechnology.[35–38] (2) Peptide-based vaccines have been developed to significantly inhibit tumor cell growth.[39] (3) In situ peptide self-assembly has been utilized to create nanoprobes for developing novel imaging systems for cancer therapy, including photoacoustic imaging, radionuclide imaging, and magnetic resonance imaging.[40] Moreover, peptide self-assembled nanostructures exhibit great diversity, and their high biocompatibility and excellent bioactivity have led to their use as multifunctional modules and nanodevices.[41] The two- and three-dimensional structures formed by self-assembled peptides can be effectively controlled by factors such as pH, temperature, ionic strength, enzymes, solvents, etc.[42] Self-assembled peptides display a broader range of functionalities compared to monomeric peptides, and their responsiveness to stimuli enables the creation of novel biomaterials. Additionally, they help mitigate the toxicity associated with peptide activity in vivo, making the development of supramolecular self-assembled systems a growing trend in biomedical research.

The self-assembly process enables the creation of diverse nanostructures such as tubes, vesicles, and hydrogels, each designed to optimize the delivery of specific anticancer agents. Injectable hydrogels, for instance, can be applied directly to tumor sites, enhancing the safety and effectiveness of cancer treatments.[43] Amphiphilic peptide-based nanovesicles are engineered to encapsulate hydrophobic drugs in their inner hydrophobic cores, while modifications to the outer layer facilitate improved cellular uptake.[44] Additionally, additional surface modifications have been incorporated to improve both targeting precision and the efficiency of drug delivery within cells.[45] Owing to their biodegradable and biocompatible nature, numerous self-assembled peptide nanostructures have been developed to carry anticancer drugs such as DOX, paclitaxel, curcumin, and fluorouracil, showing encouraging outcomes in both preclinical models and clinical studies. Thus, NP-based drug delivery systems hold great promise for improving therapeutic outcomes and reducing unwanted side effects. These nanocarriers offer several key advantages, including a high drug-loading capacity, enhanced

stability that prevents rapid clearance by the body's reticuloendothelial and renal systems, and reduced drug loss during circulation.[46]

Peptides also play a crucial role in the entire immune process, including immune surveillance, defense, regulation, and therapy. Peptide-based therapies have demonstrated remarkable efficacy in modulating immune responses and improving the immunosuppressive tumor microenvironment. Peptides with minimal epitope binding to targeted receptors can function as immunogens to induce immune responses in effector cells, positioning them as promising candidates for next-generation tumor vaccines.[43] However, despite their significant potential in immunotherapy, individual peptides face several challenges. Firstly, peptides, especially water-soluble ones, are rapidly degraded by enzymes in the body, leading to a diminished and unsustainable immune response. Secondly, short amino acid sequences often result in low receptor affinity, reducing immunogenicity. Recent work by Yan et al introduced the concept of supramolecular immunotherapy through peptide self-assembly and elucidated how this process influences immunotherapy efficacy.[47] By incorporating immune-related peptides into photoimmunotherapy (PIT) systems, complementary advantages can be achieved. This approach not only prevents the rapid degradation of immunoactive peptides in vivo but also enhances the system's intelligence and immune synergy through the effects of supramolecular immunotherapy.[48] Additionally, PIT systems constructed through the supramolecular self-assembly of photosensitizers and immunopeptides may provide synergistic anticancer effects by combining photoimmunotherapy with conventional immunotherapy. During phototherapy, hyperthermia or ROS-mediated immunogenic cell death (ICD) generated locally within the tumor can eradicate the primary tumor and trigger an anti-tumor immune response. As the PIT drugs degrade, immune-related peptides continue to exert synergistic immunomodulatory effects via various pathways, ultimately leading to a cascade expansion of immunotherapy. This approach holds promise for overcoming metastasis and recurrence in the treatment of advanced cancers.

Protein-Based Mimics

Although nanozymes hold great potential in nanomedicine, their transition to clinical use has been slowed by several obstacles, including uncontrollable catalytic activity, the harsh conditions required for synthesizing inorganic components, and concerns about biological toxicity. In contrast, proteins, being natural biopolymers, have gained significant attention in cancer nanomedicine due to a range of advantages: (1) their natural origin and abundance; (2) high biocompatibility and biodegradability; (3) structural and functional diversity; (4) distinctive three-dimensional structures, such as the hollow cavity of ferritin, and unique biological roles, including immune functions and enzymatic activity; (5) amphiphilic properties that allow interactions with both hydrophilic and hydrophobic molecules or solvents; and (6) the presence of amino, carboxyl, and hydroxyl groups, which enable easy chemical conjugation. Considering self-assembly synthesis, protein-based nanomedicines offer several advantages, including mild synthesis conditions, the absence of high temperatures, minimal involvement of toxic organic solvents, and excellent dispersion of the resulting nanomedicines.

For example, Xu et al[49] synthesized POD-like bio-nanozymes (HNPs@PPy) by self-assembling biomolecules with hemin and subsequently conducting in situ polymerization of pyrrole in an aqueous solution (Figure 5). These bio-nanozymes display exceptional photo-regulated catalytic activity. By leveraging the specific characteristics of the tumor microenvironment in combination with precise photo-induced thermal effects, this system allows for spatially and temporally controlled ROS production within tumors. In a mouse model, this approach effectively suppresses apoptosis and tumor growth, exhibiting minimal toxicity due to its adjustable catalytic properties and excellent biocompatibility. This example demonstrates the potential of biomolecule-based nanozymes with controllable activity in cancer treatment. Moreover, metalloenzymes have shown promise in overcoming chemoresistance through innovative mechanisms in cancer therapy. An example includes an artificial metalloenzyme composed of fine copper clusters embedded in bovine serum albumin, paired with tumor-targeting peptides.[50] This system can catalyze the sustained conversion of hydrogen peroxide into hydroxyl radicals and oxygen within the tumor microenvironment. Notably, the system's high biocompatibility, tumor-specific recognition, and persistent catalytic properties result in significant anticancer effects by inducing DNA damage. Additionally, the chemiluminescence signal allows for sensitive and prolonged monitoring of the effects

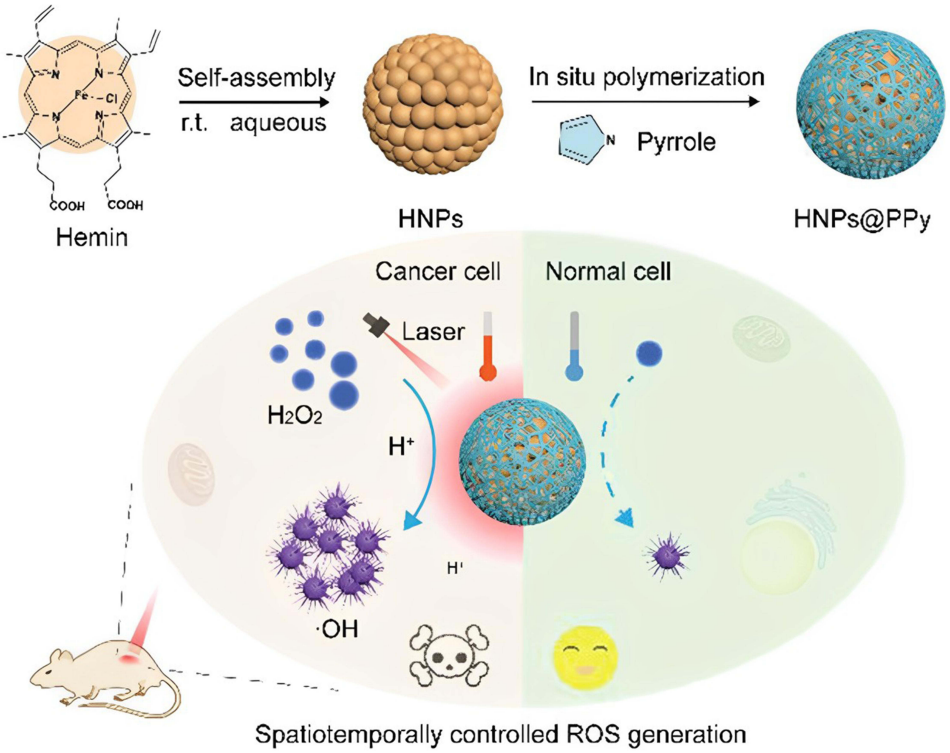

Figure 5 Illustration of the HNPs@PPy nanozyme with spatiotemporally controlled catalytic activity to enhance ROS generation in cancer cells.
Note: Reprinted from Xu Z, Zhang L, Pan M, et al. A bionanozyme with ultrahigh activity enables spatiotemporally controlled reactive oxygen species generation for cancer therapy. *Adv Funct Mater.* 2021;31(40). © 2021 Wiley-VCH GmbH.[49]

of surgical treatment. The effective integration of nanozymes with biomedical engineering represents a crucial step forward in medical research.

Oxidase

In recent years, oxidation-mediated cancer therapies have once again attracted the attention of researchers. Glucose oxidase (GOx), an important endogenous oxidoreductase, plays a crucial role in cancer starvation therapy by converting glucose and oxygen within cells into H_2O_2 and gluconate. Polymer-modified GOx nanogels have been designed to control H_2O_2 production in tumors, demonstrating a combined starvation and oxidation therapy effect in treating melanoma after direct tumor injection. To avoid the non-specific activation of GOx in healthy tissues, tumor-specific GOx-loaded nanocarriers have been developed.[51,52] Based on the pH differences between normal and cancerous cells, Li et al demonstrated a GOx-loaded polymer designed to alter membrane permeability under acidic conditions.[51] This polymer accumulates in the tumor, where its membrane permeability changes due to the hydrophilic transformation of acid-induced fragments. This allows glucose and oxygen to freely diffuse into the polymer's lumen, where GOx catalyzes the production of H_2O_2, increasing its levels in the tumor. This elevated H_2O_2 further disrupts the polymer membrane, releasing quinone methyl, depleting reduced GSH, and enhancing the cytotoxic effects on tumor cells.

Supramolecular self-assembling nanozymes with oxidase-like properties can further enhance CDT. Although insufficient H_2O_2 concentration in the TME limits •OH production necessary for effective CDT, biocatalytic reactions of GOx can boost H_2O_2 levels in tumors. Consequently, GOx has been widely co-delivered to tumors via different nanocarriers,[53–55] along with Fenton drugs, to increase H_2O_2 levels and thereby enhance CDT efficacy. Since glucose is abundant in the body, GOx has been encapsulated in nanocarriers with stimulus-responsive release properties, allowing for targeted enhancement of CDT. For instance, the Zeolitic Imidazolate Framework-8 (ZIF-8) system demonstrates that tumor acidity triggers the decomposition of GOx and the release of hemoglobin. The released GOx breaks down glucose, inducing starvation and producing H_2O_2. The generated H_2O_2, combined with endogenous H_2O_2, reacts with the heme groups in hemoglobin, leading to increased •OH production and enhanced CDT. Moreover, a polymeric nanoreactor (Fe/

G@R-NRs) containing ultra-small Fe3O4 NPs and GOx within its membrane and cavity, respectively, exhibited high tumor acid-triggered membrane permeability. This design enables glucose consumption to increase H_2O_2 concentration, lower pH, accelerate the release of iron ions from Fe3O4 NPs, and produce abundant •OH through a Fenton reaction between H_2O_2 and iron ions. The process induces a cascade reaction, leading to the release of the parent drug and effective tumor treatment.[53]

Supramolecular self-assembled nanozymes with oxidase properties can enhance PDT. Since H_2O_2 is overexpressed in the TME, chemiluminescent substrates, such as peroxalate derivatives[56,57] and the luminol system,[58,59] which react with H_2O_2 to trigger self-illumination, have been explored for chemiluminescence-activated PDT. To guarantee sufficient H_2O_2 in tumors for reacting with chemiluminescent substrates and generating enhanced chemiluminescence, Yu et al developed a biomimetic nanoreactor loaded with GOx, a photosensitizer (Ce6), a chemiluminescent substrate (CPPO), and perfluorohexane, which was coated with a tumor cell membrane. This nanoreactor (HMSNs-GOx-Ce6@CPPO-PFC/O_2@C) displayed similar adhesion and immune escape properties to tumor cells.[60] In this design, the chemiluminescent substrate interacts with endogenous H_2O_2 to produce chemiluminescence, which activates Ce6 via chemiluminescence resonance energy transfer, producing $^1O_2$ and initiating tumor PDT. Additionally, the H_2O_2 generated by glucose oxidation mediated by GOx further reacts with the chemiluminescent substrate, enhancing PDT. Moreover, the use of PFC provides O_2, significantly promoting glucose oxidation and resulting in synergistic chemically stimulated PDT against tumor metastasis.

Supramolecular self-assembled nanozymes with oxidase properties can also enhance photothermal therapy (PTT). GOx efficiently inhibits intracellular adenosine triphosphate (ATP) production by consuming glucose. Since HSP expression is highly correlated with ATP levels, inhibiting intratumoral ATP production through GOx-mediated glucose deprivation therapy offers a promising strategy for overcoming heat resistance induced by HSPs in tumors. Based on these considerations, a noble AuPtAg-GOx nanozyme was developed for photothermal therapy combined with synergistic tumor immunotherapy.[61] GOx was covalently bonded to the AuPtAg surface using SH-PEG-NH_2 as a bridging agent. AuPtAg was prepared via a simple one-pot procedure. Once tumor cells endocytose the NPs, several effects occur: (1) AuPtAg-GOx, exhibiting catalase-like (CAT-like) activity, catalyzes the conversion of intratumoral H_2O_2 to O_2. AuPtAg-GOx also consumes glucose with the aid of O_2, which can significantly impact tumor nutrition and viability. Furthermore, nutrient restriction reduces intratumoral ATP levels. (2) Upon laser irradiation at 1064 nm, AuPtAg-GOx induces localized hyperthermia in the tumor region. (3) Mild PTT enhances the recruitment of TILs, reprogramming the "cold" TME and rendering the tumor more susceptible to ICB therapy. By combining AuPtAg-GOx with PD-L1 inhibition, both primary and distant tumors can be effectively suppressed. AuPtAg-GOx enhances mild PTT through glucose deprivation therapy while also promoting immunotherapy efficacy. This cascade-driven synergistic strategy may have broad relevance for cancer treatments.

CAT

CAT, an enzyme responsible for breaking down H_2O_2 into oxygen and water, is commonly found in cellular peroxisomes and has been widely utilized as a photosensitizer in PDT due to its ability to generate oxygen, particularly in hypoxic tumor environments. PDT offers numerous advantages as a cancer treatment, including minimal invasiveness, repeatable dosages, and low systemic toxicity. However, extreme hypoxia within solid tumors poses a significant obstacle to the efficacy of both chemotherapy and PDT. To address this issue, Zhao et al developed a system using CAT-loaded hyaluronic acid NPs coupled with an adamantane-modified photosensitizer for improved PDT in solid tumors. Specifically, they designed adamantane-modified chlorin e6 (Ce6), resulting in a novel compound called aCe6.[62] This nano-system (HA-CAT@aCe6) targets cancer cells overexpressing the CD44 receptor, enhancing PDT through oxygen production under light exposure by converting endogenous H_2O_2 into oxygen. In vivo studies with MDA-MB-231 tumor-bearing mice demonstrated selective tumor accumulation of HA-CAT@aCe6, leading to significant tumor reduction under light irradiation, in contrast to a control group lacking CAT. Therefore, HA-CAT@aCe6 shows significant promise in addressing tumor hypoxia for targeted PDT. In a related effort, Cheng et al introduced a hybrid nanozyme prodrug system to mitigate hypoxia while improving the efficacy of CDT and PDT.[63] Lactic acid (LA) and DOX precursors (cis-aconitine-linked DOX, CAD) were pre-coupled to CAT side chains to form LA-CAT-CAD@Ce6 NPs (LCC@Ce6-NPs).

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LA serves as an active targeting ligand to promote cellular internalization, while CAD acts as a pH-sensitive component. Ce6 induces the production of ROS as a photosensitizer, while CAT degrades intracellular H_2O_2 to produce oxygen in situ. Oxygen production reduces the expression of HIF-1 and P-glycoprotein (P-gp), improving chemotherapy efficacy. Adequate oxygen also intensifies the elimination and apoptosis of hypoxic tumor cells induced by PDT. In vivo studies demonstrated that LCC@Ce6-NPs combined with chemotherapy and PDT effectively inhibited tumor growth (TGI >90%) and could even partially ablate tumors. This nanozyme prodrug platform has the potential to be highly effective in clinical cancer therapy and could be combined with other therapeutic agents. Peng et al created a liposome-encapsulated CAT with a lysozyme-targeting near-infrared photosensitizer (MBDP) and DOX to form FA-L@MD@CAT. This system catalyzes the conversion of high H_2O_2 levels within the tumor to oxygen, improving tumor oxygenation and enhancing the efficacy of chemotherapeutic PDT.[64] In addition to promoting the production of $^1O_2$, the increased oxygenation also modulates immune cytokines to reverse the immunosuppressive TME, significantly boosting tumor cell death. The system selectively recognizes tumors with elevated folate receptors, enhancing intra-tumoral accumulation, and shows promise for clinical application as a potent method for improving tumor-targeted therapy. Zhang et al encapsulated CAT in liposomes composed of cisplatin (IV) prodrug-coupled phospholipids, creating CAT@Pt (IV)-liposomes for enhancing cancer chemoradiotherapy.[65] After encapsulation, CAT@Pt (IV)-liposomes retained their enzymatic activity and stimulated the decomposition of tumor-generated H_2O_2, producing additional oxygen to alleviate hypoxia. In vivo experiments showed that CAT@Pt (IV)-liposomes significantly enhanced the radiotherapeutic efficacy of these NPs. By combining cisplatin chemotherapy with CAT-induced hypoxia relief in tumors, this liposomal NP system for radiotherapy and chemotherapy demonstrates a strong synergistic effect and holds great potential for clinical implementation in cancer treatment.

Carbonic Anhydrase

The acidic nature of the tumor microenvironment plays a crucial role in promoting metastasis and chemotherapy resistance. Understanding the pH-dependent mechanisms that contribute to these challenges is essential for improving drug delivery and developing novel therapeutic approaches. This includes investigating how pH affects primary tumor cells and the factors that regulate cancer cell growth. In recent years, carbonic anhydrases (CAs) have gained recognition as vital pH regulators within tumor cells. By adjusting bicarbonate and proton levels, CAs support cancer cell survival and proliferation. As a result, interest in targeting specific CA isoforms as a potential cancer treatment strategy has grown. Among the 12 active CA isoforms, CA IX and CA XII have been identified as particularly promising targets for anticancer therapy.

Acid-base balance in cancer cells is maintained through the coordinated action of CAs and various transporter proteins responsible for moving protons and acid/base equivalents, such as bicarbonate and lactate, across cell membranes. Recent research indicates that certain transport proteins directly interact with CAIX, forming complexes known as “transport metabolons”. One key metabolon, composed of CAIX and a bicarbonate transporter, relies on CAIX’s enzymatic activity and plays an essential role in cancer cell invasion and migration. Another metabolon, involving CAIX and the monocarboxylate transporter, uses CAIX as a proton sensor to drive the export of lactate and protons from cancer cells.[66] Given that CAIX is predominantly expressed in cancer cells, these transport metabolons are promising targets for disrupting the pH regulation and energy metabolism of tumors. Additionally, research by Okuyan et al demonstrated that chemically induced hypoxia triggers the expression of CAIII mRNA and protein in prostate cancer cells.[67] Their study on transcriptional regulation revealed that the most active promoter region for CAIII is located at P2-699/+86, and mutagenesis of potential HIF1α binding sites reduced DNA-protein interactions, suggesting that CAIII is regulated by hypoxia. These discoveries underscore the potential of targeting CAIII in hypoxic prostate tumors, offering new avenues for therapeutic intervention.

Other Nanozymes

Laccase (LAC) is a multicopper enzyme involved in the dioxygen-mediated oxidation of a wide range of organic compounds. It participates in various metabolic processes and exhibits anti-proliferative effects.[68] For instance, LAC purified from *Agaricus* mushrooms displays anti-proliferative activity against HepG2 and MCF-7 tumor cells.[69]

Additionally, fungal extracts from *Coriolus versicolor* and *Funalia trogii* have shown cytotoxic effects on HeLa cancer cells.[70] LAC may exert its cytotoxic effects by degrading 17β-estradiol, thereby blocking its binding to estrogen receptor (ER)-positive breast cancer cells. Since 17β-estradiol plays a crucial role in breast cancer cell migration, invasion, and proliferation through rapid intracellular kinase signaling,[71,72] LAC's ability to interfere with this pathway is particularly significant. Lee et al utilized liposome magnetic porosimetry to prepare functional single liposomes by creating pores in the liposome surface and encapsulating quercetin (QER, a model prodrug) or LAC (a bioactive enzyme) without the use of organic solvents. The pores were sealed with 3-diethylaminopropylamine (GDEAP) and pH-sensitive glycol chitosan grafted with affin (or biotin).[73] The results indicated that single liposomes containing QER and biotin-GDEAP could be effectively coupled with liposomes containing LAC and affin-GDEAP. At acidic pH (6.8), these liposomes accelerated the release of QER and LAC, enhancing LAC-mediated QER oxidation and significantly increasing tumor cell death. This approach shows promise as an effective antitumor treatment via prodrug-programmed activation.

Superoxide dismutase (SOD) is a metalloenzyme commonly found in aerobic or oxygen-tolerant organisms, known for its potent oxidative and free radical-scavenging properties. It aids in disease prevention, boosts immunity, and exhibits anti-aging, anti-tumor, and anti-inflammatory activities by catalyzing the dismutation of superoxide anions into H_2O_2 and molecular O_2.[74] SOD is categorized into three types: Cu, Zn-SOD, Mn-SOD, and Fe-SOD, with Mn-SOD being the most abundant. SOD has been shown to inhibit pancreatic cancer growth both in vitro and in vivo through various intracellular signaling pathways.[75,76] The loss of Mn-SOD function has been linked to promoting malignant cell programming in the pancreatic alveoli, while the absence of extracellular SOD (EcSOD) facilitates regulatory pathways that support the pancreatic tumor microenvironment.[77,78] SOD3, a secreted antioxidant enzyme, regulates ROS in the tumor microenvironment. SOD3 has been found to be significantly downregulated in lung cancer, and recent research is increasingly focused on its role in cancer. Zhang et al discovered that the SOD3 gene could serve as a prognostic marker for lung cancer patients, with lower expression of SOD3 correlating with poorer prognosis.[79] Thus, SOD3 may represent a novel clinical target and prognostic indicator for lung cancer treatment.

Concluding Remarks and Future Perspectives

In this review, we have summarized recent research advances in nanozymes. Nanozymes have been successfully engineered to mimic most key natural enzymes, such as POD, CAT, SOD, and oxidases. With advantages such as stable performance, tunable size, and ease of preparation compared to natural enzymes, nanozymes have found applications in various medical fields, including bioassays, anti-inflammatory treatments, antioxidant therapies, and cancer treatment. Bio-molecular nanozymes have several advantages in cancer therapy, including improving the tumor microenvironment, producing reactive oxygen species, selectively killing cancer cells, employing biomimetic strategies, and having good biocompatibility. In addition, the half-life of nanozymes can be adjusted through different strategies to meet different treatment needs. Therefore, nanozymes hold great significance in cancer therapy (Table 1). Despite some progress in the use of nanozymes for tumor therapy and diagnosis, several challenges remain. The development of catalytic systems for different types of nanozymes is still in its early stages, and the precise catalytic mechanisms and molecular pathways underlying the multiple enzymatic activities of nanozymes remain unclear. Therefore, constructing nanozyme systems with multifunctional capabilities, excellent biocompatibility, and high targeting efficiency remains an urgent goal.[80]

The future of nanozymes in biological applications is incredibly promising. Enhancing the catalytic efficiency of nanozymes will further increase their potential across various fields. However, in addition to high catalytic efficiency, improving the selectivity and specificity of nanozymes will be a crucial breakthrough. This will help to avoid unintended toxicities caused by off-target reactions, ensuring that future nanozymes offer superior safety profiles. To address this, rationally designed and controllable nanozymes with disease-specific enzyme-mimetic activities are essential. We anticipate significant advancements in drug delivery, targeted therapies, and immunological and therapeutic interventions due to the ongoing development of nanozymes. In tumor therapy, nanozymes show great potential, particularly through the use of endogenous stimuli such as the low oxygen concentration and acidic pH of the tumor microenvironment to activate their activity.[90] Additionally, exogenous stimuli, including acoustic, optical, magnetic, and thermal signals, can be employed. Ideally, nanozymes should act at specific sites within the body, and nanozymes with the ability to target

Table 1 The Tumor Microenvironment Mechanistic Aspects in Different Types of Cancer

Cancer Genus	Cancer Type	Tumor Microenvironment	Enzymatic Activities	Ref
Breast cancer cells	MCF-7 cell /4T1 cell	Hypoxia and H2O2	Glucose oxidase and Catalase	[81]
Embryonic kidney normal cells/cervical cancer cells/breast cancer cells	HEK 293/ HeLa/ 4T1	Hypoxia and GSH	Glutathione oxidase and Peroxidase	[82]
Breast cancer cells	4T1	Hypoxia, ·OH, and GSH	Catalase and GSH peroxidase	[26]
Cervical cancer cells	HeLa	Hypoxia and OH	Catalase and Peroxidase	[83]
Cutaneous melanoma cells	B16F10 cells	Acid (pH)	Peroxidase and Catalase	[84]
Cervical cancer cells	HeLa	Reactive oxygen species (ROS) and Hypoxia, and GSH	Peroxidase and Catalase	[85]
Breast cancer cells	4T1	Hypoxia and H2O2	Glucose oxidase and Catalase	[86]
Hepatocellular Carcinoma	HepG2 cells	Reactive oxygen species (ROS)	Oxidase, Peroxidase, Catalase and Superoxide dismutase	[87]
Breast cancer cells/glioblastoma cells	4T1/U87	Hypoxia and H2O2	Glucose oxidase and Catalase	[88]
Breast cancer cells	4T1	H2O2 and GSH	Glucose oxidase and Peroxidase	[89]

particular cells or organelles will be more effective. Such specificity will minimize systemic toxic effects and play a crucial role in the treatment of malignancies.

In recent years, with the development of artificial intelligence, artificial intelligence can use a large amount of information about protein sequences, multiple sequence alignments, and protein structures to learn key features of correlations.[91,92] These learned features can be applied to a variety of downstream tasks in enzyme engineering, such as predicting beneficial mutations, optimizing protein stability, and enhancing catalytic activity.[93] Therefore, artificial intelligence can predict key characteristics of nanozymes, including catalytic activity, specificity, and environmental stability are critical. And the optimal conditions for the catalytic reaction can be predicted, including the ideal temperature, pH, and reactant concentration to achieve maximum efficiency. So Artificial intelligence also play in designing and optimizing supramolecular nanozymes for the therapeutic applications.

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