Research Progress in the Application of Single-atom Catalysts in Biomedical Field

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Abstract: Single-atom catalysts (SACs) have the highest atom economy, precisely located active sites, unique metal coordination environments. These merits of SACs greatly increase the specific activity of metal atom, thus providing great potential for achieving better catalytic activity and selectivity. The metal catalytic active sites of SACs and natural enzymes are similar in structure, physical and chemical properties, and have better catalytic activity and selectivity. Theoretically, SACs can replace natural enzymes in the field of biomedicine. Based on the latest research work, the preparation technology of SACs and its application in the biomedical field are reviewed in this paper, and the challenges and future development direction of SACs in the biomedical field will be briefly prospected.

1 INTRODUCTION

Due to its inherent structural defects, the catalytic activity and selectivity of traditional nano-catalysts are very limited, which makes it difficult to replace natural enzymes in the field of biomedicine. It is found that the catalytic activity and selectivity of nano-catalyst can be greatly improved by reducing the size of nano-catalyst. Based on this, nanocatalysts have entered an era of precise atomic regulation. SACs is used to describe heterogeneous catalysts with atomically dispersed atoms in which the catalytic active site exists as an isolated single atom. The full exposure of active atoms and the increased of the intrinsic activity of active sites make SACs show broad application potential in various fields. SACs appeared as isolated single metal sites and acted as catalytic active centers on the surface of the carrier. In SACs, the M-N-C coordination structure formed by transition metal atoms (M=M=Fe, Cu, Zn, Co, etc.) with N and C elements on the carrier is chemically, electronically and geometrically alike to the metal catalytic active sites of natural enzymes. However, in terms of catalytic activity and selectivity, SACs even exceeded natural enzymes. In addition, the uniformly dispersed active sites and good stability of SACs are helpful to determine the working state of metal active atoms, which is of great significance for the clinical transformation of SACs in nanomedical science and the in-depth elucidation of the catalytic mechanism at the atomic level. In this paper, the applications of SACs in tumor therapy, biosensing and antibacterial in recent years will be summarized, and the challenges and future development directions of SACs in the biomedical field will be briefly prospected.

2 APPLICATION OF SACS IN THE FIELD OF TUMOR THERAPY

Compared with traditional chemotherapy, radiotherapy and other therapeutic methods, SACs has a good therapeutic effect and fewer side effects in the treatment of tumors and other diseases, and has become a rising star in the field of biomedicine. SACs can be used to treat cancer in two ways. One is that SACs can promote the catalytic production of endogenous H2O2 to produce toxic substance *OH, which can accelerate the cell decay. The other is a photosensitizer and a nano-enzyme like catalase (CAT), which catalyzes endogenous H2O2 to produce a large amount of O2 and relieve the hypoxic microenvironment of tumor tissues. The synergistic effect of SACs with near infrared (NIR) and photodynamic therapy (PDT) can significantly prompt apoptosis of cancer cells.

Huo et al. [1] prepared a kind of Fe SACs (named Fe/ZIF-SACs) in which Fe atoms are dispersed on N-doped carbon carriers (Figure 1A). In the acidic tumor microenvironment with excess H2O2, Fe/ZIF-SACs effectively trigger in situ tumor-specific Fenton reactions, producing a large amount of toxic *OH. These generated free radicals can not only cause the apoptosis of malignant tumor cells, but also initiate the collection of lipid peroxides, leading to the death of tumor cells. Their synergistic effect shows a tumor suppression rate of reach up to 150 %, achieving effective and specific catalytic inhibition of tumor growth. What is more important,。

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Fe/ZIF-SACs after injection can be entirely degraded by promoted Fenton reaction under gentle light and heat, indicating that SACs has minimal side effects in the treatment of cancer (Figure 1B). Zhao et al. [2] separated Fe and Co atoms in a mono-dispersed state in N-doped carbon material with spiky dodecahedron to form an independent pair of bimetallic non-alloy structure atoms (named FEC-DIA/NC). FeCo-DIA/NC can simultaneously initiate local Fenton and Fenton-like reactions to achieve effective nanocatalytic tumor therapy (Figure 1C). It is worth noting that FEC-DIA/NC can specifically and efficiently catalyze the production of toxic reactive oxygen species (**OH, O2**− and **1**O2) from low-toxic H2O2 and non-toxic O2 during the ROS cycle of tumors through the synergistic action of Fe and Co atoms without any external energy input. It has excellent killing effect on tumor cells (Figure 1D). Wang et al. [3] used Mn3[Co(CN)6]2 MOF as the carrier material and introduced monoatomic Ru into the framework with the load weight ratio up to 2.23wt %. Ru partially replaced Co as the monatomic catalytic site for the generation of internal oxygen. Ru-SACs, as CAT mimics, can catalyze endogenous H2O2 to generate O2 in situ, relieve tumor hypoxia microenvironment, and thus improve tumor PDT efficiency.

**Figure 1.** Schematic diagram of synthesizing Fe SAF NCs (A). Biological distribution of Cy5.5 and PSAF NCs in 4T1-tumor-bearing nude mice after single tail vein injection at different time points (B).[1] Synthesis schematic diagram of FeCo-DIA/NC (C). The synergetic and “division of labor” catalytic mechanism of FeCo-DIA/NC on ROS cycle and tumor parallel catalytic therapy (D).[2]

**3 APPLICATION OF SACS IN THE FIELD OF BIOSENSING**

SACs can be colorimetric sensitive to the analyte, which is a color change caused by a chemical reaction, and can be analyzed by the naked eye and by portable sets such as intelligent phone. Colorimetric sensing method has been used for the detection of acylcholinase (AChE), ascorbic acid (AA), H2O2, alkaline phosphatase (ALP), acetylcholine (ACh) and other analytics due to its simple operation and low cost [3,4]. Studies have shown that Fe-SACs, such as natural metalloproteinases, have intrinsic peroxidase similar functions. Therefore, H2O2 is catalyzed to form hydroxyl radical (**OH) at the Fe-Nx active site. In the presence of H2O2, Fe-SACs can rapidly oxidize TMB, with obvious color changes occurring at about 652 nm.
Cheng et al. synthesized a new single-atom nanocase (CNT/FeNC) by anchoring Fe atoms onto N-doped carbon nanotubes. CNT/FeNC nanomases have 100% monatomic Fe dispersion and a large surface area of 1140 m² g⁻¹. CNT/FeNC has good peroxisase-like activity in acidic media and can be used to oxidize various substrates. Such as 3,3',5,5'-tetramethylbenzidine (TMB, blue), diazo-aminobenzene (DAB, gray), 3-amino-9-ethyl carbazole (AEC, red), o-phenylenediamine (OPD, yellow), diamine salt (ABTS, green) (Figure 2A). Niu et al. used Fe-doped ZIF-8 as the precursor to produce Fe-N-C SAN through pyrolysis in the atmosphere of NH₃. The specific activity of Fe-N-C SAN was 57.76 U mg⁻¹, which was comparable to the level of natural horseradish peroxidase (HRP), because the single-atomic active Fe was dispersed 100% and the porous carrier had a large surface area. Fe-N-C SAN provides better storage stability and adaptability to harsh environments, and can achieve high-sensitivity biosensing of butylcholinesterase (BChE) activity instead of natural HRP. More importantly, SACs has great potential for applications in the field of in vivo sensing. Usually, it is difficult for any catalyst to distinguish neurochemicals in the central nervous system from other neurochemicals. It is found that regulating electron transport dynamics and ion migration is an effective method for in vivo electrochemical monitoring of brain chemistry. Hou et al. developed a Co-SAC for monitoring neurochemicals (i.e., glucose) in vivo (Figure 2B). Co-SAC has good electrocatalytic activity for the oxidation of H₂O₂. An oxidase-based glucose biosensor was prepared and an on-line electrochemical system was established to continuously monitor glucose in brain microdialysate. This study demonstrates a new approach to electrochemical biosensing in vivo and has important implications for understanding the molecular basis of brain function.

Figure 2. Schematic diagram of the synthesis and catalytic mechanism of CNT-FeNC-based SAN (A). Fabrication of Co-SAC and their morphological and structural characterizations (B).
APPLICATION OF SACS IN ANTIBACTERIAL FIELD

Nowadays, bacterial infection has become one of the most prevalent health problems in the world. Antibiotics have positive effects as antibacterial agents, but their overuse can lead to more tricky health problems and novel infectious disease. Antibiotic resistance is inevitable due to long-term use of antibiotics. It is worth noting that the multi-enzyme properties of SACS make it more useful than other nano-catalysts, and it has become a potential antibacterial agent for selective sterilization. Studies have found that Fe-SACs can produce lethal *OH, which is the key to producing antimicrobial properties. Huo et al. [6] synthesized isolated Fe atom nanocatalysts (SAF NCs) in N-doped carbon. SAF NCs specifically kill both Gram-positive bacteria (Staphylococcus aureus) and Gram-negative bacteria (E. coli) due to the strong interaction between the positively charged Fe atomic site and the negatively charged cell wall of S. aureus. The study found that SAF NCs can produce a large amount of *OH in the presence of H₂O₂ at the physiological level. Under the synergistic effect with the inherent photothermal characteristics of bacteria, SAF NCs can be used as an effective and simple method to eliminate bacteria, and can completely destroy cells or even degrade them (Figure 3A). Xu et al. [7] first reported the Zn-ZIF-8 derived carbon nanomaterials containing atomically dispersed Zn atoms, which can be used as efficient mimics of monatomic peroxidase. Through theoretical calculation, it is found that unsaturated Zn-N₄ active site is the main reason for the high peroxiase-like activity, which can cause the decomposition of H₂O₂ and the formation of *OH. The inhibition rate of ZN-C SAC against Pseudomonas aeruginosa was up to 99.87%, which opened a new field for the exploration and biological application of SACs in enzyme catalysis. Wang et al. [8] successfully constructed Cu single atom bit /N doped porous carbon (Cu SASs/NPC) through pyrolytic-corrosion-adsorption-pyrolysis (PEAP) strategy, which can be used for photothermal catalytic antibacterial treatment. Compared with undoped NPCS, Cu SASs/NPC has stronger peroxide-like catalytic activity, glutathione (GSH) consumption function and photothermal properties. In the presence of H₂O₂, Cu SASs/NPC can effectively induce peroxide-like activity and produce a large amount of *OH, which has an excellent sterilization effect (Figure 3C). In addition, Cu SASs/NPC can be used as GSH peroxidase like nanoenzyme, which can consume GSH in bacteria, thus remarkably improving the bactericidal activity. The antibacterial efficiency of this catalytic synergistic antibacterial performance against Escherichia coli and methicillin-resistant Staphylococcus aureus is almost 100%.

5 SUMMARY AND OUTLOOK

In recent years, thanks to the rapid development of SACS synthesis strategies and characterization techniques, notable achievements have been made in understanding the relationship between the atomic coordination structure and the unique biocatalysis properties of SACS. In this review, we highlight the important role of SACS with multi-enzyme similar functions in the fields of tumor therapy, biosensing, and antibacterial. Thanks to the high dispersion of metal atoms and the uniqueness of metal-Nx coordination structure, SACS has shown great application potential in the biomedical field. However, there are still three problems in the application of SACS in the biomedical field. Firstly, the
catalytic performance of SACs is sometimes far inferior to that of few atomic clusters for specific chemical reactions, especially for reactions requiring multi-site assisted activities. Secondly, the metal loading of SACs is low, generally not more than 2%, and too low metal loading cannot provide sufficient catalytic activity. Thirdly, SACs is still lacking in durability, and catalyst deactivation often occurs after long-term testing. Undeniably, the biomaterials of most interest to SACs in biomedical applications today have a lot of work to do to break down fundamental barriers and create innovative pathways to address application challenges in clinical therapy, in addition to the significant advances already made.

The methods to solve the above problems are as follows: 1) to develop the synthesis method of high purity SACs with a single active component; 2) By introducing heteroatoms (such as N, P, S) to form more metal-heteroatom coordination structures, improve the load capacity and stability of metals; 3) The enzyme-like characteristics of SACs at the atomic level were thoroughly analyzed by various detection techniques. It is believed that SACs will play an important role in the future biomedical field.

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