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Editorial

Diabetic wound healing activated by supramolecular cascade reaction

Diabetes is a chronic disease, and its complications such us diabetic foot ulcer and other chronic wounds often cause great pain to patients. Diabetic wounds are more prone to bacterial infection due to the environment of high blood sugar, resulting in difficult wound healing [1]. Therefore, how to protect the wound and cure drug-resistant bacterial infections in diabetes is an important scientific problem that needs to be solved.

In recent years, supramolecular nano-functional materials have been extensively applied in various research fields such as biomedicine, bioimaging, catalysis [2,3]. In particular, supramolecular catalytic material that can produce reactive oxygen species (ROS) such as hydroxyl radicals ($^\bullet$OH) by the catalytic reaction has been effectively used for bacterial elimination [4].

Recently, Liu and coworkers from Nankai University constructed a supramolecular nanoconfined cascade reactor, which could generate hydroxyl radical to inhibit resistant bacterial infection and initiate the radical polymerization process of vinyl monomers to form hydrogel *in situ* [5]. The supramolecular cascade reactor was assembled in a stepwise manner (Fig. 1). Firstly, chitosan (CS) and sulfobutylether-β-cyclodextrin (SBE-β-CD) interacted electrostatically to form CS@SBE-β-CD supramolecular nanoparticles in acetic acid buffer (pH 4.83). Subsequently, the coordination of amino groups in CS and ferrous ions promoted the transformation of the assembly from nanoparticles to nanospheres. The coordination process was verified by optical transmittance, zeta potential, XPS, DLS and TEM experiments. Finally, CS@SBE-β-CD@Fe^{2+} co-assemble with glucose oxidase (GOx) to form the supramolecular cascade reactor CS@SBE-β-CD@Fe^{2+}-GOx. The existence of GOx in cascade reactor was evidenced by FT-IR, SEM, TEM and EDS experiments.

It is very interesting that the constructed supramolecular nanoconfined cascade reactor can response to glucose at diabetic wound, and then activate GOx to produce H_2O_2, further forming $^\bullet$OH by Fenton reaction, not only initiating *in situ* polymerization of vinyl monomer to form supramolecular hydrogel for wound protection, but also generating elimination effect of drug-resistant bacteria, which achieved successfully diabetic wound healing. As shown in Fig. 2, the catalytic mechanism of the nano-supramolecular cascade reactor is that the substrate glucose can activate the GOx in the CS@SBE-β-CD@Fe^{2+}-GOx, initiating the cascade reaction, and the catalytic product (H_2O_2) further generated $^\bullet$OH in the presence of Fe^{2+} through a Fenton reaction. The generation of $^\bullet$OH in cascade reactor was captured by 5,5-dimethyl-1-pyrrolidine-*N*-oxide (DMPO) and validated by electron paramagnetic resonance (EPR) spectra. In the *in vitro* antibacterial experiments, only CS@SBE-β-CD@Fe^{2+}-GOx showed the obvious antibacterial effects against drug-resistant bacteria under the hyperglycemic environment, compared with PBS, CS, SBE-β-CD, CS@SBE-β-CD or CS@SBE-β-CD@Fe^{2+}. Simultaneously, the generated $^\bullet$OH can be used as initiators for polymerization of poly(ethylene glycol)

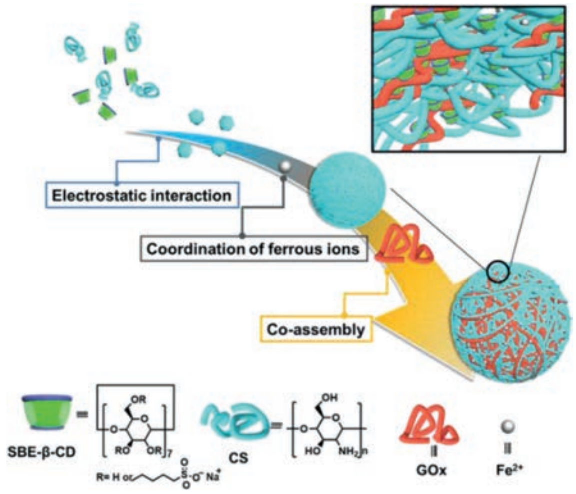

Fig. 1. Step-by-step construction process of the supramolecular cascade reactor CS@SBE-β-CD@Fe^{2+}-GOx. Reproduced and adapted with permission [5]. Copyright 2022, American Chemical Society.

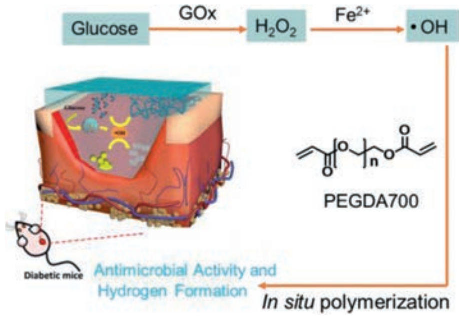

Fig. 2. The mechanism of the nano-supramolecular cascade reactor for generation of $^\bullet$OH, used for eliminating drug-resistant bacteria and *in situ* generation of supramolecular hydrogel for wound protection. Reproduced and adapted with permission [5]. Copyright 2022, American Chemical Society.

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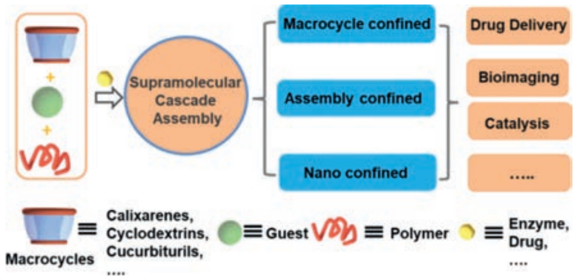

Fig. 3. The construction of supramolecular cascade assembly and its applications.

diacrylate (PEGDA700) with good biocompatibility and degradability to form supramolecular hydrogel *in situ*, which can be used as wound dressing. *In vivo* experiments verified the effect of the cascade reactor on drug-resistant bacteria killing and wound protection. After the wound in a bioluminescent *S. aureus* Xen36-infected diabetic rat was treated with CS@SBE-β-CD@Fe^{2+}-GOx + glucose + PEGDA, the diabetic wound surface was significantly reduced within 7 days by recording the bioluminescent intensities.

Lius' work confirms that nano-supramolecular cascade reactor can be constructed by multi-charge and multi-component supramolecular cascade assembly, which can *in situ* catalyze reactions to produce $^{\bullet}$OH for antibacterial use and the formation of supramolecular hydrogel wound dressing, promoting diabetic wound healing. We believe that this multi-charge supramolecular cascade assembly strategy could also be applied to other macrocyclic compounds, such as calixarenes, cucurbiturils (Fig. 3). Supramolecular cascade assembly could be stimulated by light, electricity, enzymes or pH, which might not only release drugs *in situ* and inhibit tumor growth, but also be used as catalyst for *in situ* catalytic reaction and optical probe for *in situ* imaging. Overall, such supramolecular cascade assembly strategy has great potential in materials science and biomedicine.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107761.

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