Biomaterials Translational

Catalytic biomaterials: driving innovation in biology, pharmacy, and medicine

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Catalytic biomaterials are biocompatible materials with catalytic activity at the nano-, micro-, and macroscopic scales. These materials can trigger specific biochemical or chemical reactions *in situ* within a targeted physiological environment, thereby enabling therapeutic functions.[1] Compared to conventional biomaterials, catalytic biomaterials exert therapeutic effects through the intermediates or products of catalytic reactions. This eliminates the need for small-molecule drugs that often cause adverse side effects, ensuring inherently low toxicity.[2,3] In addition, a key advantage of catalytic reactions is their ability to sustain chemical processes over time, ensuring prolonged therapeutic efficacy. Furthermore, these biomaterials generally possess stimulus-responsive properties, selectively interacting with specific substrates in the pathological microenvironment or external physical stimuli to confine their therapeutic effects to the disease site. Owing to their outstanding biosafety, high efficiency, and specificity, catalytic biomaterials have garnered significant attention in the biomedical field in recent years.

Based on the activation source of the catalytic reaction, catalytic biomaterials can be classified into two types: endogenous-responsive and exogenous-responsive. Endogenous-responsive catalytic biomaterials interact with specific biomolecules, initiating biochemical reactions. A classic example is the Fenton/Fenton-like catalytic reaction. In this process, iron- or copper-based biomaterials act as catalysts and react with the overexpressed hydrogen peroxide in the tumor microenvironment, generating highly cytotoxic hydroxyl radicals. These radicals can induce tumor cell death and inhibit tumor growth. In contrast, exogenous-responsive catalytic biomaterials utilize external physical fields to activate the biomaterials and generate active species with specific therapeutic effects. For instance, traditional semiconductor photocatalysts undergo electron-hole pair separation under light exposure, leading to *in situ* redox reactions that produce reactive oxygen species (ROS) or selectively deplete intracellular bioactive molecules, thereby modulating biochemical or metabolic processes to intervene or treat diseases.[4] Furthermore, external energy sources can further enhance enzyme-like catalytic activity, such as under light or ultrasound stimulation, where the enzyme-like activity of nanocatalysts is significantly boosted, resulting in synergistic therapeutic effects.

The continuous advancement of materials science offers significant opportunities for developing catalytic biomaterials. Researchers have significantly enhanced the catalytic properties of biomaterials by tailoring composition, structure, and physicochemical characteristics. Strategies such as introducing oxygen vacancies and constructing heterojunctions have been employed to modulate the bandgap of semiconductor biomaterials, thereby improving charge carrier separation efficiency and increasing carrier concentration, ultimately leading to more efficient ROS generation. In addition, the development of single-atom nanocatalysts has emerged as a promising strategy for optimizing catalytic performance.[5] Atomic dispersion of active sites maximizes surface exposure, boosting catalytic efficiency and significantly increasing atomic utilization. Furthermore, the unique coordination environment of single-atom catalysts enables fine-tuning of their electronic structures, facilitating precise control over catalytic activity and selectivity.

Beyond biomaterial optimization, the integration of interdisciplinary approaches has further enriched the design of catalytic biomaterials and broadened their biomedical applications. Inspired by natural enzyme catalysis, researchers have engineered nanocatalysts to mimic the activity of peroxidase, superoxide dismutase, glucose oxidase, lactate oxidase, glutathione peroxidase, and other oxidases.[6] By leveraging the catalytic properties of these biomaterials, it is possible to generate hydrogen gas or other bioactive molecules *in situ*, as well as deplete key metabolic substrates such as glutathione and glucose, thereby inducing distinct biological effects.

In recent years, piezoelectric and thermoelectric catalysis have garnered increasing attention. Unlike conventional photocatalytic materials,

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these systems utilize mechanical stress or temperature gradients to generate an internal electric field, significantly enhancing catalytic efficiency.[7] Moreover, catalytic biomaterials can facilitate specialized chemical reactions, such as bioorthogonal catalysis mediated by copper- or palladium-based nanocatalysts, enabling the *in situ* synthesis of small-molecule drugs at disease sites. This approach holds great promise for highly efficient and minimally toxic chemotherapy.[8] Last but not least, the inherent functional versatility of catalytic biomaterials allows the integration of these biomaterials with cutting-edge biotechnologies, enabling more precise and efficient therapeutic strategies. For instance, catalytic reactions can be harnessed to achieve stimuli-responsive drug release, prodrug activation, gene editing, targeted protein degradation, and synthetic biology.[9,10]

Overall, catalytic biomaterials have emerged as powerful tools for developing innovative therapeutic strategies against various pathological conditions, showing great potential in cancer therapy, regenerative medicine, antibacterial, and other biomedical scenarios. Their physicochemical properties can be meticulously customized using modern material engineering methods, including compositional tuning, morphological control, defect engineering, and heterojunction creation, to meet various biomedical requirements. A diverse range of catalytic biomaterials has been created, encompassing antioxidant nanozymes, Fenton-like catalysts, and photo- or sono-activated nanosensitizers. Utilizing the aberrant diseased microenvironment and external physical cues, these biocompatible catalysts exhibit remarkable therapeutic efficacy, elevated disease specificity, and minimal off-target consequences. Nonetheless, despite their great potential, the clinical translation of catalytic biomaterials continues to encounter various hurdles and unresolved issues.

From a materials science standpoint, a significant challenge is the accurate synthesis and large-scale manufacturing of catalytic biomaterials. Although most nanoscale catalytic biomaterials may be synthesized in laboratory settings, their intricate preparation techniques, protracted optimization procedures, dependence on specialized apparatus, and variability across batches impede scaled production. Moreover, maintaining their colloidal stability and safeguarding their physicochemical qualities during transportation and prolonged storage is essential for prospective therapeutic applications. A significant concern is biosafety, particularly regarding their *in vivo* pharmacokinetics, biodegradation, and biodistribution. Thus, a thorough evaluation of these parameters is required before practical use. Numerous catalytic biomaterials are inorganic, metal-based nanocatalysts that frequently demonstrate inadequate biodegradability and potential safety issues despite their elevated catalytic effectiveness. Creating biocompatible alternatives, such as organic catalytic biomaterials, would expand the range of catalytic biomaterials while enhancing their safety profile.

Establishing definitive links between the physicochemical properties of catalytic biomaterials and their biological effects is a crucial prerequisite for clinical translation. Numerous studies have examined the impact of composition, particle size, surface chemistry, and crystal structure on catalytic performance. Nonetheless, conventional trial-and-error methodologies continue to be ineffective. Recent advancements in computer simulations and machine learning present intriguing opportunities for expediting the development and optimization of catalytic biomaterials. These methods allow accurate prediction of material-property correlations, hence facilitating the systematic design of biomaterials with specific catalytic functions.

While most contemporary research emphasizes cellular-level assessments and treatment effectiveness, comprehensive studies on the interactions between catalytic biomaterials and biological systems at the molecular and genetic levels remain limited. Moreover, although ROS-scavenging catalytic biomaterials have demonstrated effectiveness in inflammation-related illnesses, there is still a lack of understanding of their specific function in influencing immune responses and cytokine signaling pathways. The intricacy of *in vivo* biological systems and the diverse diseased milieu hamper mechanistic research. High-throughput methodologies, including transcriptomics, proteomics, and genomes, can yield profound insights into these connections. Furthermore, organoid technology, which more accurately mimics the *in vivo* tissue milieu, offers a cost-efficient and physiologically pertinent platform for investigating the biological impacts of catalytic biomaterials, thus overcoming the drawbacks of traditional disease models.

The amalgamation of materials science, catalysis, and biology has accelerated the advancement of catalytic biomaterials and expanded their potential applications. Nonetheless, substantial obstacles persist in the journey toward clinical translation, necessitating further research into material design, scalable production methods, and functional optimization. For instance, improving biodegradability to ensure minimal long-term residue in the body. The ongoing exploration and enhancement of catalytic biomaterials, together with improvements in biological evaluation techniques, are anticipated to facilitate their effective application in clinical environments, hence creating new opportunities for catalysis-based therapeutics.

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