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Review

Advancing biomaterial innovation for tissue engineering through microbial synthetic biology: A review

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ABSTRACT

Microbial synthetic biology is a burgeoning discipline of resplendent innovation. Its primary objective is to enable microorganisms to synthesize specific substances or acquire diverse biological functions by modifying microbial genomes or regulating metabolic processes. With the ceaseless advancement of synthetic biology technology and the continuous deepening of research, microbial synthetic biology has achieved remarkable breakthroughs in the realm of biomaterial science, offering a new direction for designing advanced biomaterials for tissue engineering. In this review, we first outline commonly used microbial hosts and synthetic biology approaches related to biomaterials production. Then we focus on the classification of biomaterials produced by engineered microbes, explaining the production strategies for these different categories of biomaterials and the specific advantages of producing them using engineered microbes. We discuss the advancements and profound impacts of these innovative microbial-synthesized materials in the field of tissue engineering. Despite the challenges that lie ahead, the prospects for the application of these biomaterials in the field of tissue engineering remain exceedingly vast. In the future, microbial synthesized materials are expected to bring more innovations and breakthroughs to the field of tissue engineering.

1. Introduction

Synthetic biology is an engineering discipline that utilizes gene manipulation tools to regulate and modify the behaviors of life forms or to create novel forms of life [1]. It centers on gene regulation and engineering design, combining and regulating specific genes so that cells can perform designated biological functions.

Biomaterials refer to materials that interact with biological systems for medical applications. This concept was first proposed in the 1950s and has undergone several generations of evolution and development [2]. Currently, biomaterials are evolving toward precision and intelligence and have extensive medical and clinical applications, such as improving nerve injury repair [3], cardiac tissue reconstruction [4], and the healing of bone and soft tissue injuries [5,6]. These materials hold significant potential for the treatment of various complex clinical conditions.

The production of traditional biomaterials predominantly relies on chemical approaches, such as metallurgy, polymerization reactions, sintering, molding, and surface modification [7], but these methods pose numerous challenging issues, including the susceptibility of material composition and structure to alteration, low production efficiency and scale, and the difficulty in ensuring biocompatibility. However, microbial synthetic biology has paved a resplendent path for the production of biomaterials (Fig. 1). An increasing number of compounds have been discovered that can be derived from engineered microorganisms. Due to their low cost and sustainability, a new trend in the synthesis of biomaterials is the utilization of microorganisms for production. There is also an ongoing pursuit for the ability to efficiently and precisely modify

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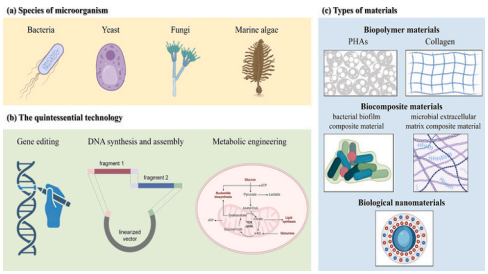

Fig. 1. Microbial synthetic biology and its principal applications in the field of biological materials. (a) Species of microorganism. (b) The quintessential technology. (c) Types of materials. Figure was created using BioRender (https://www.biorender.com/).

microorganisms [8,9]. Microbial synthetic biology achieves specific biological functions or chassis production goals with precision and control by modifying existing microbial cells or designing and creating new microbial components, integrating gene manipulation and other technologies [10], thereby intelligently fulfilling their application value across tissue engineering and various other domains.

2. Microbial synthetic biology approaches and common host systems

2.1. Synthetic biology methodologies relevant to biomaterial production

2.1.1. Gene editing technology

Gene editing plays a crucial role in the field of microbial synthetic biology. Traditional gene manipulation techniques, such as homologous recombination, suffer from prolonged operation times and low efficiency, making it almost infeasible to simultaneously target multiple genes [11]. Therefore, to address these issues, researchers have progressively developed various more efficient and precise gene editing technologies, such as TALEN (Transcription activator-like effector nucleases) and CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-associated protein 9), which demonstrate broad application prospects in areas like the synthesis of biological materials, targeted disease therapies, and more.

2.1.1.1. CRISPR-Cas9. CRISPR-Cas9 is a gene editing tool that has been embraced currently. Its system is primarily composed of two integral components: CRISPR sequences and the Cas9 gene. Among these, Cas9 is a related protein that possesses nuclease activity. In gene editing, Cas9 selectively cuts the double-stranded DNA at specific locations, and during the repair of the resulting DNA breaks, mutations can be introduced, allowing for gene replacement, insertion, or knockout, thereby endowing microorganisms with new functions or characteristics [12]. Compared to traditional methods, CRISPR-Cas9-based gene editing technology is more efficient, precise and user-friendly.

2.1.1.2. Talen. TALEN is also a very useful gene editing tool, which can specifically recognize and bind to target DNA sequences, followed by cutting and editing. Compared to CRISPR-Cas9, TALEN may exhibit higher editing precision in certain scenarios. By utilizing live-cell single-molecule imaging techniques to directly investigate the behavior of CRISPR/Cas9 and TALEN, it has been found that TALEN is a more effective gene editing tool than Cas9 in applications related to heterochromatin, which suggests that it can be used as guidelines for selecting genome-editing proteins used in the engineering design of heterochromatic regions that are difficult to edit in mammalian cells [13].

2.1.2. DNA synthesis and assembly technology

Compared to the chemical method for DNA synthesis, the biosynthesis method, which utilizes the enzyme systems within microorganisms for DNA synthesis, is more cost-effective and economical. Common methods for assembling multiple synthesized DNA fragments into longer DNA molecules with specific functions include Gibson assembly [14], Golden Gate assembly [15] and so forth. These methods allow for the assembly of multiple DNA fragments, thereby constructing complex metabolic pathways or genetic circuits.

2.1.3. Metabolic engineering technology

Metabolic engineering technology primarily involves the modification of microbial metabolic pathways to boost the yield of target products or to synthesize new substances. By regulating the metabolism of microorganisms such as *Escherichia coli* to synthesize various nanomaterials, production costs can be significantly reduced, enabling environmentally friendly and sustainable manufacturing [16]. Furthermore, the development of high-performance engineered microbial strains through metabolic engineering strategies has also garnered considerable attention, paving an entirely novel pathway for the large-scale production of non-natural polyesters [17].

2.2. Various microbial hosts employed in manufacturing biomaterials

In this field, commonly used microbial hosts include bacteria, fungi, yeast, algae, etc. Through synthetic biology, various microbial hosts can be reasonably engineered to provide specific advantages for the production of biomaterials.

2.2.1. Bacteria

Bacteria are the most commonly used microbial hosts, including *Escherichia coli*, *Bacillus subtilis* and others. Some specific types of biomaterials can achieve higher yields by appropriately modifying bacteria through modules such as expression regulation, gene editing. A study has established a complete synthetic biology toolkit that includes expression regulation module, gene editing module and validation module. For the first time, a programmable synthetic biology platform has been established in K.oryzendophytica, integrating a tunable expression element library and a CRISPR/Cas9 traceless editing system, providing a solid foundation for the customized design and large-scale industrial production of next-generation bacterial cellulose functional materials [18].

2.2.2. Fungi

Fungi can also be used to establish efficient cell factories for producing enzymes and some bioactive materials. Recently, the application of synthetic biology in fungi has been increasing, highlighting the necessity of developing synthetic biology toolkits for these organisms. A new toolkit has been introduced that enables faster assembly of synthetic transcription units containing established promoters, fusion proteins, or synthetic transcriptional regulatory devices in a standardized and modular manner, enabling the establishment of novel fungal cell factories to improve production efficiency and promote large-scale manufacturing [19].

2.2.3. Yeast

Yeast is a distinctive type of fungus, which is also a very important type of microorganism, and commonly used engineered yeasts include Pichia pastoris, *Saccharomyces cerevisiae*, etc. For the sake of sustainability and economic manufacturing, novel toolkits are continuously under development. A novel toolkit called RT-EZ (*R. toruloides* Efficient Zipper) has been developed, which was aimed to streamline *R. toruloides* engineering with improved efficiency and flexibility, providing a streamlined method for addressing genetic engineering challenges in the yeast [20]. This will provide a promising platform for the development of novel biomaterials, pharmaceuticals and other chemical products, and can lead to the reduction of production costs.

2.2.4. Algae

Algae, as photosynthetic microorganisms, offer novel hosts for synthetic biology technology. Their distinctive characteristics, including relatively rapid photosynthetic growth, availability of redox capabilities and robust sustainable production capacity [21], unveil a completely new palette for strategies of mass production for microbial synthesis of materials. To this end Crozet et al. have developed a new toolkit for *Chlamydomonas reinhardtii*, which comprises 119 openly distributed genetic parts and contains promoters, terminators, reporters, UTRs and introns cloned in various positions to allow maximum modularity, enabling rapid building of engineered cells for both algal biotechnology and efficient synthesis of biomaterials [22]. These engineered strains were cultured and the obtained biomass was converted into biomaterials such as thermoplastic polyurethane (TPU) or other biological products, indicating that these engineered strains have the potential for scaling up [23].

3. Classes of biomaterials from engineered microbes

Advances in microbial synthetic biology have enabled engineered microbes to serve as efficient cell factories for the sustainable production of a wide range of biomaterials. These biomaterials can be grouped by their chemical composition and structural features into major classes such as polysaccharides, polyesters, protein-based biopolymers, composite and hybrid. Each of them offers unique properties tailored to specific uses. Some representative patented products obtained so far and their applications are listed in Table 1.

3.1. PHA/PHB

Polyhydroxyalkanoates (PHAs) are natural polyesters synthesized by various bacteria under specific conditions, serving as storage substances for carbon sources and energy within the bacterial cells, and among the family of PHAs, polyhydroxybutyrate (PHB) is the most representative homopolymer. They exhibit exceptional characteristics such as biodegradability, thermoplasticity, and biocompatibility, possessing significant potential as sustainable and environmentally friendly alternatives for synthetic plastics. Currently, researchers have employed bacteria such as *Pseudomonas* [32,33], *Cupriavidus* [33], *Alcaligenes* [33,34], *Escherichia coli* [35] and *Aeromonas hydrophila* [36] for the production of PHAs. However, traditional microbial chassis used in industrial biotechnology face challenges such as low production efficiency, high costs, poor thermomechanical properties and unstable product quality [37]. Microbial synthetic biology techniques can optimize the processes for the production of PHAs, effectively addressing these issues to some extent.

Table 1
Representative patented products obtained and their applications.

Invention Names	Applications	References
A recombinant human-derived soluble high-activity type I collagen	Active ingredients or additives in cosmetics and medical consumable dressings	[24]
A porous composite material capable of adsorbing heavy metal ions	Recycling heavy metals and addressing heavy metal pollution issues	[25]
Depilatory enzyme preparations produced using *Bacillus subtilis*	Pollution control in leather manufacturing	[26]
Poly-beta-hydroxy alkanoate (PHA) copolymer and PHA copolymer blend	Manufacturing different kinds of films and various plastic molds	[27]
Ligilactobacillus salivarius and its products	Reduce skin keratin damage and alleviate symptoms of atopic dermatitis	[28]
Kombucha cellulose-based derivative refined from a symbiotic colony of bacteria and yeast	Manufacturing additives, bioplastics, cosmetics, wound dressings	[29]
Injectable preparation of recombinant human type III collagen	Collagen regeneration and tissue replenishment at the site of trauma	[30]
A novel brain function enhancer containing Bifidobacterium-fermented materials	Prevention and treatment of dementia and other brain function decline disorders	[31]

Microbial synthetic biology techniques can optimize metabolic pathways and enhance the efficiency and yield of microbial synthesis of PHAs by modifying and regulating the genes involved in the production of PHAs. For instance, halophiles (Fig. 2) [38,39] and thermophiles [39] designed through synthetic biology can not only produce intracellular PHAs at a low cost but also secrete extracellular soluble substances, improving process economics and increasing production efficiency. Through wcaJ gene deletion from *Cupriavidus* sp. L7L and mini-Tn5 transposon insertion mutations, it is also possible to increase its production of PHAs and improve the conversion efficiency from levulinic acid to PHAs during the production process [40]. By transferring genes related to PHB biosynthesis from *Streptomyces aureofaciens* NRRL2209 into *E. coli*, the efficient synthesis of PHB can be achieved [41].

In addition, microbial synthetic biology technology can impart different performance to PHAs through precise regulation of its structure, thereby meeting the demands of various application scenarios. Through microbial synthetic biology approaches, the *Pseudomonas Entomophila* has been reprogrammed to synthesize PHAs copolymers of short-chain (SCL) and medium/long-chain (MCL/LCL) from glucose and fatty acids, which exhibit adjustable thermomechanical properties [42] and can be utilized in a variety of products such as medical implants, coating films and flexible packaging materials.

3.2. Polysaccharides

Polysaccharide-based biomaterials are functional materials constructed primarily from natural polysaccharides, and due to their advantages such as renewability, degradability, and good biocompatibility, they are widely used in fields such as medicine, environmental protection, and electronic technology.

3.2.1. Bacterial cellulose

Bacterial cellulose (BC) is an extracellular polysaccharide that is synthesized by bacteria in the form of a biofilm [43]. Since its discovery, the complex fiber structure and high biocompatibility of BC have attracted researchers attempting to create unique materials based on it. It is precisely due to its fibrous structure that BC exhibits high mechanical strength, elevated Young's modulus values, high surface area and high water-holding capacity, which can fulfill the demands of some specific applications [44,45]. Meanwhile, BC has a wide range of applications in tissue engineering and regenerative medicine because of its high biocompatibility. For example, Cao et al. introduced a novel bone repair composite scaffold, which, due to the incorporation of bacterial cellulose, demonstrated markedly enhanced mechanical properties and water retention capabilities. This new scaffold also exhibited commendable in vivo stability, thus facilitating bone formation effectively [46].

3.2.2. Hyaluronic acid

Hyaluronic acid (HA) is a polysaccharide identified within the extracellular matrix, renowned for its exceptional biocompatibility and viscoelastic properties [47]. It plays a pivotal role in modulating wound microenvironment [48], providing hydration, and exhibiting anti-aging effects, thus garnering extensive attention across various domains, including healthcare, cosmetology, and drug delivery. Among the various methods for preparing HA, the extraction of it through microbial fermentation is relatively straightforward, efficient and high-yielding [49]. The unique known HA synthase gene from Gram-negative bacteria was successfully expressed through metabolic engineering, and the fed-batch fermentation employing the engineered strain achieved an HA yield of up to 3.8 g/L, which is the first recombinant *E. coli* strain with

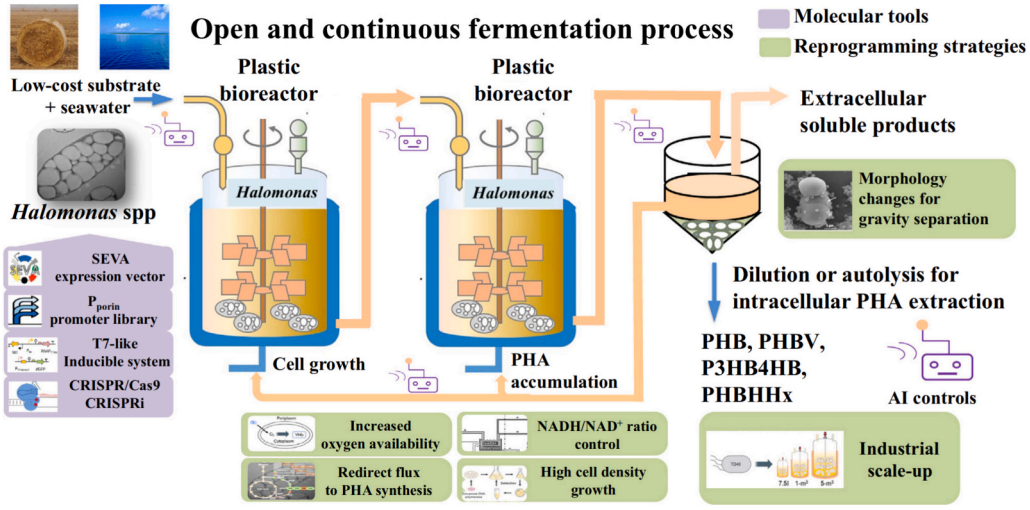

Fig. 2. Next-Generation Industrial Biotechnology based on engineered extremophilic *Halomonas* spp. grown on low-cost substrates and seawater under open and continuous process with recycling of culture broth and inducible gravity separation of cells during downstream processing. Bioprocessing is controlled by artificial intelligence (AI), which helps to stabilize the product quality. The coproduction of intracellular PHAs with extracellular products further improves the economics of NGIB [38].

HA titer in grams per liter level [50]. Additionally, in order to increase the yield of HA, A two-stage induction strategy has been utilized in the *B. subtilis* 168, achieving a maximum yield of 6.8 g/L [51].

3.3. Protein-based materials

3.3.1. Collagen

Collagen is the main component of animal connective tissue, widely distributed in the human body, including the skin, bones, tendons and ligaments, which serves functions such as providing support and protection, promoting cell proliferation and maintaining skin hydration. Due to its high biocompatibility, biodegradability, non-toxicity and immunogenicity, collagen and its derivatives have become one of the most valuable biomaterials currently. The biomaterials derived from collagen exist in various forms and can be applied in multiple areas like tissue engineering and pharmaceuticals [52].

As traditional extraction methods are no longer sufficient to meet diverse market demands, utilizing synthetic biology techniques for the heterologous expression of recombinant collagen has emerged as a promising option. Recombinant collagen that is functionally similar to natural collagen or possesses specific functions can be synthesized by introducing the gene sequences that encode collagen or specific gene sequences optimized for design into suitable host cells and through a series of processes such as fermentation, culture and purification. This approach not only overcomes the limitations of traditional methods but also makes the entire process of production more controllable.

Presently, the most extensively utilized expression system is *Escherichia coli*, which is renowned for its clear expression mechanics, defined genetic backdrop, low costs of fermentation, the sublime efficiency of expression and abbreviated cultivation cycles [53], exhibiting the significant potential for large-scale protein production. By designing and expressing functional segments of human collagen (I) and conducting temperature-controlled expression at 42 °C in *Escherichia coli*, the expression yield achieved a resplendent 36.3 % of the total protein [54]. Recombinant type II collagen obtained through the fermentation of *Escherichia coli* can achieve a maximum yield of 10.8 g/L [55]. However, *Escherichia coli* lacks prolyl hydroxylase, rendering it incapable of producing hydroxylated collagen during its solitary expression, which consequently hampers the self-assembly process of natural structural collagen molecules into collagen fibers [56]. This concern can be addressed by transducing hydroxylases [57,58], yet the overall yield of the final products remains low, necessitating further research to meet the substantial market demand.

Escherichia coli, as a prokaryote, has an incomplete post-translational modification system, and the cultivation of *Escherichia coli* in clinical settings may result in the production of endotoxins [53]. In contrast, eukaryotic expression systems, like yeast and marine algae, possess a fulfilled post-translational modification mechanism and do not produce endotoxins. Consequently, a large number of researchers utilize yeast expression systems to express human collagen, such as *Pichia pastoris* and *Saccharomyces cerevisiae* [59,60]. However, the yeast expression system also has some shortcomings, such as safety concerns and a low level of proline hydroxylation. Therefore, further research and development of new methods for production are necessary.

In addition, apart from expression systems that are conducive to industrial-scale production, researchers have also studied the feasibility of preparing recombinant collagen in other systems like insect cells, mammalian cells and plants. The commonly employed expression systems in the preparation of various types of recombinant collagen are listed in Table 2.

3.3.2. Silk

Silk is a naturally occurring biopolymer, primarily composed of fibroin and sericin proteins [78]. Silk fibroin (SF) exhibits unique biocompatibility, mechanical properties and biodegradation, leading to its widespread application in multiple fields like drug delivery systems, tissue engineering and regenerative medicine. Producing silk through the modification of microorganisms can significantly enhance synthesis efficiency, offering a promising new method for the mass production of silk. For example, through gene optimization and modular design approaches, a system is constructed to harness the T3SS encoded within Salmonella Pathogeneity Island 1 to export silk, and the rate of secretion can up to 1.8 $mg{\cdot}L^{-1}{\cdot}h^{-1}$ [79]. What's more, metabolic Engineering of *E. coli* can allow 10 to 35 times higher level production of the recombinant silk proteins with a molecular weight of 285 kDa [80].

3.3.3. Elastin-like polypeptides

Elastin-like polypeptides (ELPs) are functional polypeptides that seamlessly integrate the intrinsic properties of natural elastic proteins with artificial tunability. They exhibit remarkable temperature responsiveness, biocompatibility, and customizability, offering significant potential for applications in the development of biosensors, tissue scaffolding materials and related domains. It can be seen that achieving large-scale production is necessary. Currently, researchers have utilized

Table 2
Representative production of recombinant collagen in all sorts of expression systems.

Host cells	Expression vectors	Collagen types	Molecular weight (kDa)	Expression level	References
E. coli	pKK223–3	Human collagen (III)	110	/	[61]
	pET-28a	Human collagen (III)	120	0.8 $g{\cdot}L^{-1}$	[57]
	pET-28a(+)	Human-like collagen	13	3.02 $g{\cdot}L^{-1}$	[62]
	pACDuet-1	Human-like collagen	35	0.26 $g{\cdot}L^{-1}$	[63]
	pET-32a	Human-like collagen	30	/	[64]
	pET28a/pET16b	Human collagen (III)	38	0.09 $g{\cdot}L^{-1}$	[58]
P. pastoris	pPIC9K/pPICZB	Human collagen α1(III) chain	120	/	[65]
	pPIC9K	Human collagen (VI)	32	0.04 $g{\cdot}L^{-1}$	[66]
	pPIC9K/pPICZB	Human collagen α1(III) chain	130	0.7 $g{\cdot}L^{-1}$	[67]
	pPIC9K	Human collagen α1(III) chain	130	4.68 $g{\cdot}L^{-1}$	[68]
	pPIC9K	Human collagen (II) fragment	/	3.04 $g{\cdot}L^{-1}$	[59]
	pPIC9K	Human collagen α1(III) chain	120	1.27 $g{\cdot}L^{-1}$	[69]
S. cerevisiae	YEplac195	Human collagen (III)	190, 270	/	[60]
H. polymorpha	pHIPX4/pHIPX7	Recombinant gelatin	15, 38	/	[70]
Tobacco leaves	pUC18	Human collagen (I)	86	20 $g{\cdot}L^{-1}$	[71]
Barley seeds	pEW33/pEW44/pJAM01	Human collagen α1(I) chain	45, 130	13–45 $mg{\cdot}kg^{-1}$ dry seeds	[72]
Silkworm	pMSG1	Human collagen (I)	120	4.24 mg per cocoon	[73]
Sf9 cells with baculovirus	pFBDM	Human collagen (II)	130, 300	/	[74]
HEK-293 cell	pGGH31	Human collagen (V)	200	0.015 $g{\cdot}L^{-1}$	[75]
	pRC/CMV	Human collagen (VII)	290, 900	0.005 $g{\cdot}L^{-1}$	[76]
human fibrosarcoma cell	pYIC	Human collagen (II)	142	0.15 $g{\cdot}L^{-1}$	[77]

engineered *Escherichia coli* for recombinant production of ELPs and have addressed the stability issues of nitration modifications through genetic engineering techniques, providing a comprehensive solution for the scalable production of functionalized ELPs [81].

3.4. Composite and hybrid

3.4.1. Bacterial biofilm-based composite materials

Bacterial biofilm refers to the complex microbial community formed when bacteria attach to contact surfaces, secrete large amounts of lipids, polysaccharides, and proteins, and encapsulate themselves within [82]. It serves as a defense against unfavorable external environments. This community manifests as a three-dimensional structure that may contain the same or different bacterial species, exhibiting high adhesiveness, biocompatibility and biological stability [83]. In this composite material, bacterial biofilms are used as reinforcement materials, integrated with traditional composites to significantly enhance their performance. For instance, incorporating *Escherichia coli* biofilm into traditional knitted textiles to create self-healing textile composites, these composites maintain breathability and enhance mechanical strength after integration [84]. Genetically fuse the biofilm matrix protein CsgA of *Escherichia coli* with the influenza virus binding peptide (C5) to form the CsgA-C5 fusion protein. Due to its excellent adhesion properties, the CsgA-C5 biofilm can be fixed onto polypropylene filler material to form a biocomposite material, which is used for disinfecting river water samples and exhibits better efficacy compared to existing water disinfection technologies [85]. In addition, using engineered bacterial biofilm as a carrier, CdS semiconductor nanoparticles are deposited on biofilm nanofibers via in-situ mineralization, experimentally proving that the biofilm-CdS composite not only retains the excellent photoelectric performance of CdS nanoparticles but also effectively isolates CdS from bacterial cells, reducing light damage [86], offering a solution for constructing stable, biocompatible bio-inorganic interfaces. However, these materials also have some limitations. For example, the mechanical performance of the materials are inferior compared to those of traditionally chemically synthesized materials. Besides, living cells find it difficult to grow and survive in dry or barren environments [87]. These issues need to be addressed in the future research.

3.4.2. Microbial extracellular matrix composite materials

The extracellular matrix (ECM) is an excellent scaffold material itself, capable of inducing cell adhesion and promoting cell proliferation, thus having wide applications in the field of biomaterials. A polypeptide material with properties similar to the ECM can be synthesized by using genetically engineered *Escherichia coli*, which can enhance the ability of cell adhesion and proliferation [88]. In recent years, the synthesis of ECM-mimicking cell scaffolds using microbial self-assembly has emerged as a new research direction. By employing M13 bacteriophage as chiral colloidal particles, functional scaffold materials are formed through self-assembly, exhibiting unique optical and photonic characteristics and the ability to orderly guide the growth of soft and hard tissues, showing great potential in engineered synthetic materials [89]. Leveraging the M13 bacteriophage, an evolutionary selection process was used to isolate hydroxyapatite (HA) to secure HA-binding phage (HAPh). It fibers not only promote HA crystal mineralization but also support adhesion and proliferation of osteoblasts, forming an orderly cellular network [90], providing an important technical method for the development of hierarchical structured tissue engineering materials.

3.4.3. Hybrid molecular materials

The utilization of microbial synthetic biology techniques paves the way for the development of novel hybrid molecular materials, often exhibiting remarkable performance capabilities. For instance, a hybrid molecular material synthesized by fusing the expression of mussel foot protein and the Curli specific gene A protein of *Escherichia coli* has emerged, boasting phenomenal underwater adhesion prowess, with adhesive strength surpassing all previously reported protein-based underwater adhesives by 1.5 times [91]. Thus, it can be discerned that microbial synthetic biology techniques hold immense potential in the realm of the development of novel biomaterials.

3.4.4. Biological nanomaterials

Nanomaterials typically possess unique properties such as chemical reactivity, compressive strength, quantum effects, and optical characteristics, which are closely related to their unique structural organization and the high ratio of their surface area to volume [92]. The use of microorganisms to manufacture nanomaterials does not require any toxic chemical reagents, and all processes are carried out at ambient temperature without the need to add complex physical or chemical steps. The only requirement seems to be maintaining a sterile environment and culture conditions to prevent cross-contamination from other microorganisms [93]. Due to its high environmental friendliness and cost-effectiveness, the biosynthesis method of nanomaterials has attracted increasing attention in recent years. Distinct characteristics

can be imparted by modifying their metabolic pathways to control certain nanoparticle properties. Certain enzymes and other metabolites secreted by microbial cells may play an important role in the process of metallic ions' reduction. For example, bacteria are capable of producing a periplasmic nitrate reductase enzyme (NAP) that exhibits strong reducing power, playing an important role in the synthesis of silver nanoparticles [94]. By utilizing recombinant *Escherichia coli* to express plant phytochelatin synthase (PCS) and metallothionein (MT), the intracellular synthesis of various metal nanoparticles can be achieved (**Fig. 3a-g**) [95]. Furthermore, certain metabolites secreted by microorganisms can provide biological templates, transfer electrons to metal ions, and modify the surface of nanoparticles, thereby promoting its process of adhesion and aggregation to assist in the biosynthesis of nanomaterial [96].

The method of synthesizing various metal nanoparticles through different biological precursors has been widely adopted by many researchers. The synthesized nanoparticles often have very broad applications (Table 3). These studies are sufficient to elucidate the advantages and prospective applications of bio-nanomaterials synthesized by microorganisms.

Compared to the traditional synthesis methods, synthesizing nanomaterials through the use of microorganisms or their derivative metabolites and secretions is often more secure and environmentally friendly. However, it is of vital importance for us to note that the interactions of these biological nanomaterials with living systems whose long-term effects on the ecological system are not well perceived yet [96]. Uncontrolled exposure to nanoparticles or nanomaterials might pose potential health hazards. It has found that certain nanoparticles can directly enter cells and even penetrate cell nuclei, leading to tumor formation [97]. Therefore, how to reduce or avoid the adverse effects of biological nanomaterials on the human body requires researchers to engage in deeper reflection and research.

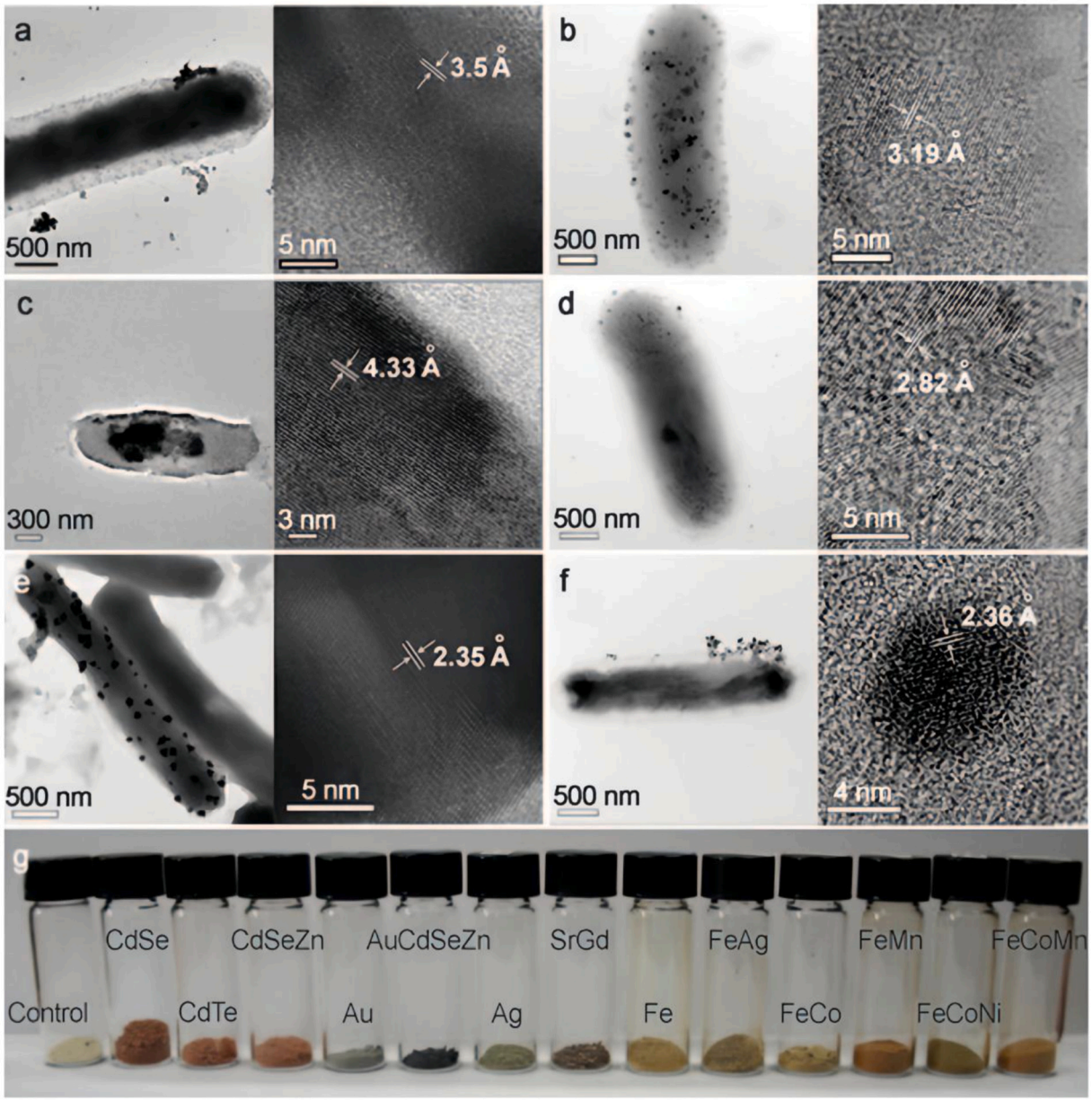

Fig. 3. (a–f) TEM images of various NPs synthesized in EcMP cells(the distance indicated on each HRTEM image is the interplanar distance of the NP lattice). New types of NPs, including CdSeZn (a), PrGd (b), CdCs (c), and FeCo (d), could be synthesized in recombinant *E. coli* expressing AtPCS and PpMT by incubating the cells with the corresponding metal ions (5 mm each). Also, Au (e) and Ag NPs (f) could be synthesized by incubating cells with Au (1.25 mm) and Ag ions (5 mm), respectively. g) Multicolored freeze-dried *E. coli* cellscontaining a variety of NPs. All NPs showed well-defined crystalline nanostructures [95].

Table 3
Synthesis of various nanoparticles by microorganisms.

Species of microorganism		types of nanoparticles	Size and shape	Application	Refs
Bacteria	Streptomyces sp.	Au	43–46 nm; almost spherical	Vaccine adjuvant, bio-imaging	[98]
	Pseudomonas aeruginosa	Ag	13.899 ± 4.036 nm; spherical	Antibacterial, antibiofilm, antitumor	[99]
	Nocardiopsis dassonvillei	Ag	29.28 ± 2.20 nm; spherical	Antimicrobial, antioxidant, insecticidal, anticancer	[100]
	Escherichia coli	Fe	23 ± 1 nm; spherical	Anticoagulant	[101]
	Bifidobacterium animalis H15	Se	122.37 ± 25.32 nm; spherical	Anti-inflammatory	[102]
	Bacillus subtilis	Se	280–630 nm; spherical	Antioxidant, antimicrobial	[103]
	Ochrobactrum sp. MPV1	Te	76.1–78.5 nm; spherical	Antibiofilm	[104]
	Shewanella oneidensis	Pd	6.33 ± 1.69 nm; spherical	Removal of hexavalent chromium	[105]
	Shewanella oneidensis	Cu	20–50 nm; spherical	Work as catalysts in click chemistry	[106]
	Halomonas sp. RAM2	TiO_2	15.45–19.48 nm; cubical	Natural dye-sensitized solar cells	[107]
	Neobacillus niacini AUMC-B524	Ag_2O	6.44–18.80 nm; spherical	Wound dressing agents	[108]
	Bacillus tequilensis ASFS1	Fe_3O_4	10–100 nm; spherical	Anticancer	[109]
	Pseudomonas aeruginosa	Fe_3O_4	35–50 nm; cubo-octahedra, parallelepipedal, bullet-shaped	Magnetic hyperthermia	[110]
	Streptomyces spp.	ZnO	51.40–65.13 nm; spherical	Antimicrobial, antioxidant, anti-inflammatory, antibiofilm	[111]
	Bacillus atrophaeus	Ag, CuO	15.2–61.9 nm, 4.6–28.3 nm; spherical	Antibacterial	[112]
	Ralstonia solanacearum	AgCl	5–35 nm; spherical, oval	Antibacterial	[113]
	Bacillus thuringiensis	Bt-Ag_2O	18.24 nm; spherical	Insecticide, antifungal	[114]
	Escherichia coli	Au-Ag	14–18 nm; round	Antibacterial	[115]
Fungi	Alternaria sp.	Au	9.5 ± 2.9 nm; spherical, quasi-spherical	Develop SERS sensor devices	[116]
	Trichoderma saturnisporum	Au	8–30 nm; spherical	Antibacterial, antibiofilm, antitumor, antioxidant	[117]
	Trichoderma saturnisporum	Ag	10–70 nm; spherical, hexagonal, triangular	Antibacterial, antibiofilm, antitumor, antioxidant	[117]
	Trichoderma viride	ZnO	63.3 nm; hexagonal	Antimicrobial, antioxidant	[118]
	Alternaria tenuissima	ZnO	15.62 ± 4.51 nm; spherical	Antimicrobial, anticancer, antioxidant	[119]
	Agaricus bisporus	CdS	5–8 nm; spherical	Get rid of the domestica larvae	[120]
Yeast	*Saccharomyces cerevisiae*	Ag	16.07 nm; oval	Antimicrobial agents, targeted drug delivery	[121]
	Pichia kudriavzevii	Fe	16.20–18.55 nm; spherical	Treatment of wastewater, antimicrobial	[122]
	Candida pseudojiufengensis	Se	12 nm; spherical	Anticancer	[123]
	Rhodotorula mucilaginosa PA-1	Ag_2Se	12.3 ± 2.9 nm; round	Antibacterial	[124]
Marine algae	Desertifilum sp.	Ag	4.5–26.0 nm; spherical	Anticancer, antibacterial	[125]
	Anabaena sp.	Au, Ce	4.8 nm, 5.2 nm; spherical	Work as a pollutant-removal material	[126]
	Chlorella vulgaris	ZnO	33.4 nm; rod	Antimicrobial	[127]
	Spirulina platensis	CeO_2	75–125 nm; square	Antibacterial, anti-inflammatory	[128]
	Padina boergesenii	CuO	76 nm; tetragonal crystalline structure	Antibacterial, anticancer	[129]

4. Applications of microbial synthetic materials in tissue engineering

Tissue engineering is an area based on cells and scaffolds that studies new tissue and organ growth [130]. It aims to construct functional tissues or organs by combining cells, biomaterials and biofactors together to repair or replace damaged ones. Among the three, biomaterials are the most crucial, which often regulates cell proliferation and differentiation, guiding tissue regeneration. Microbial synthetic materials, as novel biomaterials, have unique properties and advantages, attracting wide attention in tissue engineering.

4.1. Common material types

4.1.1. Protein-based biopolymers

Protein-based biopolymers synthesized by microorganisms serve as the foundation for a class of biomaterials crafted through the sophisticated art of synthetic biology and related biological disciplines. These biomaterials boast remarkable biocompatibility and biodegradability, rendering them invaluable in the realms of tissue engineering. For instance, by introducing genes encoding silk fibroin into certain bacteria or fungi, it becomes feasible to synthesize silk fibroin or materials akin to it for the creation of scaffolds crucial for tissue engineering. Two opulent silk fibroin-based nanoscaffolds have been developed by Mohammadzadeh et al., exhibiting excellent biocompatibility and antibacteria properties and promoting cellular proliferation and differentiation [131]. Thus, it holds great promise for widespread application in the realm of tissue engineering, especially in skin regeneration. Furthermore, specific bacteria possess the ability to synthesize elastin, collagen and their analogous compounds, being equally potent in fashioning biodegradable tissue-engineering scaffolds. An exquisite recombinant fusion protein, called the name of hCol-ELP, which is composed of elastin-like polypeptide (ELP) and humanized collagen (hCol), has been invented and proficiently expressed in *Escherichia coli*. In murine wound models, hCol-ELP significantly enhanced healing rates, expediting wound closure by mitigating inflammation and encouraging collagen regeneration, reducing the time required for crust detachment and unveiling a scar-free healing effect [132]. Therefore, as an innovative biomaterial, it possesses substantial potential for application in wound healing.

4.1.2. Non-protein-based biopolymers

The synthesis of non-protein-based biological polymers by microorganisms refers to a class of polymeric materials composed of other biological macromolecules such as polysaccharides and polypeptides, synthesized by microorganisms, which hold significant applications in the realm of tissue engineering. By introducing heterologous pathways through genetic engineering, *Escherichia coli* can endogenously produce polylactic acid (PLA) and copolymers of lactic acid (LA) and polyhydroxybutyrate (PHB) [133]. By transferring genes related to PHB biosynthesis from *Streptomyces aureofaciens* NRRL2209 into *E. coli*, the synthesis of PHB can be achieved [41]. The various biopolymer

materials produced by these methods, such as PHB and PLA, all possess unique properties of biocompatibility and degradability, thus making them widely used as scaffolding materials for tissue engineering. For example, PHB can serve as a cardiac repair scaffold to counteract left ventricular dilatation and improve cardiac function [134], while polymers like medium-chain PHAs offer new approaches and methods for developing antibiotic-free antibacterial bone regeneration scaffolds and enhancing bone regeneration [135]. Additionally, bacterial cellulose, an important polymer synthesized by bacteria, holds significant application value in tissue engineering. A novel bone repair composite scaffold has been introduced, which, due to the incorporation of bacterial cellulose, demonstrated markedly enhanced mechanical properties and water retention capabilities. This new scaffold also exhibited commendable in vivo stability, thus facilitating bone formation effectively [46]. An immunomodulatory and osteogenic bacterial cellulose scaffold was prepared through a straightforward one-pot method, and experiments revealed that the improved immune microenvironment could promote osteogenic differentiation of stem cells in vivo (Fig. 4) [136], providing an efficacious avenue for the creation of innovative scaffolds for bone tissue engineering.

4.1.3. Engineered living materials(ELMs)

In the realm of ELMs, living cells are regarded as integral constituents. Such materials can harness their living components to dynamically modulate their performance and structure, possessing unique capabilities such as self-adaptation, assembly characteristics, self-replication and self-healing (Fig. 5) [137,138].

Bacteria, due to their ease of genetic manipulation and rapid proliferation, dominate research in ELMs. Therefore, researchers are employing synthetic biology techniques to meticulously control the expression of engineered microbial communities, enabling them to express target proteins in accordance with human demands, thereby bestowing the materials with specific properties [139]. This advancement allows for superior application in fields like tissue engineering. Embedding spores of *Bacillus subtilis* into dressings crafted by 3D printing to conform to human wound model shapes leads to the creation of functional living materials, possessing the ability to sense and eradicate *Staphylococcus aureus* [140], offering certain potential for applications in tissue repair and prevention of wound infection. Utilizing *Bacillus subtilis* formulations combined with thermoresponsive hydrogels which have corroborated the efficacy of such live bacterial formulations in promoting skin wound healing and combating fungal infections [141], illustrating potential clinical significance in combating fungal infections in wounds. An innovative material comprised of active lactic acid bacteria and heparin-poloxamer thermosensitive hydrogel has been developed (Fig. 6). Experiments verified its ability to accelerate the healing of diabetic wounds by fostering angiogenesis and modulating immune responses [142], providing a new therapeutic approach for diabetic foot care.

However, these materials also present some limitations, such as the leakage of microorganisms which can enter the human bloodstream and trigger severe immune responses [8]. Moreover, there is a need for close attention to the potential adverse effects of genetically modified organisms on ecological environments.

4.1.4. Microbial-inorganic hybrid materials

The techniques and methods of synthetic biology intertwine with self-assembling biomaterials, propelling researchers into the realm of biohybrid materials. Microbial-inorganic hybrid materials arise as novel compounds born from the physical or chemical interactions between

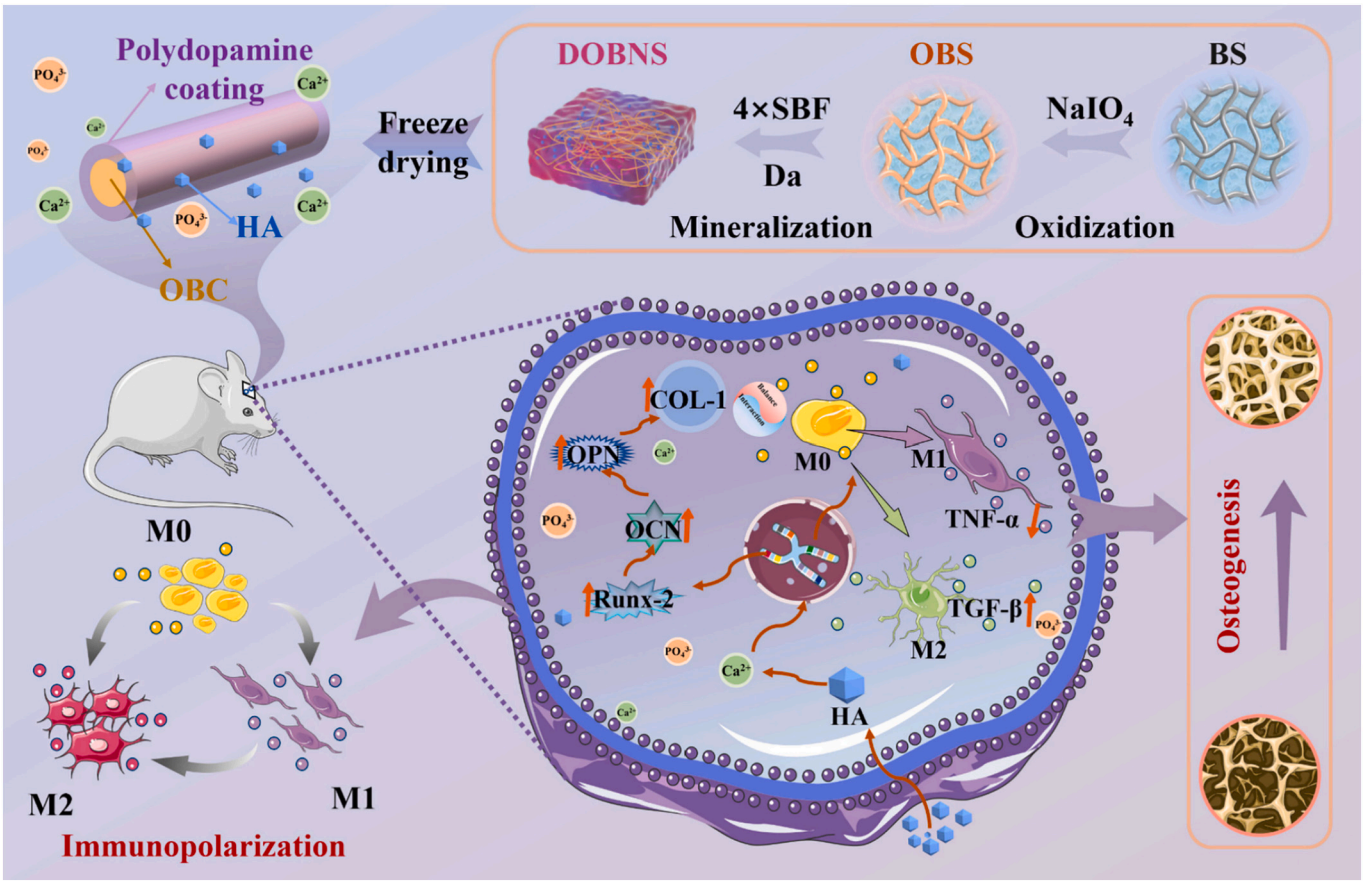

Fig. 4. Schematic diagram of the process of the immunomodulatory and osteogenic oxidation of the bacterial cellulose scaffold in a rat cranial defect model via regulation of the bone immune microenvironment [136].

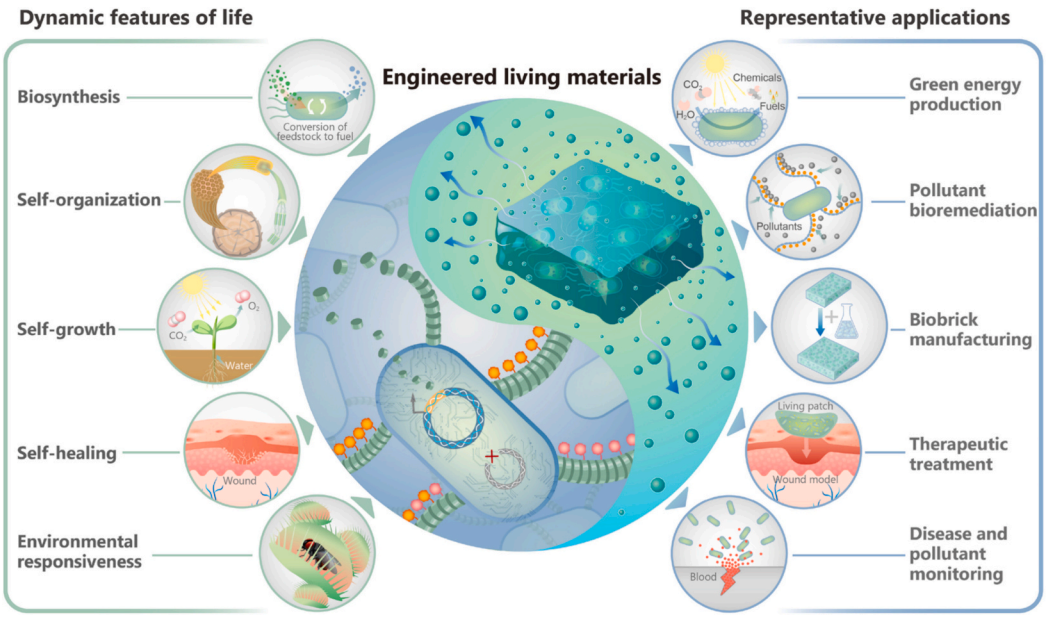

Fig. 5. Schematic of the features and sustainable applications of ELMs. Living materials consist of cells embedded in self-regenerating matrices of their own or artificial scaffolds. They possess various dynamic features of life, such as biosynthesis, self-growth, self-organization, self-healing, and environmental responsiveness. The application of living materials has now been extended to various sustainable applications, including the bioproduction of green energy, bioremediation of pollutants, manufacturing biobricks, and detecting and treating chronic diseases [138].

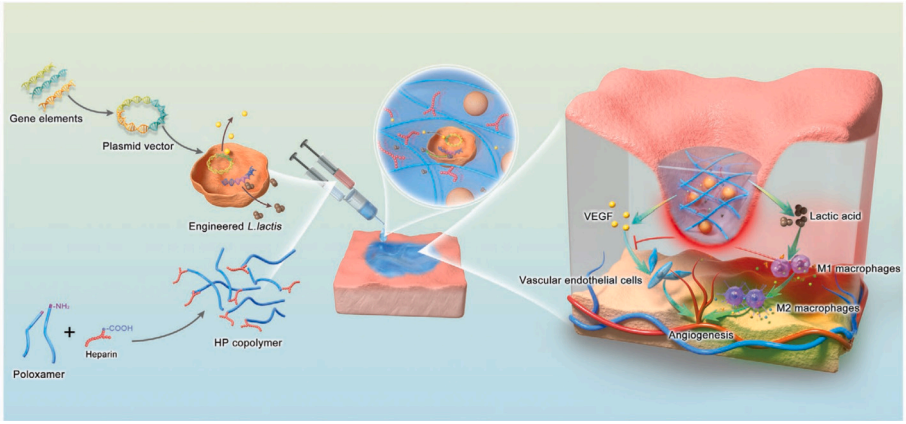

Fig. 6. Engineering bacteria activated multifunctionalized hydrogel for diabetic wound repair and regeneration. A sketch showing the facile development of living hydrogel for accelerating angiogenesis in diabetic wounds by promoting the angiogenic capacity of endothelial cells and inducing macrophages toward M2 polarization [142].

microorganisms and inorganic substances, often exhibiting characteristics of excellent biocompatibility, multifunctionality, adaptability, and safety. Through synthetic biology method, foreign gene clusters linked to the synthesis of magnetic nanomaterials were expressed in *Magnetospirillum gryphiswaldense*, leading to the successful in vivo creation of magnetic nanoparticles within these bacteria [143], which find broad application in the areas of bone tissue engineering and regenerative medicine [144,145]. However, the manner in which these magnetic nanoparticles influence angiogenesis without an external magnetic field remains a mystery requiring further inquiry [146]. A series of stretchable and biocompatible materials were crafted by utilizing a hydrogel-elastomer with high mechanical toughness and stretchability, embedding *Escherichia coli* modified through synthetic biology techniques [147]. By designing or modifying the genetic circuits of cells and the spatial structure of the hydrogel-elastomer, these biohybrid materials are endowed with the ability to perform a range of specific functions, holding significant potential for application in tissue engineering.

4.2. *Expand the characteristics of materials*

The applications of microbial synthetic materials for tissue engineering is gradually becoming a current research hotspot. Unlike traditional and primarily chemically synthesized materials, microbial synthetic biology technology can expand their performance by manipulating microbial metabolic activities through gene editing and other methods, thereby better meeting the needs of tissue engineering.

4.2.1. *Stimuli responsive biomaterials*

Through microbial synthetic biology techniques, it is possible to introduce environmentally stimulus-sensitive genetic components into microbial synthetic materials, endowing the materials with stimuli-responsiveness to undergo reversible physical or chemical changes in response to environmental variations such as pH, temperature and light, which enables the regulation of cell growth, migration and differentiation. A bio-composite material containing cyanobacteria was created by

using synthetic biology and 3D printing technologies. It can respond to external chemical stimuli, especially theophylline. By employing theophylline-responsive riboswitches, gene expression can be modulated, thereby controlling the production of specific proteins such as yellow fluorescent protein (YFP) and laccase, leading to multiple functional outputs, including bioremediation [148]. Composed of poly(lactic-*co*-glycolic acid) (PLGA) and black phosphorus nanosheets (BPs), the osteoimplant (BPs@PLGA) is fashioned to orchestrate bone regeneration from afar. Experiments have demonstrated that even when covered by the biological tissue whose thickness reaches 7 mm, BPs@PLGA can still exhibit an efficient near-infrared (NIR) photothermal response. Through low-intensity and periodic NIR irradiation, the expression of heat shock proteins can be effectively upregulated, ultimately promoting osteogenesis both in vitro and in vivo [149]. Incorporating $SrCl_2$ and BPs into PLGA to form BP-$SrCl_2$/PLGA microspheres, which can also display efficient NIR absorption and photothermal response. Controlled release of Sr^{2+} from BP-$SrCl_2$/PLGA microspheres via NIR light can significantly improve bone regeneration [150]. These studies provide new insights into the development of novel materials for tissue engineering and clinical treatment of bone defects.

4.2.2. Self-healing biomaterials

Microbial synthetic biology technology can design and synthesize biomaterials with self-repairing capabilities. Employing genetic engineering techniques allow these biomaterials to possess proteins that can secrete adhesives or perform self-repair. Upon damage, these proteins can quickly respond and repair the damaged areas, thus enhancing the longevity and reliability of materials. A self-healing semi-interpenetrating polymer network (sIPN) material was fabricated by using engineered bacteria, possessing an intrinsic self-repairing capacity. This characteristic arises from the engineered bacteria's ability to continuously produce and release monomers, which can reassemble polymeric proteins into a protein network, thereby swiftly mending areas of the material damaged by transient or sustained disturbances [151]. Materials of this nature of self-repairing properties hold substantial potential for application in tissue engineering, serving as scaffold materials to provide a stable microenvironment that is conducive to cellular growth and proliferation, facilitating tissue regeneration.

5. Challenges faced by microbial synthetic materials

5.1. The restrictions of synthetic biology technology

The techniques and methodologies of microbial synthetic biology have currently propelled significant advancements in the research and development of biomaterials. A large number of microbial synthetic materials developed possess immense potential for application in various areas. However, synthetic biology technology itself has certain limitations, as its gene editing and biosynthesis aspects may pose unpredictable effects on the ecological environment or human health, such as biocontamination. And it may also incite ethical debates, including the moral boundaries of gene editing and the potential risks of biological weapons. Consequently, alongside technological advancements, it is imperative for the departments concerned to formulate regulations and policies concerning environmental protection and ethics to minimize the likelihood of these risks. Furthermore, in the quest to achieve the desired product of production, there arises the conundrum of volatile productivity [8]. Some current studies have the potential to ameliorate this issue. For instance, custom-designed and synthesized the genome of a eukaryotic organism from scratch, resulting in a highly modified genome with an approximate 8 % reduction in size [152]. Such an approach can significantly diminish metabolic redundancy in life systems, promising to optimize the transformation of cellular resources into target products, thereby steadily increasing the yield of target products.

5.2. The shortcomings of microbial synthetic materials

While the materials designed and synthesized through microbial synthetic biology methods can possess certain unique properties, but they often present specific limitations at the same time. For instance, there is still no clear understanding of the long-term impacts of biologically synthesized nanomaterials within living systems. Prolonged exposure to environments containing certain nanoparticles may cause these particles to directly penetrate human cells, even reaching the cell nucleus, thereby significantly increasing the risk of diseases such as malignant tumors [96,97]. Microbially synthesized materials like ELMs, under certain conditions, might leak pathogenic microorganisms, such as some strains of pathogenic *E. coli*. These pathogens and the various toxins they release can enter the human bloodstream, potentially triggering severe immune responses and toxic reactions [8]. These serious biosafety issues are one of the primary obstacles currently limiting these materials' market entry. Therefore, it is crucial for their further development and large-scale application to enhance the safety of microbial synthetic materials.

Additionally, materials mainly composed of biological components exhibit distinct deficiencies in mechanical properties, and most live microbial cells find it difficult to grow and survive in arid and barren environments [87], adversely affecting the stability of the materials and the exertion of their biological functions. Some current research and endeavors are attempting to address this issue. A programmable approach leveraging engineered bacteria to grow polyprotein on cross-linked polymer scaffolds to fabricate semi-interpenetrating polymer networks aims to enhance the material's interference resistance and dynamic modulus, thereby improving its mechanical properties [151]. Furthermore, the induction and expression of humectants within organisms can, to some extent, aid microbial survival under extremely dry conditions [153].

What's more, certain biomolecules of microbial biofilms, such as including exopolysaccharides (EPSs), proteins, lipids, DNA and other metabolites, can cause material degradation through corrosion, leading to significant losses in industrial production [154]. Therefore, it is crucial to conduct in-depth research on the corrosion mechanisms of biomolecules to provide valuable theoretical support for the interface design of biomaterials, the development of functional coatings, and the formulation of bio-protection strategies. It is also believed that there will be more in-depth research in the near future to resolve these challenges.

6. Summary

With the advent and advancement of microbial synthetic biology technology, their application in the realm of biomaterials science has achieved remarkable progress, pioneering novel developmental trajectories for biomaterials production. The utilization of microorganisms in manufacturing biomaterials holds profound significance for enhancing production efficiency, scaling up manufacturing processes, and innovating new materials. Microbial synthetic biology employs metabolic engineering techniques, gene-editing technologies such as CRISPR-Cas9, and DNA synthesis and assembly methods to rationally reconfigure microbial metabolic pathways or to efficiently and precisely edit microbial genomes, thereby endowing microorganisms with new functions and characteristics. This enables the generation of specific target products which can possess distinctive properties.

At present, microbial synthetic biology has achieved significant advancements in the area of biomaterials. Firstly, microbial synthetic biology enhances the synthesis processes of biological macromolecular materials, leveraging various microorganisms for the production of polyhydroxyalkanoates and the expression of recombinant collagen, thereby improving synthetic efficiency and yield. This approach also enables the generation of a wider variety of polyhydroxyalkanoates and collagen with diverse properties. Secondly, genetic editing of microorganisms, such as bacteria, facilitates the secretion of specific proteins,

polysaccharides and other biological macromolecules, which, when combined with inorganic or organic materials, form bio-composite materials. The successful fabrication of these bio-composites provides essential technical methodologies for research in areas such as the production of novel textile materials, the development of tissue engineering materials, and the treatment of environmental pollutants. Moreover, utilizing microorganisms to synthesize various individual or composite nanoparticles, alongside modifying their metabolic pathways to control nanoparticle properties, imparts unique functionalities to the synthesized nanomaterials, which holds profound significance in disease treatment, environmental protection and the creation of innovative materials.

Researchers, employing various modified or newly engineered microorganisms, have successfully developed numerous high-performance synthetic biomaterials, making significant contributions to the research and advancement of the tissue engineering field. Materials commonly utilized in tissue engineering include protein-based biopolymers, non-protein-based biopolymers, engineered living materials and microbial-inorganic hybrid materials. During the process of modifying or engineering these microorganisms, gene manipulation is integrated to synthesize genetically programmable and precisely controllable gene circuits within the microorganisms [10], enabling them to intelligently express specific products in response to certain signals, thereby better fulfilling the demands of tissue engineering.

Nevertheless, synthetic biology technology and microbial synthetic materials face some challenges, such as unstable yields of target products [8], the need for optimization of mechanical properties [87] and biosafety issues arising from microbial synthetic materials [96,97]. It is believed that these issues can be effectively resolved through more in-depth research in the future.

Envisioning the future, the application prospects of microbial synthetic biology in the biomaterials field remain very promising. With the continuous advancement of technological levels and the deepening of interdisciplinary research, researchers will develop more microbial synthetic materials with unique properties through more precise regulation of microbial metabolic pathways. These materials not only cater to the diverse demands of tissue engineering and regenerative medicine but also achieve further advancements in environmental protection and safety, offering novel solutions to complex challenges across multiple domains like biomedicine, environmental management, and sustainable industries. This will facilitate a deeper integration of microbial synthetic biology and biomaterial science, creating unparalleled value for human society.

CRediT authorship contribution statement

Ruikai Ma: Writing – original draft, Resources, Investigation, Data curation, Conceptualization. **Shuao Zhao:** Writing – original draft, Visualization, Resources, Formal analysis, Data curation. **Yesheng Jin:** Writing – original draft, Validation, Resources, Data curation. **Yinhao Li:** Investigation. **Huxin Tang:** Resources. **Mingyang Hu:** Data curation. **Xinyu Hu:** Writing – review & editing, Visualization, Validation, Supervision, Resources. **Yong Xu:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Wenge Ding:** Writing – review & editing, Supervision, Resources, Funding acquisition, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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