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Review

Structure-optimized and microenvironment-inspired nanocomposite biomaterials in bone tissue engineering

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Abstract

Critical-sized bone defects represent a significant clinical challenge due to their inability to undergo spontaneous regeneration, necessitating graft interventions for effective treatment. The development of tissue-engineered scaffolds and regenerative medicine has made bone tissue engineering a highly viable treatment for bone defects. The physical and biological properties of nanocomposite biomaterials, which have optimized structures and the ability to simulate the regenerative microenvironment of bone, are promising for application in the field of tissue engineering. These biomaterials offer distinct advantages over traditional materials by facilitating cellular adhesion and proliferation, maintaining excellent osteoconductivity and biocompatibility, enabling precise control of degradation rates, and enhancing mechanical properties. Importantly, they can simulate the natural structure of bone tissue, including the specific microenvironment, which is crucial for promoting the repair and regeneration of bone defects. This manuscript provides a comprehensive review of the recent research developments and applications of structure-optimized and microenvironment-inspired nanocomposite biomaterials in bone tissue engineering. This review focuses on the properties and advantages these materials offer for bone repair and tissue regeneration, summarizing the latest progress in the application of nanocomposite biomaterials for bone tissue engineering and highlighting the challenges and future perspectives in the field. Through this analysis, the paper aims to underscore the promising potential of nanocomposite biomaterials in bone tissue engineering, contributing to the informed design and strategic planning of next-generation biomaterials for regenerative medicine.

Keywords: Structure optimization; Bone microenvironment; Biomaterials; Tissue engineering

Highlights

- This article reviews the development and application of structure-optimized and microenvironment-inspired nanocomposite biomaterials in bone tissue engineering.
- Nanocomposite biomaterials exhibit optimized biocompatibility and bioactivity, excellent mechanical properties, and adjustable biodegradability, which are crucial for promoting bone regeneration.
- These biomaterials offer innovative solutions for bone repair scaffolds, delivery systems, and microenvironments, addressing current challenges in bone tissue engineering.

Background

Bone tissue engineering (BTE) is an interdisciplinary field aimed at repairing, replacing, maintaining or enhancing the function of bone tissue. This field necessitates the convergence of diverse scientific disciplines, including cell biology, stem cell research, molecular biology, biomechanics, biomaterial science, immunology and transplantation technologies, to overcome the constraints associated with conventional bone graft repair techniques [1, 2]. Critical-size bone defects (CSBDs) caused by trauma, bone tumours and osteomyelitis are bone defects that do not regenerate spontaneously and require surgical intervention with bone grafts or substitutes for treatment. Currently, the use of autologous bone grafts for the treatment of CSBDs is considered the 'gold standard'. However, there are several limitations to autologous bone grafting, such as secondary injury and infection, high donor-site morbidity and insufficient autologous bone [3]. Allogeneic bone grafting is a new method of bone grafting. Allogeneic bone grafting is an alternative method but has problems such as poor mechanical stress, immune rejection and transmission of infectious diseases [4]. BTE generates bone grafts by creating temporary artificial environments. Driven by rapid advances in materials and manufacturing processes, BTE has become a highly viable treatment for CSBD [5].

The components of BTE mainly include stem cells, bioactive factors and scaffolding materials, which need to meet the biological performance criteria required for bone regeneration [6–8]. A schematic diagram of nanocomposite biomaterials used in BTE is shown in Fig. 1. Stem cells are the cornerstone of BTE and are capable of self-renewal and differentiation into progeny of multiple cell types. The stem cells

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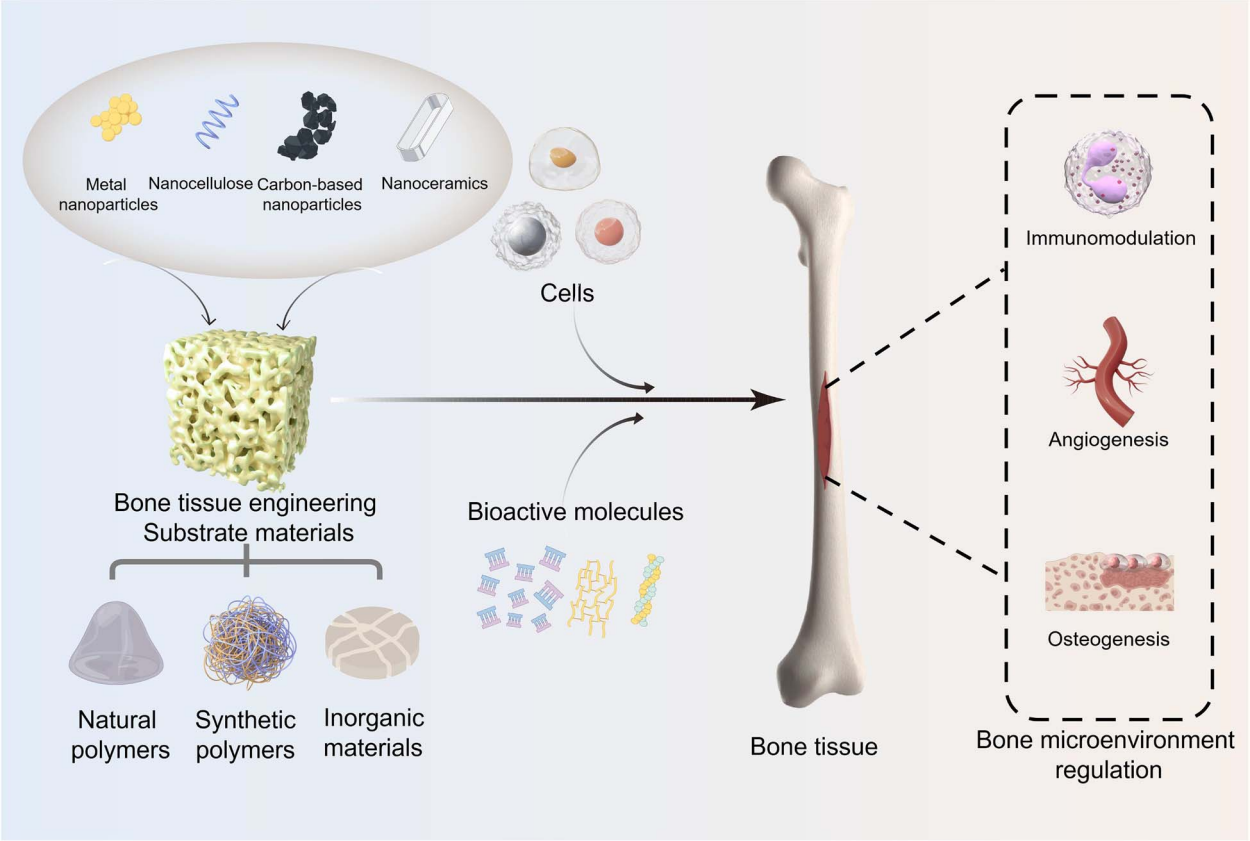

Figure 1. Schematic representation of structure-optimized and microenvironment-inspired nanocomposite biomaterials applied to bone tissue engineering. Prepared by Figdraw

commonly used in BTE include mesenchymal stem cells (MSCs) [9, 10], haematopoietic stem cells [11] and induced pluripotent stem cells, among others [12, 13]. Bioactive factors include cytokines, growth factors, peptides and hormonal signals that stimulate the osteogenic differentiation and proliferation of cells by activating signalling cascades associated with ossification or angiogenesis [14–16]. Scaffolding materials provide a supportive matrix for cell growth, migration and differentiation and act as a delivery system for bioactive factors [17]. Ideal BTE scaffold materials should provide a unique microenvironment with biochemical components and physical factors, such as proteins, peptides, amino acids, shape, porosity, stiffness and mechanical stimulation, which can regulate the proliferation and differentiation of stem cells to renew, repair and form bone tissue. BTE materials should meet certain requirements, such as biocompatibility, biodegradability, osteoconductivity, osteoinductivity, osteostructural properties, porosity, mechanical resistance, ease of use, safety and cost-effectiveness [18].

An important criterion during the synthesis of BTE is the selection of suitable biomaterials as scaffolds, which must take into account all of the features of both materials and tissues to simulate the natural structure of bone tissue, including the specific microenvironment. BTE scaffolds are widely synthesized using natural and synthetic polymers as well as inorganic materials such as bioceramics and metals [19]. The advantage of naturally sourced polymers is their biocompatibility, which allows cells to adhere and migrate within their structures; however, the lack of supply, concerns regarding immunogenicity and potential for batch-to-batch variability of the material reduce the predictability of results [20]. Synthetic polymer materials have the desired shape with relatively high mechanical strength; however, they lack bioactivity and biocompatibility [21]. In addition, the degradation products of synthetic polymers often include acidic byproducts that may hinder regeneration [22, 23]. Inorganic restorative materials have several limitations. Decalcified bone matrix (DBM), bioceramics and metallic materials generally may elicit immune responses and exhibit low bioactivity [24, 25]. Although DBM has high porosity and good biocompatibility, its low cell seeding efficiency and poor osteoinductive microenvironment greatly restrict its application in large-scale bone regeneration [26]· Hydroxyapatite (HA), a representative bioceramic, is highly biocompatible and induces the repair of bone defects through osteoconductivity and osteoinductivity, but the resorption of HA is very slow [27]. Metallic materials have excellent mechanical properties, and their main problems are their lack of corrosion resistance, which may lead to surgical implantation failure, as well as the side effects of releasing toxic metal particles [28, 29]. Therefore, the development of safe and efficacious structure-optimized biomaterials that can be easily used in the clinic with a microenvironment compatible with that of natural bone is urgently needed.

To overcome the limitations of existing bone repair materials, researchers have begun to investigate the application of nanotechnology in BTE. Nanocomposite biomaterials are beginning to receive widespread attention as novel structure-optimized materials with potential for clinical applications. BTE combines biopolymers and biodegradable material structures with biologically active and easily absorbed

nanoscale fillers [30, 31]. The incorporation of nanosized fillers transcends the capabilities of traditional materials, not merely in an additive manner but also synergistically, where the resultant properties of the composite far exceed the sum of its parts, embodying an optimized structure. Compared with traditional tiny fillers, nanoparticle fillers can enhance the mechanical properties of the material due to their large specific surface area, which allows them to form a tight interface with the polymer matrix while retaining the good osteoconductivity and biocompatibility of the filler, thus influencing protein adsorption, cell adhesion, pro-activation and differentiation, and promoting the formation of new tissues [32, 33]. Furthermore, nanocomposite biomaterials show great potential by mimicking the structure and microenvironment of natural bone tissue at the molecular level. By adding different nanomaterials and selecting different matrix materials, the degradation rate of the materials can be controlled to match the rate of new bone tissue formation [34]. Multiple functions, such as drug delivery and antibacterial activity, can also be achieved by surface modification or the doping of specific functional nanoparticles [35, 36]. The introduction of nanocomposite biomaterials not only addresses some of the limitations of traditional bone repair materials but also provides more innovative solutions for BTE. The development and application of these materials herald a new direction in the field of bone tissue repair and regenerative medicine. This paper presents a variety of nanocomposite biomaterials from existing research, highlights the properties and advantages they exhibit in bone defect repair and tissue regeneration, discusses the latest advances in the application of structure-optimized and microenvironment-inspired nanocomposite biomaterials for BTE, and presents the challenges and opportunities they face. This review provides readers with preliminary information that will help in the design and planning of future nanocomposite biomaterials for BTE. Therefore, several typical structure-optimized and microenvironment-inspired nanocomposite biomaterials with general properties and applications are summarized in Table 1.

Review

Basic concepts of nanocomposite biomaterials

Nanocomposite biomaterials represent a class of advanced composites engineered by integrating nanomaterials into a polymer matrix. This integration markedly enhances the composite's mechanical strength, biological performance and electrical conductivity, fostering an environment conducive to bone regeneration and cell proliferation. The foundation of these composites is a diverse array of substrate materials, encompassing natural and synthetic polymers along with inorganic substances. The nanomaterials incorporated as fillers encompass a wide range, including metal nanoparticles, nanoceramics, nanocellulose and carbon-based nanomaterials, among others. The composition of nanocomposite biomaterials is shown in Fig. 2.

Substrate materials

Natural polymers, such as chitosan, collagen, gelatine, silk fibroin and alginate, are biocompatible and biodegradable natural materials [54–56]. These materials inherently support cellular guidance, improve cell adhesion and induce chemotactic responses, thereby augmenting the biological interplay between scaffolds and surrounding tissues. Synthetic polymers, including polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA) and hydrogels, offer customizable properties [19]. Integrating nanofillers into these polymer substrates creates biomaterials with a balanced array of physical, chemical and biological characteristics that closely resemble the natural extracellular matrix of bone [57]. Inorganic materials, notably bioceramics, bioactive glasses and metallic substances, provide additional options for bone restoration. Bioceramics are known for their biocompatibility and bioactivity, which facilitate osteoblast attachment, proliferation and the formation of strong chemical bonds with bone tissue [58]. HA is widely used as a filler material for bone defects and bone repair scaffolds due to its similarity in composition to natural bone minerals [59, 60]. Bioactive glass can rapidly form a layer of bioactive HA in body fluids, which promotes the proliferation of bone cells and regeneration of bone tissue [61]. Among metallic materials, titanium and its alloys are widely used in BTE due to their excellent biocompatibility and corrosion resistance [62].

Nanoparticles

Nanoparticles (NPs) are tiny particles with a size of 1–100 nm and can exist in many forms, such as particles, wires, tubes, rods and spheres. These nanostructures, particularly metal NPs, are known for their biocompatibility and unique optical, electrical, magnetic and chemical properties. Gold NPs and iron oxide NPs can be used in drug carriers, biodetection and clinical therapies and have important applications in bioengineering and biomedical fields [63, 64]. In the realm of nanoceramics, materials such as calcium phosphate NPs, mesoporous silica NPs and titanium dioxide NPs can transport proteins, peptides and drugs while preserving their bioactivity. Notably, HANPs are extensively utilized in tissue engineering due to their excellent bioactivity and mechanical strength [65, 66]. Furthermore, nanocellulose is classified into three types: cellulose nanofibres, cellulose nanocrystals (CNCs) and bacterial nanocellulose [67]. Because of their excellent biodegradability, mechanical properties and biocompatibility, they can be used in the medical field, especially in vascular grafts, tissue engineering and other applications [68]· Carbon-based nanomaterials, including carbon nanotubes (CNTs), graphene, fullerenes and carbon quantum dots (CQDs), exhibit unparalleled physicochemical characteristics and have been widely developed for use in various fields of biomedicine [69, 70]. The nanoscale dimensions of these materials endow them with unique functionalities that enhance their mechanical properties, foster cell growth and differentiation, and improve their biocompatibility and biodegradability [71].

Fabrication method

Nanocomposite biomaterials represent a strategic amalgamation of matrix materials with NPs aimed at forging new materials endowed with superior properties. The synthesis of these NPs and composite materials is achieved through diverse methods, the particulars of which are outlined in Table 2. The overall enhancement of nanocomposite biomaterial properties hinges on the precise tuning of material selection, preparation methodologies and mixing techniques. Advanced processing technologies play a pivotal role in crafting scaffold materials tailored to meet specific clinical demands [72]. As a prominent research avenue within BTE, structure-optimized and

Table 1. Summary of several typical structure-optimized and microenvironment-inspired nanocomposite biomaterials.

Material type	Substrate material	Nanoparticle	Fabrication method	General properties	Application	Ref.
Natural polymers	Collagen	Strontium-graphene oxide	Covalent cross-linking	Cell adhesion; osteogenic differentiation; secretion of angiogenic factors	Bone repair stent; angiogenesis	[37]
	Celastrol (CEL)	Enzyme-responsive nanoparticles (PRNPs)	Integrin interaction	Number of OCs and inflammatory macrophages was reduced	Bone repair stent; immunoregulatory microenvironment	[38]
	Hydrated sodium alginate molecule	Comprising bacterial cellulose (BC) nanofibre-network	Heterogeneous crosslink-and-hydration (HCH)	Shape flexibility; excellent wet mechanical properties	Bone repair stent	[39]
Synthetic polymers	Butylene succinate	Cellulose nanocrystals	Temperature variation and a two-step depressurization	Good mechanical compressive properties; hydrophilicity; Excellent *in vitro* degradation rates	Bone repair stent	[40]
	Core-shell SF/PCL/PVA	Nanofibrous mats	Coaxial electrospinning and layer-by-layer (LBL)	The sustained release of BMP2; A rapid release of CTGF	Bone repair stent; bioactive factors delivery system	[14]
	Polyethylene glycol (PEG)-based hydrogels	Magnetic nanoparticles (MNPs)	Coassembly	Osteoblastic; vasculogenic; potentials of engineered bone tissue grafts	Bone repair stent; angiogenesis	[31]
	Nanocomposite hydrogel	Whitlockite nanoparticles	Precipitation	good mechanical strength; drug release; protein adsorption; angiogenic and osteogenic properties;	Bone repair stent; angiogenesis; cell delivery system	[41]
	Hydrogel microspheres	Nanofibres	Electrospinning	well-preserved viability; phenotype and functions of endothelial cells; improved vascularization	Bone repair stent; cell delivery system; angiogenesis	[42]
	PLGA	nHA	Fused deposition modelling 3D printing	Biocompatible; high cell viability	Bone repair stent. Cell delivery system	[43]
	PCL	nHA@GRgel	Non-covalently composited	Cell proliferation and osteogenic differentiation; osteoimmunomodulation ability; improved angiogenesis	Bone repair stent; cell delivery system; angiogenic, immunoregulatory microenvironment	[44]
	PCL	Mesoporous bioactive glass (MBG)	Freeze-drying	Promote osteoblast differentiation; induce ectopic bone formation; broad-spectrum antibacterial capacity	Bone repair stent; bioactive factors delivery system.	[45]
	Poly(glycolic acid) (PGA)	Silk fibroin (SF) nanofibre membranes	Electrospinning and hot-melt	Cell proliferation and osteogenic differentiation was promoted;	Bone repair stent	[46]
	PLA/GEL	nHA	Electrospun nanofibres.	favourable biocompatibility and osteoinductivity;	Bone repair stent	[47]
	PLA-HA	DFO@PCL NP	Double emulsion-solvent evaporation	lessening inflammatory response; vascular formation; improved bone regeneration	Bone repair stent; angiogenic; immunoregulatory microenvironment	[48]
	SF/PCL/PVA	Nanofibrous mats	Coaxial electrospinning and layer-by-layer (LBL)	Bone formation was enhanced; angiogenic effect	Bone repair stent; bioactive factors delivery system.	[14]
	PLGA	Magnesium peroxide	Low-temperature rapid prototyping (LT-RP) 3D printing	Osteogenic differentiation of cells was promoted; osteopromotive immune microenvironment; apoptosis and ferroptosis in tumour cells	Bone repair stent; immunoregulatory microenvironment	[49]
	Titanium dioxide (TiO_2)-based polymeric	n-HAp	Freeze-drying method	Proved more biocompatible, showed interconnected porosity and substantial mechanical strength;	Bone repair stent	[50]
Inorganic materials	Bioceramic	Pure-phase lithium calcium silicate ($Li_2Ca_4Si_4O_{13}$, L2C4S4)	Sol–gel	stimulated the proliferation and maturation of chondrocytes; osteogenic differentiation of rBMSCs was promoted	Bone repair stent. Cell delivery system	[51]
	CCNWs	AgNPs	Freeze-drying	Improved mechanical strength; angiogenesis and vascularization	Bone repair stent; angiogenic; immunoregulatory microenvironment	[52]
	SiO_2-CaO-P_2O_5	Mesoporous bioactive glasses (MGN)	Sol–gel chemistry	Bacterial growth in planktonic state was reduced; cytocompatible behaviour	Bone regeneration capacity; antibacterial properties	[53]

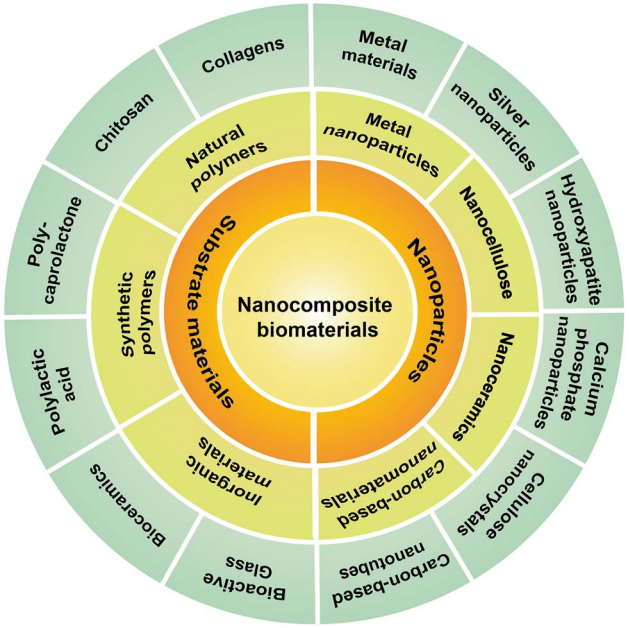

Figure 2. Schematic diagram of the composition of nanocomposite biomaterials

microenvironment-inspired nanocomposite biomaterials are meticulously selected and engineered to fulfil the requisites of optimal repair and regeneration for designated applications. Techniques such as self-assembly and electrospinning, surface modification, the design of porous structures, and the incorporation of drugs and growth factors are leveraged to improve the physical, chemical and biological characteristics of materials.

Properties and advantages of structure-optimized and microenvironment-inspired nanocomposite biomaterials in BTE

Structure-optimized nanocomposite biomaterials are composed of biocompatible materials such as polymers and bioceramics, and their bioactivity is enhanced by the addition of NPs; these materials can provide a microenvironment similar to that of the natural extracellular matrix [84]. This sophisticated combination promotes cell proliferation and differentiation towards osteoblasts through surface properties and the release of bioactive factors to promote bone regeneration. The strategic incorporation of NPs not only amplifies the bioactive potential of these materials but also significantly bolsters their mechanical attributes—strength, toughness and modulus. Such enhancements align the composite's mechanical properties more closely with those of natural bone, bridging a crucial gap in biomaterials engineering [39, 85]. Furthermore, the degradation rate of these nanocomposite biomaterials can be meticulously calibrated by adjusting their composition and structural makeup. This adaptability ensures that biomaterial degradation is synchronized with the timeline of bone regeneration, obviating the need for secondary surgeries to remove the materials [86]. The advantages of structure-optimized and microenvironment-inspired nanocomposite biomaterials are shown in Fig. 3.

Optimized biocompatibility and bioactivity

Biocompatibility requires that the material support cell activity without toxic effects on the host tissue and should also allow cells to adhere and proliferate within its pores as well as on its surface. By selecting appropriate materials and employing strategic surface modifications, the structure and microenvironment of natural bone tissue can be manipulated, thereby enhancing the biocompatibility and bioactivity of nanocomposite biomaterials. These materials are engineered to minimize immune responses while promoting cell attachment, proliferation and differentiation into bone tissue when applied *in vivo*. PLA nanofibrous scaffolds have received significant attention, mainly as emerging materials for use in the field of regenerative medicine. Recently, researchers have used FDM-3D printing technology to prepare PLA/nano-tricalcium phosphate composite BTE scaffolds. The composite scaffold has good biocompatibility, osteogenic ability and personalized porosity and shape, and the BMSCs attached to the surface of the composite scaffold grow normally and naturally [87]. In addition, PLGA is a polymer material with good biocompatibility and spheroid-forming properties that is widely used in the medical field [88]. Liu *et al*. prepared PLGA nanofibres incorporated with a hyaluronic acid oligosaccharide-collagen mineralized microparticle scaffold and found that the scaffold exhibited ideal biocompatibility and tissue regenerative capacity, mediated orderly cell arrangement and stimulated cell proliferation [89]. In addition, Kumar *et al*. evaluated chitosan–nanoHA (CTS–nHA) and chitosan–nanobioglass (CTS–nBG) scaffolds, and experiments showed that the two prepared scaffolds were favourable for cell growth and had good compatibility, and that fibroblasts (L929, ATCC) and MG-63 were able to adhere, proliferate and migrate through the porous structures [90]. These advancements underscore the potential of nanocomposite biomaterial scaffolds to provide an optimal environment for cell proliferation and differentiation.

In addition, biocompatibility extends beyond merely supporting cell activity without toxicity; it also requires materials to be osteoconductive and capable of promoting vascularization. The osteoinductive and osteoconductive properties of nanocomposite biomaterials were improved by the doping of inorganic fillers such as CNTs, which allowed the materials to better mimic the properties of natural bone tissue [91]. Recently, researchers have constructed short nanofibre aggregate-enriched dual-factor delivery scaffolds via 3D printing and electrospinning techniques. The results demonstrated that the scaffold has excellent biocompatibility and significantly promotes angiogenesis and osteogenesis by stimulating endothelial cells and osteoblasts (Fig. 4a, b) [92]. In addition, a study used electrostatic force to apply ssDNA@CNT nanocomplexes to 3D-printed scaffolds via simple one-step coating, which significantly improved the adhesion, proliferation and differentiation of preosteoblasts, resulting in good biocompatibility (Fig. 4c–h) [93]. Furthermore, blood vessel formation (angiogenesis and vascular endothelial growth) is essential for the provision of necessary nutrients and oxygen and for the removal of waste products, especially in the repair of larger bone defects. Yegappan *et al*. developed an injectable nanocomposite hydrogel containing calcium white phosphorite NPs and the angiogenic drug dimethyloxalenylglycine, and human umbilical vein endothelial cells (HUVECs) exposed to the dimethyloxalenylglycine-containing nanocomposite hydrogel showed enhanced cell migration and formation of capillary-like structures [41]. By tailoring these materials to support biocompatibility, bioactivity osteoconductivity, osteoinductivity, and vascularization, the field of

Table 2. Summary of some fabrication methods of nanocomposite biomaterials.

Fabrication method	Description	Properties	Ref.
Direct mixing	Mixed without any solvents; polymers and nanofillers can be mixed in solution	Improved mechanical properties; enhanced thermal stability	[73]
In situ polymerization	Dispersion of nanoparticles in a monomer medium and polymerization process under appropriate conditions	Biocompatibility; enhanced mechanical properties	[74]
Sol–gel method	Interconnected transformation of colloidal suspensions of solid nanoparticles (sols) with a connecting network of solid particles (gels) followed by hydrolysis procedures	Biocompatibility; enhanced surface area; uniform distribution of components	[51, 75]
Electrochemical deposition	Deposition of nanoparticles on conductive substrates	Precise control of the thickness and composition of the deposited layer	[76]
Layer-by-layer assembly	Deposition to spontaneously form a thin film with a complete structure and function on the surface of a template through the forces of electrostatic interactions between molecules	Precise design and fabrication of thin multilayer films	[77]
Coatings	Applying a liquid coating substance to a substrate and then drying and curing it to form a film	Protection against corrosion; enhanced wear resistance; poor scalability	[78]
Electrospinning	Designed by adjusting the components of precursor or subsequent procedure	Simple; versatile; low cost	[42, 79, 80]
3D printing	Using a digital model file as the basis for constructing an object by printing layer by layer, using a bondable material such as powdered metal or plastic	Produce innovative material; superior pore interconnectivity; improved mechanical strength	[81–83]

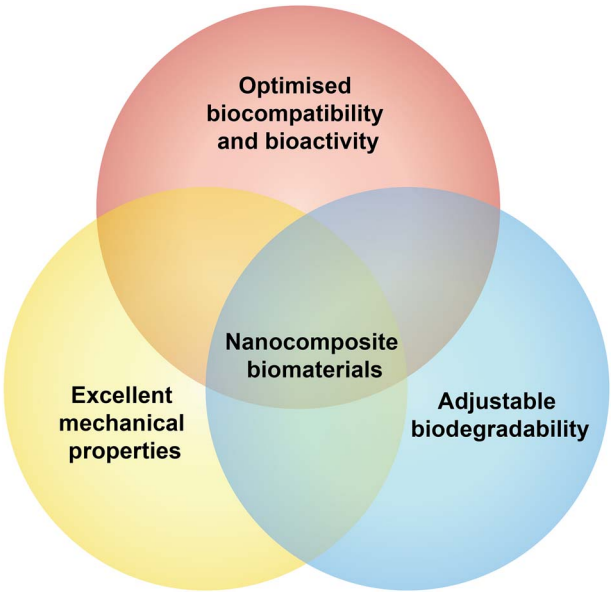

Figure 3. Schematic illustration of the advantages of structure-optimized and microenvironment-inspired nanocomposite biomaterials

BTE is significantly advancing the capabilities for efficient and effective repair of bone defects.

Excellent mechanical properties

In BTE, the development of nanocomposite biomaterials aims to mimic the structure and microenvironment of natural bone to facilitate the repair and regeneration of bone defects. The Young's moduli of cortical and cancellous bone in natural bone are 15–20 GPa and 0.1–2 GPa, respectively, and the compressive strengths of cortical and cancellous bone should be ~100–200 MPa and 2–20 MPa, respectively. Wang *et al.* utilized a synthetic fibrous glycopeptide hydrogel (GRgel) noncovalently composited with a 3D-printed PCL/nHA scaffold for cranial bone regeneration. The tensile and compressive moduli of these nanocomposite biomaterials were in the ranges 180–506.6 MPa and 44.9–56.43 MPa, respectively, and increased with increasing nHA content in the composites (Fig. 5a–e) [44]. In addition, Zhang *et al.* loaded a nanodiamond phospholipid complex (NDPC) into biodegradable PLGA. Compared to a pure PLGA matrix, the introduction of 10 wt% NDPC resulted in a significant improvement in the material's mechanical and surface properties, including a decrease in the water contact angle from 80 to 55°, an ~100% increase in the Young's modulus and an ~550% increase in hardness, thus closely resembling that of human cortical bone [94]. By adjusting the composition and structure of the materials, researchers can create scaffolds with mechanical characteristics closely resembling those of cortical or cancellous bone. This customization ensures optimal support for bone regeneration in specific clinical scenarios, leading to more effective treatments and improved patient outcomes.

In recent years, carbon-based nanomaterials have attracted great interest in the field of BTE scaffolds due to their excellent mechanical strength, stable chemical properties, tuneable surface functionality, optimized biocompatibility and economic accessibility [95]. CNTs, a prominent member of this family of materials, exhibit exceptional tensile strength and mechanical stiffness. CNTs are widely used as filler materials in combination with polymers or bioceramics due to their nanoscale diameter and strong sp2 carbon bonds [96]. A recent study used an enhanced hydrogel scaffold of hydroxylate multiwalled carbon nanotubes, and the results showed that the maximum compressive strength and elongation at break were 10.4 MPa and 1032%, respectively [97]. Researchers used electrostatic spinning to prepare PLA/CNC composite scaffolds, and the mechanical properties of the nanocomposite scaffolds were significantly improved compared with those of the pure polymer due to stronger interactions between the polymer chains and the cellulose nanocrystals (Fig. 5f, g) [98].

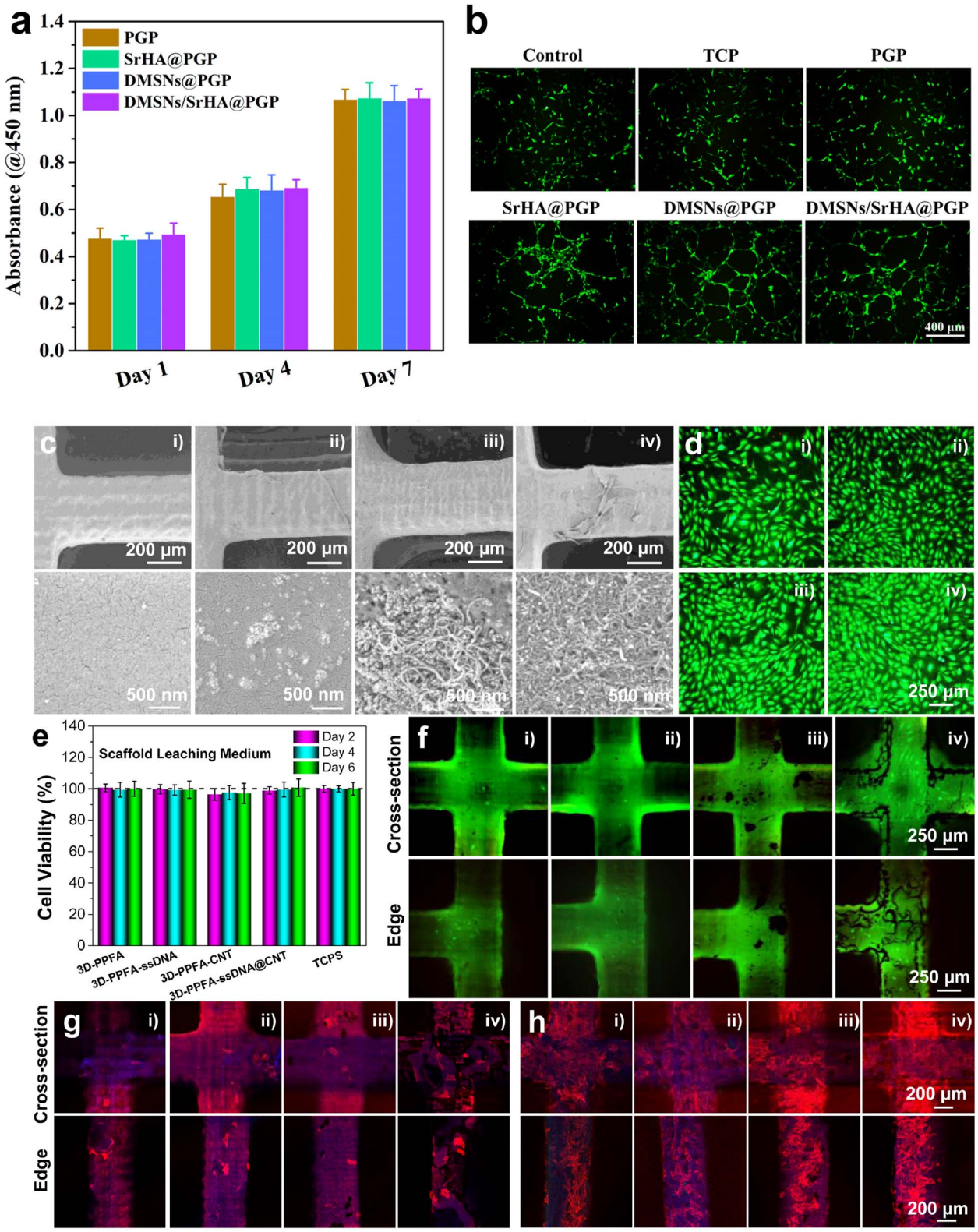

Figure 4. Nanocomposite biomaterials have optimized biocompatibility and bioactivity. (**a**, **b**) *In vitro* biocompatibility and angiogenic effect of composite scaffolds. (a) Quantitative analysis of BMSCs proliferation after culturing with different scaffolds for 1, 4 and 7 days by CCK-8 assay. (b) Evaluation of tube formation in HUVECs by calcein-AM staining at 6 h. Reproduced from [92]. Copyright 2023, American Chemical Society. (**c**–**h**) Differences in 3D-propylene fumarate aminated (PPFA) scaffolds before and after functionalization; the biocompatibility of functionalized scaffolds was assessed using both methods of co-culturing in a transwell and with cells, and culturing cells directly onto the scaffold surface. (c) SEM images of 3D-PPFA scaffolds before and after functionalization. (d) Live/dead imaging and (e) cell viability of MC3T3 pre-osteoblast cells after exposure to the scaffold leaching medium. (f) Live/dead imaging of MC3T3 cells after direct seeding onto scaffold surfaces. Confocal immunofluorescence imaging of MC3T3 cells at (g) 1 day and (h) 7 days post-seeding on the scaffolds (red: F-actin; blue: cell nuclei). (i) 3D-PPFA; (ii) 3D-PPFA-ssDNA; (iii) 3D-PPFA-carbon nanotubes (CNT); (iv) 3D-PPFA-ssDNA@CNT. Reproduced from [93]. Copyright 2020, Acta Materialia Inc. Published by Elsevier Ltd. H*UVECs* human umbilical vein endothelial cells, *BMSCs* bone marrow mesenchymal stem cells

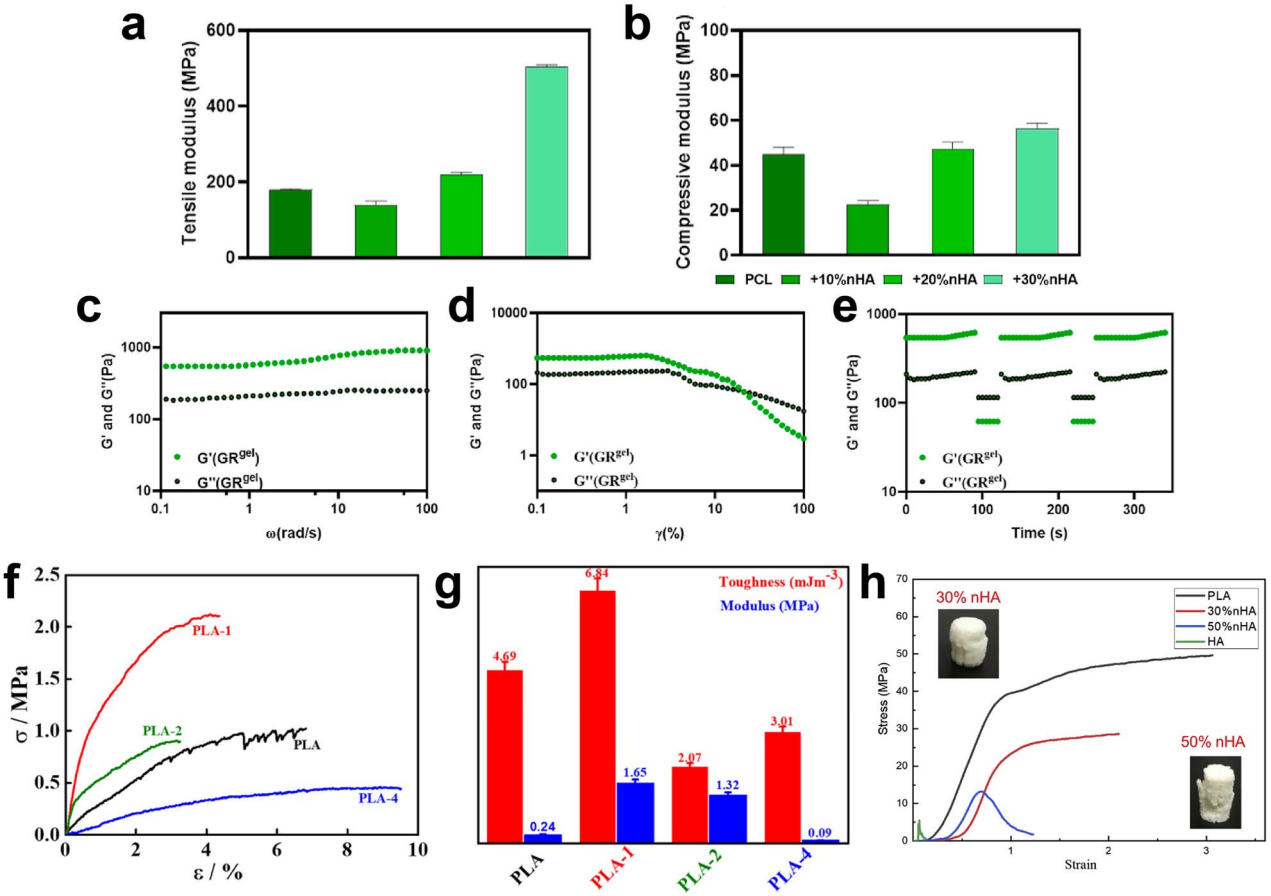

Figure 5. Nanocomposite biomaterials have excellent mechanical properties. (**a–e**) Tensile and compressive moduli of prepared scaffolds, and extracellular matrix (ECM)-inspired rheological testing of fibrous glycopeptide hydrogel (GRgel). Mechanical properties for PCL/nHA (PH) scaffolds including tensile modulus (a) and compressive modulus (b). (c, d) Rheological analysis of GRgel as a function of angular frequency (c) and shear strain (d) at 25°C, respectively. (e) The self-healing analysis of GRgel under continuous strain sweep with an alternative large oscillation force (50%) and a small one (2%) at 25°C. Reproduced from [44]. Copyright 2022, Elsevier Ltd. (**f**, **g**) Mechanical behaviour of the pure poly(lactic acid) (PLA) polymer and its indicated composite scaffolds. (f) Stress–strain curve and (g) change in the modulus and toughness values of the pure PLA polymer and its indicated composite scaffolds. Reproduced from [98]. Copyright 2020, Elsevier B.V. (**h**) Stress–strain curves of different scaffolds. Reproduced from [99]. Copyright 2021, The Author(s). Published by Elsevier Ltd

In addition, Zhang *et al*. successfully prepared comprehensively optimized L-polylactic acid/nHA porous bone repair composites. The results showed that the highly loaded nHA scaffolds had better compressive strength, which was significantly greater than that of the pure HA ceramic scaffolds and cancellous bone (Fig. 5h) [99]. The addition of nanocellulose or CNTs enhances the strength and toughness of the material, and the incorporation of PHA improves its stiffness and osteoinductivity. Li *et al*., by developing polydopamine-mediated graphene oxide (PGO) and PHA incorporated into gelatine (AG) scaffolds, reported that due to the nanoenhancement of PGO and PHA, the PGO–PHA–AG scaffolds exhibited good mechanical properties, and the compressive strength of the scaffolds increased with the addition of PHA from 30 to 50 kPa; moreover, with increasing PGO content, the compressive strength of the scaffolds increased from ~50 kPa to 140 kPa [100]. These materials not only provide a robust and supportive structure for new bone formation but also closely mimic the natural mechanical environment of bone, thereby enhancing the overall efficacy of bone regeneration strategies in BTE.

Adjustable biodegradability

In the realm of BTE, developing structure-optimized nanocomposite biomaterials with tuneable biodegradability is pivotal. This characteristic ensures that these materials can gradually degrade in synchronization with the rate of new bone tissue formation, providing temporary structural support during the healing process. As the new bone materializes, the scaffold is naturally replaced, eliminating the need for a secondary procedure to remove the scaffold, thereby enhancing patient recovery and reducing the risk of complications. One study reported the use of collagen hydrogels as a platform for transporting BMSCs and cadmium selenide quantum dots, resulting in an injectable composite hydrogel (CGQ) with appropriate biodegradability and excellent biocompatibility. These results suggest that the excellent degradation rate of the nanocomposite biomaterials *in vivo* is consistent with the cartilage regeneration rate (Fig. 6a) [101]. Zhou *et al*. prepared biocomposite nanofibres using HANPs and collagen as composite materials by one-step electrostatic spinning and investigated *in vitro* scaffold degradation by observing and monitoring morphology and weight loss

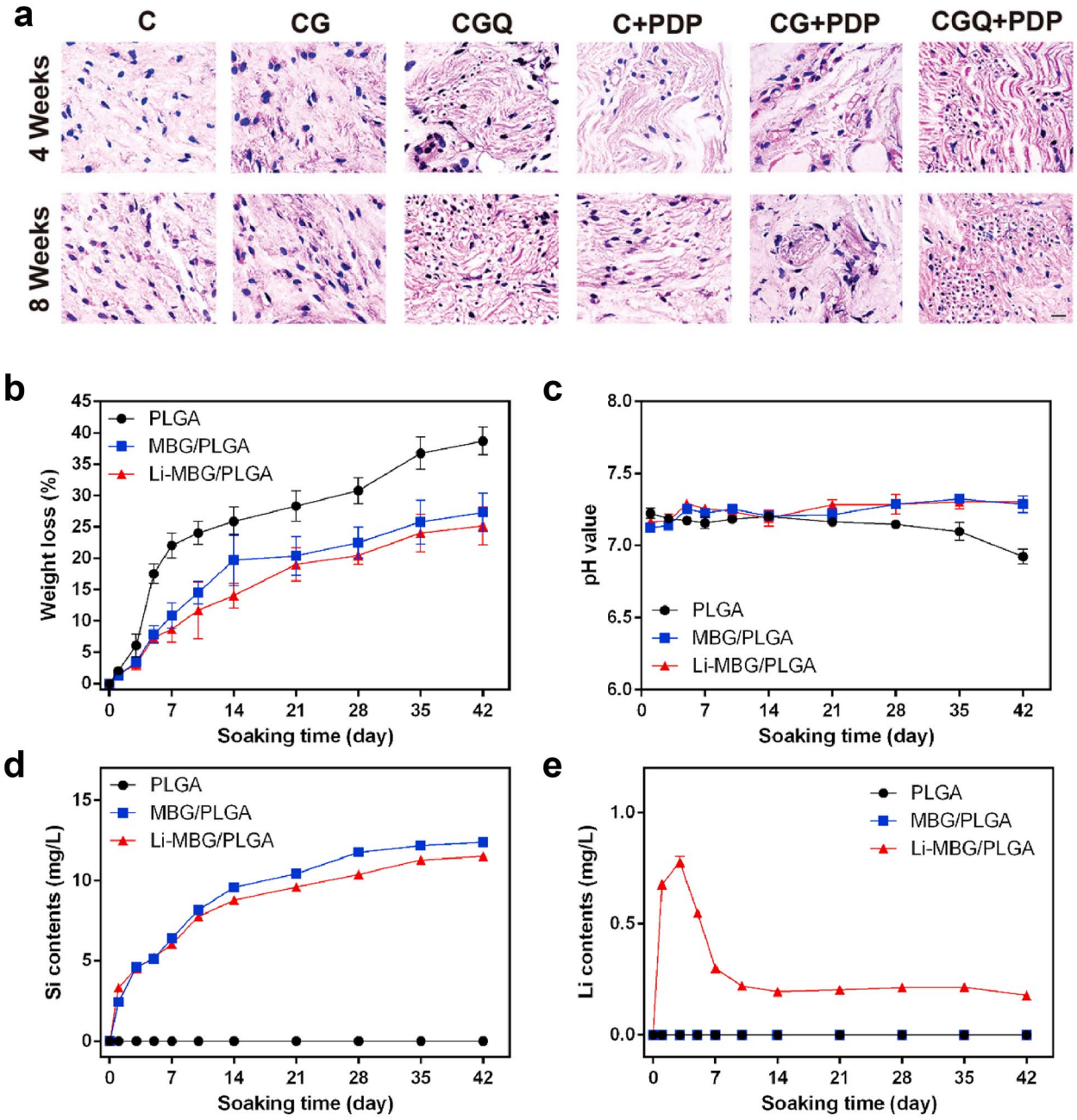

Figure 6. Nanocomposite biomaterials have adjustable biodegradability. (**a**) Pathological examination by hematoxylin and eosin (HE) staining 8 weeks post-injection suggests an excellent degradation rate *in vivo* that is consistent with the cartilage regeneration rate. HE staining for tissues with subcutaneous implantation in nude mice with or without photodynamic provocation (PDP) for 4 and 8 weeks (scale bar = 40 μm). C = collagen + BMSCs, CG = collagen crosslinked with genipin + BMSCs, CGQ = collagen crosslinked with genipin and QDs + BMSCs, C + PDP = collagen + BMSCs + irradiation with an 808 nm laser at fluence of 3 Jcm^{-2} for 3 min, CG + PDP = CG scaffold + BMSCs + irradiation with an 808 nm laser at fluence of 3 Jcm^{-2} for 3 min, CGQ + PDP = CGQ scaffold + BMSCs + irradiation with an 808 nm laser at fluence of 3 Jcm^{-2} for 3 min. Reproduced from [101]. Copyright 2019, The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (**b–e**) Degradation performance and ion release performance of the scaffolds. (b) Weight loss conditions with material degradation, (c) changes in pH value, (d) changes in Si ion concentrations, (e) changes in Li ion concentration. Reproduced from [103]. Copyright 2021, Elsevier Ltd. *BMSCs* bone marrow mesenchymal stem cells, *PLGA* poly(lactic-co-glycolic acid), *Li-MBG* lithium-containing mesoporous bioactive glass

for up to 80 days, which showed that the L-polylactic acid/collagen/HA scaffolds had good biodegradability [102].

Integrating nanocomposite scaffolds with advanced imaging modalities, such as MRI, CT or ultrasound, could enable the noninvasive tracking of scaffold degradation, tissue ingrowth and vascularization over time. Moreover, incorporating sensors or biomarkers directly into the scaffold structure could provide valuable insights into the healing process, facilitating early intervention in cases of complications. Ideally, bone repair scaffold materials should degrade over the course of 2 months of bone repair, and rapid *in vivo* biodegradation is generally considered to reduce the mechanical properties of the material. Chen *et al.* prepared lithium-containing mesoporous bioactive glass (Li-MBG)/PLGA composite scaffolds using 3D printing technology and reported that ~25–30% of the Li-MBG/PLGA

Table 3. Summary of several properties and disadvantages of nanocomposite biomaterials.

Nanocomposite biomaterials	Biocompatibility	Mechanical property	Biodegradability	Disadvantages	Ref.
PLLA (L-polylactic acid)/ nano-HA (nHA)	rMSCs proliferation was noticeable with the increase of culture time	Compressive strength: 44.02 MPa; elastic modulus:43.00 MPa	Alleviate the acidity of PLLA degradation products; Modify the degradation rate	In the early stage of degradation, the solution pH of composite scaffolds was lower than that of PLLA scaffolds	[99]
CNWs (CCNWs)-silver nanoparticles (AgNPs)	MG-63 cells were able to adhere onto the surface as well as penetrate inside the 3D structures	Compressive strength: 0.35–3.95 MPa	The degradation rate decreased sequentially with the increase of CCNWs-AgNPs nanocomposite	Protein adsorption reduced on increasing the content of nanocomposite	[52]
(Polyhydroxybutyrate-Chitosan) PHB-CTS	Proliferation and viability of MG-63 cells are significantly higher	Tensile strength: 2.81 MPa; tensile modulus: 126.3 MPa	Biodegradable	PHB-CTS/3% Al_2O_3 degradation performance improved but not optimal	[104]
PLGA composit nanodiamond-phospholipid compound (NDPC)	The numbers of hFOB1.19 osteoblasts increased at day 1, day 4 and day 7	Young's modulus value: 5.74 GP	The addition of NDPC could impede the fast degradation of PLGA	Increased NDPC content affects osteoblast cells viability	[94]
Poly (ε-caprolactone) PCL/nHA@glycopeptide hydrogel (GRgel)	The BMSCs continually proliferated during the 7 days' culture period	Tensile modulus: 180–506.6 MPa; compressive modulus: 44.9–56.43 MPa	PCL is biodegradable	Due to 3D printing availability limitations, the HA content in the scaffold cannot exceed the 30% range	[44]
Li-MBG/PLGA	The proliferation, migration and osteogenic differentiation of BMSCs are promoted	Compressive strength: 1.46 MPa	Biodegradable	Long-term studies of bone remodeling in diabetic mice were not performed because of scaffold degradation and impaired osteogenic capacity	[103]
Silk fibroin (SF)-poly(glycolic acid) (PGA)	The MC3T3-E1 celll seeding efficiency decreases with increasing pore lengt	Compressive modulus:11.9 MPa	The biodegradation rates facilitate healthy bone tissue formation	Scaffold exhibited lower compressive modulus	[46]
GelMA-BG-MWCNT nanocomposite hydrogels	The interactions and differentiation multipotent of mesenchymal progenitor cell (10 T1/2) are promoted	MWCNT improved the mechanical strength and moduli	Biodegradable	Delayed cell proliferation observed in hydrogels due to low initial cell adhesion/retention capacity at 24 h	[105]

scaffolds degraded within 42 days, while ~40% of the pure PLGA scaffolds degraded (Fig. 6b–e) [103]. This composite scaffold with nanomaterials can avoid rapid degradation *in vivo*. The biodegradability of the nanocomposite biomaterials allowed them to be gradually resorbed after the formation of new bone tissue, avoiding complications that may arise from long-term retention in the body. We have summarized the advanced properties of several nanocomposite biomaterials and reflected on their disadvantages, as detailed in Table 3.

Application of structure-optimized and microenvironment-inspired nanocomposite biomaterials in BTE

Nanocomposite biomaterials play multifaceted roles in BTE. Nanocomposite biomaterials, with their meticulously engineered pore structures and nanoarchitecture, adeptly replicate the microenvironment of natural bone. This design not only fosters significant biological activity but also optimizes the transport of nutrients and the elimination of metabolic waste [106]. These scaffolds can be custom-tailored to fit the specific contours of a patient's bone damage, thereby offering a precise fit at the site of the bone defect [107]. This customization is crucial for facilitating the regeneration and repair of bone tissue. In addition, these materials not only provide carriers to protect cells and reduce cell death during transplantation but also provide suitable attachment sites for cells to promote cell proliferation and differentiation through their bioactivity. In addition, these biomaterials function as versatile delivery platforms for growth factors, genes, proteins or drugs. Through controlled release mechanisms, these materials can ensure the sustained availability of cytokines, increase cell survival and increase the effectiveness of BTE efforts [108]. Nanocomposite biomaterials can also be used to promote vascularization. They can also promote the formation and maturation of blood vessels, which can promote effective neovascularization and accelerate the regeneration process of bone tissue in bone defect areas [109].

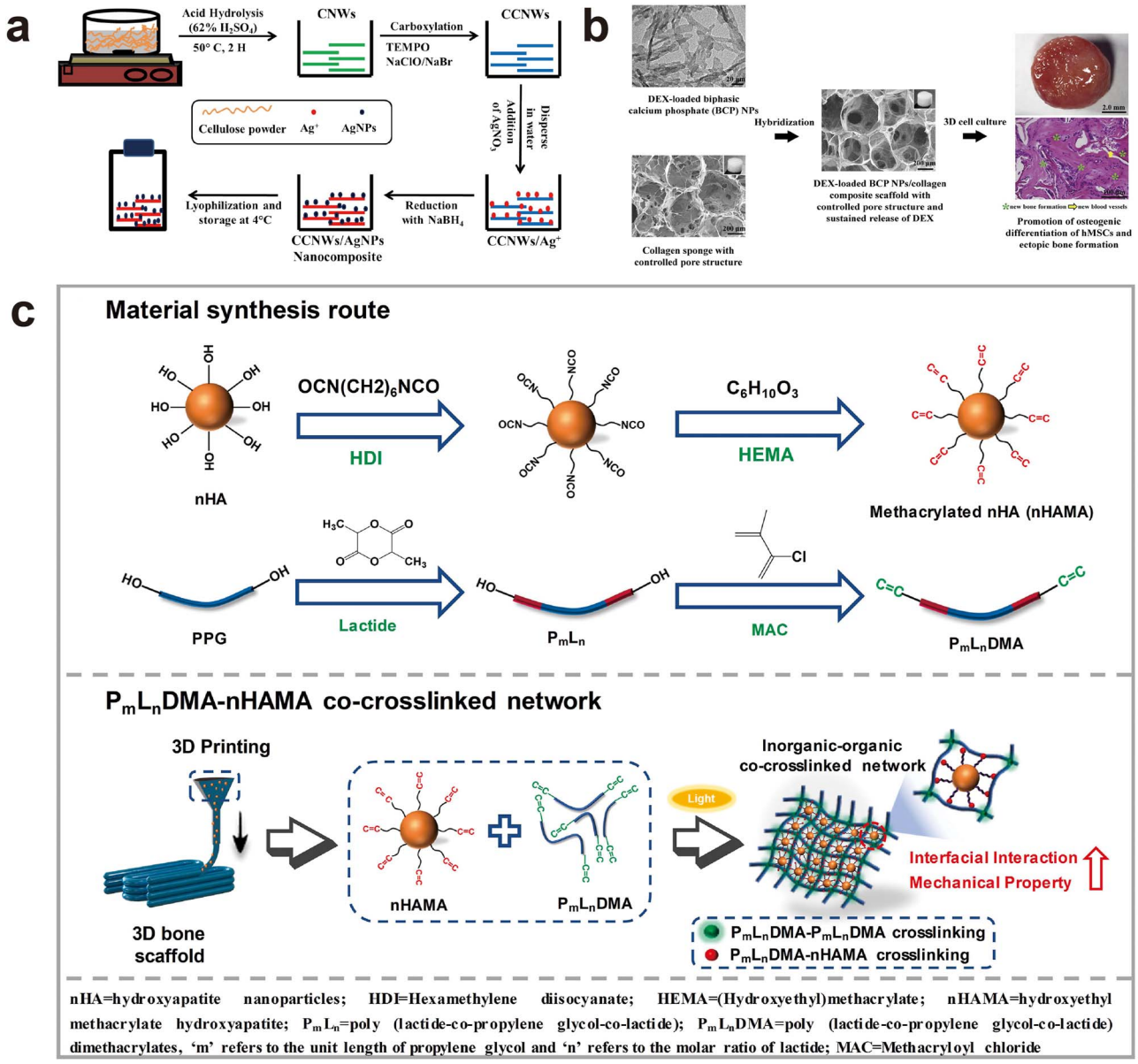

Figure 7. Nanocomposite biomaterials as bone repair scaffolds. (**a**) Detailed illustration of carboxylated carbon nanofibres - silver nanoparticles (CCNWs-AgNPs) nanocomposite synthesis. Reproduced from [52]. Copyright 2018, Elsevier B.V. (**b**) This study is the first research to prepare dexamethasone (DEX)-loaded biphasic calcium phosphate nanoparticles (BCP NPs)/collagen porous composite scaffolds; the superior performance of the composite scaffolds indicates the composite scaffolds should be useful for bone tissue engineering. Reproduced from [111]. Copyright 2017, Acta Materialia Inc. Published by Elsevier Ltd. (**c**) Schematic illustration of synthesis route of photo-crosslinkable nanocomposites consisting of PmLnDMA and nHAMA, and 3D printing of bone scaffolds with PmLnDMA/nHAMA nanocomposites. The nHAMA with reactive HEMA chains was designed to covalently interact with PmLnDMA and form an organic–inorganic co-crosslinked network within the nanocomposite, which was expected to improve the nanofiller-matrix interfacial compatibility and further enhance the mechanical strength. Reproduced from [112]. Copyright 2020, Elsevier Ltd

Bone repair scaffolds

Natural bone is composed of ~35% organic components (mainly type I collagen) and ~65% inorganic components (nanocrystalline calcium phosphate, CaP), and the molecular organizational arrangement of organic and inorganic components is one of the most important biochemical phenomena in the process of bone formation [110]. A study reported a nanocomposite polymer BTE scaffold with adjustable pore size and mechanical strength, where nanocomposites (CCNWs-AgNPs) were prepared by modifying silver nanoparticles (AgNPs) on carboxylated carbon nanofibres (CCNWs) (Fig. 7a). The incorporation of the nanocomposites in the scaffold-preparation process helped to achieve a desirable porosity of 80–90% with a pore size range of 150–500 μm, which improved the mechanical strength and enhanced the resistance to enzymatic degradation, exhibiting excellent antimicrobial activity. In addition, the scaffolds had sufficient protein adsorption and mineralization capacity to support cell adhesion, proliferation and bone tissue regeneration [52]. In another significant contribution to the field, Chen *et al.* introduced dexamethasone (DEX) into biphasic calcium phosphate nanoparticles (BCP NPs) and hybridized it with collagen scaffolds during the preparation of BCP NPs to prepare DEX-loaded BCP NP/collagen composite

scaffolds (Fig. 7b). The porosity of these scaffolds was ingeniously controlled using preprepared ice particles as a porogen, resulting in a well-defined and interconnected pore architecture. These composite scaffolds not only boasted high mechanical strength and excellent biocompatibility but also facilitated cell adhesion, migration and uniform distribution. Crucially, they enhanced the differentiation of human MSCs into osteoblasts, thereby promoting new bone formation [111]. The use of nanocomposite biomaterials as bone repair scaffolds for BTE is increasing due to their optimized biocompatibility, bioactivity and mechanical strength.

Moreover, Yang *et al*. invented a photo-crosslinkable nanocomposite ink consisting of tri-block poly(lactide-co-propylene glycol-co-lactide) dimethacrylate (PmLnDMA) and hydroxyethyl methacrylate (HEMA)-functionalized HANPs (nHAMA) (Fig. 7c). Their findings revealed that nHAMA could swiftly photocrosslink with PmLnDMA, forming an inorganic–organic co-crosslinked nanocomposite network in merely 140 s. This rapid formation process significantly bolsters the mechanical properties of the resulting nanocomposites. Additionally, these nanocomposite biomaterials exhibit easy-to-adjust properties as bone scaffolds, degradability and printability, as well as osteogenic capabilities *in vitro* and *in vivo* [112]. These studies underscore the paramount importance of replicating the molecular organization and structural characteristics of natural bone in the design of BTE scaffolds. By integrating various components, such as polymers, bioceramics and NPs, researchers can capitalize on the unique properties of each material to achieve superior mechanical strength, biological activity and tissue regeneration capacity. This synergistic approach holds promise for the development of next-generation bone repair scaffolds in BTE.

Delivery systems for cells, bioactive factors and drugs

Nanocomposites are being increasingly utilized as carriers for the delivery of growth factors, cytokines or drugs, facilitating localized and controlled release at bone defect sites. This targeted approach promotes effective repair and regeneration of bone tissue. A notable advancement involves the development of cell-laden BTE scaffolds. Researchers prepared cell-laden BTE scaffolds consisting of osteogenic peptide (OP)-loaded β-tricalcium phosphate/PLGA nanocomposite struts and rat bone marrow-derived BMSC-laden gelatine/GelMA hydrogel rods through dual-nozzle low-temperature hybrid 3D printing. This nanocomposite scaffold design not only enables excellent cell transfer and uniform distribution but also allows rBMSCs to migrate from the hydrogel rods to the surfaces of adjacent struts, thereby enhancing *in vivo* bone formation capabilities (Fig. 8a) [113]. Jiang *et al*. uniformly and stably modified adipose-derived stem cell-engineered nanovesicles (ADSC-ENs) onto a bionic scaffold surface using a perfusion device. This modification endows the scaffolds with exceptional biocompatibility and osteogenic potential, thereby improving the osteogenic microenvironment at defect sites. The ADSC-ENs also promoted angiogenesis, enhanced macrophage polarization towards the M2 phenotype and facilitated the recruitment of BMSCs, which are all crucial steps for successful bone regeneration (Fig. 8b) [114]. Furthermore, nanocomposite biomaterials are effectively used to deliver key osteogenic growth factors, such as bone morphogenetic proteins (BMPs), transforming growth factor-β and vascular endothelial growth factor. These factors are essential for the proliferation and differentiation of osteoblasts, as well as for initiating new bone formation. In a pioneering approach, researchers used functional exosomes (50–200 nm) to replace seed cells to establish cell-free tissue engineering systems. This finding demonstrated that engineered exosomes could induce osteogenic differentiation of MSCs and trigger extensive vascularized bone regeneration [115]. Engineered exosomes offer several advantages over traditional cell-based therapies, including greater stability, easier storage and reduced immunogenicity. Wang *et al*. used 3D bioprinting to create a PCL/MBG/doxycycline scaffold. This scaffold was designed to actively secrete BMP2, thereby promoting osteoblast differentiation and inducing ectopic osteogenesis. Additionally, the composition of the scaffold endows it with broad-spectrum antimicrobial resistance, which is crucial for protecting cells within the BTE scaffold from infection risks [45].

Nanocomposite biomaterials are emerging as vital components in BTE, serving as advanced stimulus-responsive platforms for smart delivery. Chen *et al*. prepared DEX@BCP/collagen composite scaffolds that sustained the release of moderate amounts of DEX, Ca^{2+} and $PO4^{3-}$ after degradation. The DEX, Ca^{2+} and $PO_4{}^{3-}$ ions released synergistically upregulate the expression of osteogenic genes and proteins and promote the differentiation of human MSCs to osteoblasts [111]. Some researchers have immobilized BMP-2 through layer-assembly technology to make polyelectrolyte-modified bionic scaffolds with large pores and nanofibre structures so that the resulting composite scaffold can sequentially release BMP-2 and Sr ions. This strategic release not only promotes cell proliferation and osteogenic differentiation but also enhances tissue infiltration and the formation of new microvessels (Fig. 8c, d) [116]. In addition, highly dispersed core-shell magnetic nanocomposites have been developed by integrating iron oxide particles and MBGs, and these composite particles can be separated under external magnetic fields, thus allowing drug-targeted delivery in the human body [117]. By precisely controlling the release of bioactive molecules, these scaffolds not only support the structural and functional requirements for bone regeneration but also enhance the biological processes underlying bone repair. Using nanocomposite biomaterials as delivery systems for cells, bioactive factors and drugs, researchers can develop more effective and responsive treatments for bone regeneration.

Microenvironment of angiogenesis and immunomodulation

Nanocomposite biomaterials can promote the formation of blood vessels and solve the problem of blood supply during the repair of large-volume bone defects. Local angiogenesis is crucial for promoting bone regeneration because it provides cells with the oxygen and nutrients needed for survival [118]. Insufficient blood supply is a major contributor to nonhealing fractures, underscoring the importance of neovascularization, which facilitates the transport of nutrients, metabolites and cells to injury sites, thereby enhancing tissue regeneration [119]. Key proangiogenic mediators, such as transforming growth factor-β, PDGF, vascular endothelial growth factor and FGF, are integral to the bone repair process. In a significant advancement, Wu *et al*. developed highly bioactive nanocomposites by freeze-casting biocompatible hydrogels with *in situ* coprecipitation of SiCaP-containing hybrid nanocoatings (SCPNs) (Fig. 9a). These materials

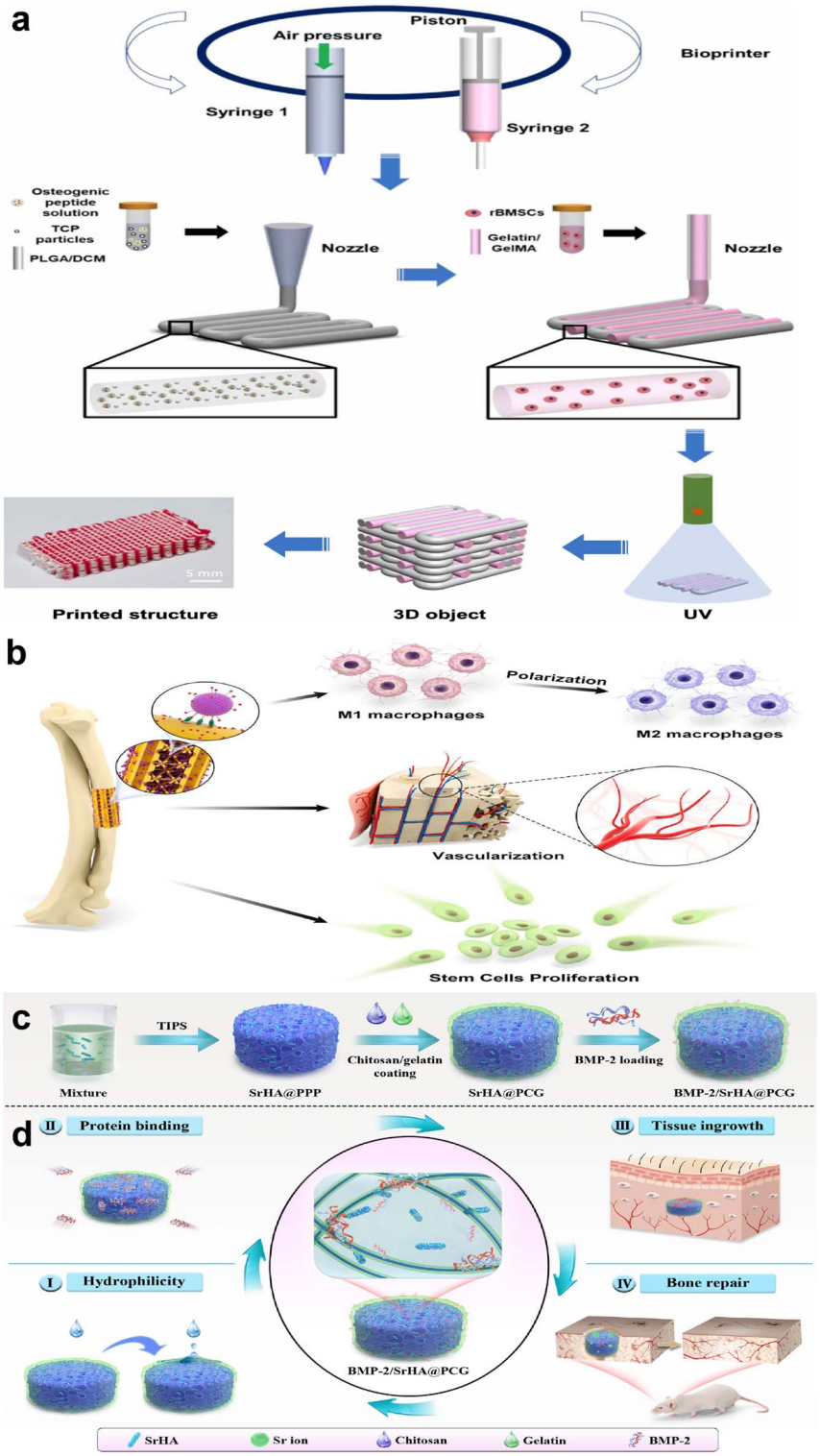

Figure 8. Nanocomposite biomaterials as delivery systems for cells, bioactive factors and drugs. (**a**) Schematic illustration of the fabrication of osteogenic peptide (OP) loaded β-tricalcium phosphate (TCP)/poly(lactic-co-glycolic acid) (PLGA) nanocomposite struts and rat bone marrow derived mesenchymal stem cell (rBMSC)-laden gelatin/GelMA hydrogel rods (designated as GGOTP) scaffolds with *in situ* delivery of OP and rBMSCs via low-temperature hybrid 3D printing. Reproduced from [113]. Copyright 2022, IOP Publishing. (**b**) Schematic illustration of the mechanism for local osteogenic microenvironment regulation by biomimetic osteoinductive scaffolds. The integration of adipose-derived stem cell-engineered nanovesicles (ADSC-ENs) within highly biomimetic scaffolds holds the potential to enhance the local microenvironment at the defect site, thereby expediting the restorative course of substantial segmental bone defects. This is achieved through the orchestrated modulation of M1-to-M2 transition, augmentation of angiogenic processes and facilitation of osteoblast aggregation. Reproduced from [114]. Copyright 2024, Elsevier Ltd. (**c**) Schematic diagram for the fabrication of the strontium-substituted hydroxyapatite (SrHA) was synthesized by hydrothermal treatment and further incorporated into PLLA/PLGA/PCL scaffold with macroporous and nanofibrous structure, followed by the treatment of chitosan/gelatin multilayers for bone morphogenetic proteins-2 (BMP-2) immobilization to obtain dual-factor delivery system (denoted as BMP-2/SrHA@PCG scaffold). (**d**) BMP-2/SrHA@PCG scaffold showed excellent hydrophilicity and improved protein binding capacity as well as rapid tissue ingrowth due to polyelectrolyte modification. With the controlled release of BMP-2 and Sr ions, BMP-2/SrHA@PCG scaffold significantly accelerated the healing of bone defect via a synergistic osteogenic response. Reproduced from [116]. Copyright 2023, The Authors. Published by Elsevier Ltd

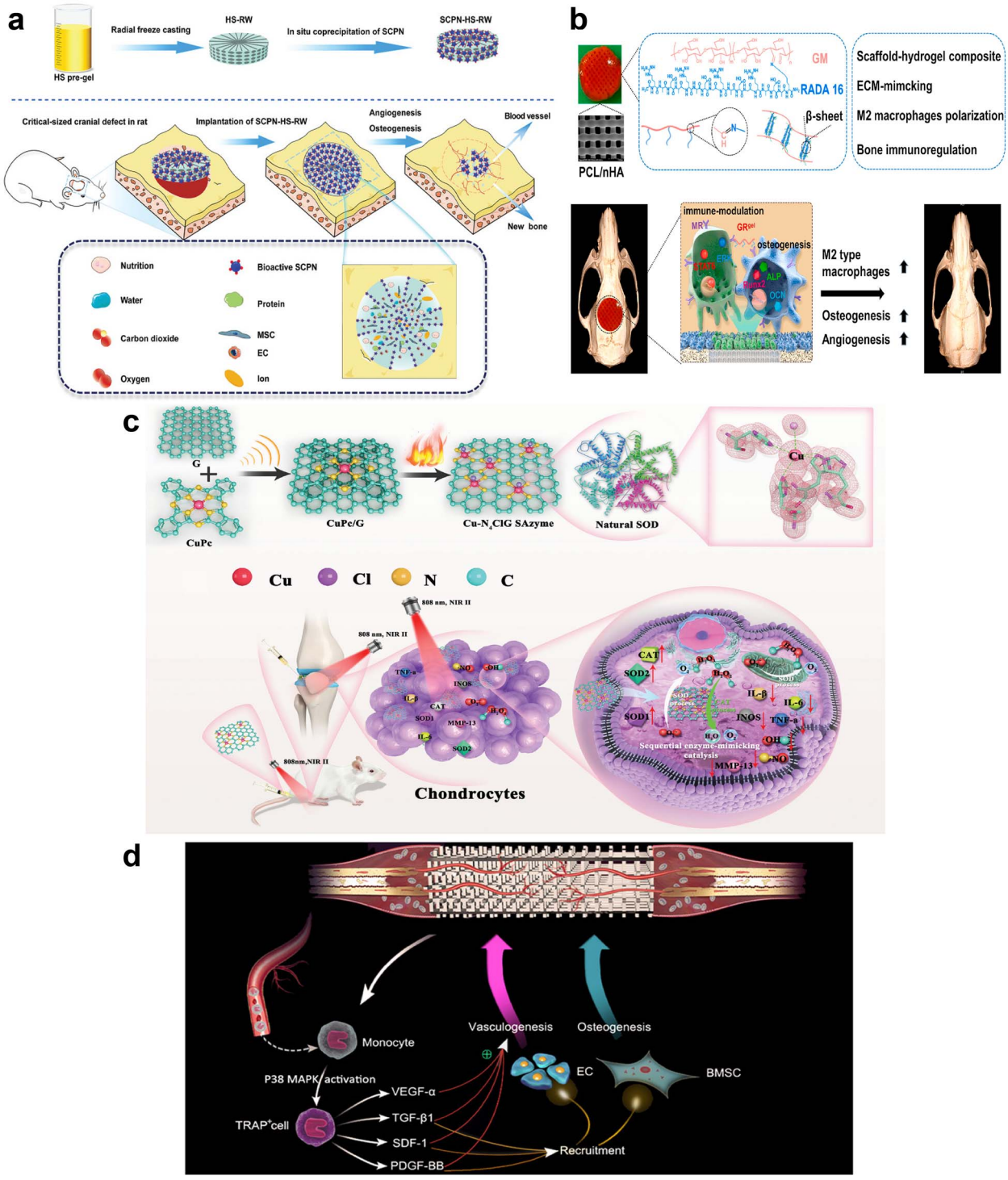

Figure 9. Nanocomposite biomaterials as microenvironment of angiogenesis and immunomodulation. (**a**) Schematic illustrations of the application in bone repair of Si-containing CaP hybrid nanocoating (SCPN)-modified redwood-like biomimetic materials. Reproduced from [120]. Copyright 2021, Wiley-VCH GmbH. (**b**) Diagram of the preparation and function of PH@GRgel implant for bone defect repair. Extracellular matrix-inspired GM-RADA16 hydrogel (GRgel) was composited with PCL/nHA scaffold, which significantly promoted *in vivo* regeneration of skull defect by GR-mediated immune-modulation and RADA16-induced osteogenesis in the local tissue microenvironment. Reproduced from [44]. Copyright 2022, Elsevier Ltd. (**c**) Schematic illustrations of Cu-N4ClG SAzyme synthesis and the principles of biomimetic superoxide dismutase (SOD) and catalase (CAT) for reactive oxygen species (ROS) scavenging. Reproduced from [122]. Copyright 2022, Wiley-VCH GmbH. (**d**) 10 wt % zinc silicate/nanohydroxyapatite/collagen scaffolds (10ZS/HA/Col) scaffolds modulate monocytes and thereby create a favourable osteogenic microenvironment that promotes BMSC migration and differentiation and vessel formation by activating the p38 signaling pathway. Reproduced from [123]. Copyright 2020, American Chemical Society

not only achieved a nanosized surface morphology and low swelling rate but also retarded enzyme degradation, enhanced protein uptake, and provided sustained and orderly release of Si and Ca ions. These actions synergistically promote osteogenesis and angiogenesis, ultimately fostering the adhesion, diffusion, proliferation and migration of BMSCs and HUVECs, thereby creating a microenvironment conducive to bone repair [120]. A study reported that a composite hydrogel patch was constructed by layer-by-layer 3D bioprinting, in which nHA and silicon quantum dots significantly improved the mechanical strength of the scaffold and accelerated angiogenesis [121].

The study of the effects of nanocomposite biomaterials on cell behaviour, such as cell adsorption, migration, differentiation and modulation of immune cells, is gradually becoming a hot topic. When the chemical composition and structure of these materials is optimized, they enhance the functionality of beneficial cells and suppress inflammatory responses that hinder bone regeneration. A recent study reported that a glucomannan (GM)-peptide hydrogel mimicking the physicochemical and biological properties of natural extracellular matrix was prepared by grafting RADA 16 peptide onto oxidized GM via dynamic imine bonding, which was composited with 3D-printed PCL/nHA scaffolds to make a novel ready-to-use bone substitute (Fig. 9b). Remarkably, this nanocomposite material significantly promoted the proliferation and osteogenic differentiation of BMSCs, which was further augmented by GRgel-induced M2 macrophage polarization and effective M2 macrophage–BMSC crosstalk [44]. In one study, a Cu-N4 ClG SAzyme material was prepared that protected chondrocytes from oxidative stress-induced apoptosis, succeeded in upregulating intracellular antioxidant factors such as CAT and SOD, and normalized the inflammatory microenvironment to alleviate osteoarthritis (Fig. 9c). This nanomaterial exhibited unparalleled catalytic activities and kinetics to degrade $O_2\bullet^-$ into H_2O_2 and O_2 and to sequentially decompose H_2O_2 and •OH into H_2O and O_2 [122]. Song *et al*. produced a zinc silicate/nHA/collagen composite scaffold material (Fig. 9d). This scaffold not only activates the p38 signalling pathway in monocytes to promote bone regeneration and angiogenesis *in vivo* but also stimulates monocytes to differentiate into TRAP+ cells and release multiple cytokines to generate a favourable osteogenic microenvironment [123]. These studies collectively demonstrate the transformative potential of nanocomposite biomaterials in BTE. Because they are designed to mimic the porous structure and chemical composition of natural bone tissue, nanocomposite biomaterials provide a conducive, bone-like microenvironment that supports the intricate processes of bone repair and regeneration.

Challenges and outlook

The progress made in nanobiomaterials in recent decades has significantly influenced the medical field, leading to groundbreaking changes in tissue engineering, drug delivery, immunoengineering and the creation of medical devices. Despite these advances, the development of nanocomposite biomaterials, especially within BTE, is met with challenges that demand attention and resolution. One primary concern is that nanomaterials may exhibit potential cytotoxicity and immunoreactivity due to their small size and high reactivity [124]. The cytotoxic effects of carbon-based nanomaterials in particular have raised alarms, with studies such as that of Yuan *et al*. revealing that the risks of lung and liver damage, and even fatality, are associated with higher doses of carbon materials [125]. While many promising developments have been made in the laboratory, the translation of nanocomposite scaffold technologies into clinical practice requires careful consideration of regulatory requirements, scalability and long-term safety. Despite a study in which enamel mimics that can be produced at scale were designed [126], the precise fabrication and scalable production of nanocomposite biomaterials still present significant technical challenges. In BTE, the mechanical strength, biodegradability and bioactivity of nanocomposites must be finely tuned. However, achieving this level of control, especially for large-scale production that meets clinical demands, remains a complex task.

The development of nanocomposite biomaterials in BTE holds immense promise, with several exciting research directions and potentials on the horizon. The advent of responsive nanocomposite biomaterials capable of intelligent drug and growth-factor delivery represents a significant breakthrough. These materials could adjust drug-release rates based on specific physiological changes (such as pH, temperature or enzymatic activity) during bone repair, enabling more precise and synergistic treatment approaches. Bioprinting technology offers a platform for tailoring scaffold properties to match the unique needs of individual patients, considering factors such as age, sex, underlying health conditions and the specific nature of the bone defect. Future research could explore innovative strategies for customizing nanocomposite scaffolds using bioprinting technology to optimize outcomes in diverse patient populations. Furthermore, with the popularization of the concept of sustainable development, the development of environmentally friendly nanocomposite biomaterials has also become a focus of research, which requires that the production, application and degradation processes of the materials have minimal impact on the environment. Moving forwards, efforts should focus on optimizing fabrication techniques, scalability and regulatory approval processes to facilitate the widespread adoption of these innovative materials in real-world health care settings.

Conclusions

Nanocomposite biomaterials have the advantages of enhanced biocompatibility, bioactivity and mechanical properties, and adjustable biodegradability. The application of structure-optimized nanocomposite biomaterials in bone repair scaffolds, delivery systems and microenvironments offers remarkable potential. Exploring the structure-optimized and microenvironment-inspired intricate architecture of natural bone tissue could further enhance the efficacy and clinical translation of nanocomposite-based bone repair therapies. These materials are poised not only to advance the fields of materials science and BTE but also to offer more effective, safer and personalized therapeutic solutions for bone defect treatment and related conditions.

Abbreviations

FDM: Fused deposition modeling; PHA: Polydopamine-mediated hydroxyapatite nanoparticle; AG: Alginate/gelatin; MRI: Magnetic resonance imaging; CT: Computed tomography; BMSCs: Bone marrow mesenchymal stem cells; rBMSCs: rat bone marrow derived mesenchymal stem cells; ssDNA: single-stranded deoxyribonucleic acid;

GelMA: Gelatin methacryloyl; PDGF: Platelet-derived growth factor, FGF: Fibroblast growth factor.

Authors' contributions

Conceptualization, WZ and KZ; methodology, WZ and KZ software, ZL and YJ; investigation, ZL YJ, GW and XL; resources, ZL and YJ; writing—original draft preparation, ZL and YJ; writing—review and editing, ZL, YJ KZ and WZ; supervision, WZ and KZ. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

None declared.

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