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Layered double hydroxides for regenerative nanomedicine and tissue engineering: recent advances and future perspectives

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Abstract

With the rapid development of nanotechnology, layered double hydroxides (LDHs) have attracted considerable attention in the biomedical field due to their highly tunable composition and structure, superior biocompatibility, multifunctional bioactivity, and exceptional drug delivery performance. However, a focused and comprehensive review addressing the role of LDHs specifically in tissue regeneration has been lacking. This review aims to fill that gap by providing a systematic and in-depth overview of recent advances in the application of LDHs across various regenerative domains, including bone repair, cartilage reconstruction, angiogenesis, wound healing, and nerve regeneration. Beyond presenting emerging applications, the review places particular emphasis on elucidating the underlying mechanisms through which LDHs exert their therapeutic effects. Although LDHs demonstrate considerable promise in regenerative medicine, their clinical translation remains in its infancy. To address this, we not only provided our insights into the personalized problems that arise in the application of various tissues, but also focused on discussing and prospecting the common challenges in the clinical translation of LDHs. These challenges include optimizing synthesis techniques, enhancing biosafety and stability, improving drug-loading efficiency, designing multifunctional composite materials, and establishing pathways that facilitate the transition from laboratory research to clinical practice.

Keywords 2D nanomaterial, Layered double hydroxides, Regenerative nanomedicine, Tissue engineering

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Introduction

In recent decades, two-dimensional (2D) nanomaterials have gained significant attention in the biomedical field due to their high specific surface area, abundant anchoring sites, tunable mechanical properties, and high anisotropy [1–3]. Among these, LDHs have emerged as a promising class of 2D nanomaterials with substantial potential in regenerative medicine and tissue engineering [4, 5]. Outstanding biocompatibility, high structural and compositional tunability, and superior drug-loading capacity with controllable release profiles constitute the notable advantages that distinguish LDHs from other 2D nanomaterials (e.g., transition metal dichalcogenides, graphene) and even traditional biomaterials (Table 1). They effectively address persistent limitations in traditional platforms used for tissue regeneration [1, 6–10]. For instance, unlike most 2D nanomaterials composed of single or limited elemental species, LDHs exhibit remarkable compositional flexibility, capable of incorporating a broad spectrum of metallic elements—from alkali to lanthanide metals, offering broader functions for tissue regeneration. And this addresses the limitation that most traditional materials are only suitable for the repair of specific tissues and lack versatility in interdisciplinary applications. Furthermore, materials such as metals, ceramics, transition metal dichalcogenides (TMDs), and graphene are challenging to degrade in vivo, potentially leading to toxic accumulation and limiting their functional applications. Whereas the biodegradability of LDHs ensures their safe application. Additionally, traditional drug carriers such as hydroxyapatite and calcium phosphate suffer from limitations, including low drug-loading capacity and the inability to achieve targeted release. While LDHs exhibit potent drug-loading properties and can facilitate targeted delivery through electrostatic interactions. And the drug-loading capacity of LDHs has been reported surpasses that of most 2D nanomaterials, such as hexagonal boron nitride (h-BN) and graphitic carbon nitride (g-C3N4) [11]. The advantages of LDH-based medical applications will be discussed in greater depth in Chap. 2.

Initially discovered in natural rocks by Hochstetter in 1842 and synthesized artificially by Feitknecht et al. in 1942, LDHs have been extensively studied using modern analytical and characterization techniques [1, 2, 10]. These studies reveal a "sandwich-like" layered structure, where positively charged metal hydroxide layers act as the "bread," and interlayer anions serve as the "filling" [2]. The general chemical formula of LDHs is $[M_{1-x}{}^{2+}Mx^{3+}(OH)_2]^{x+}[A^{n-}]x/n{\cdot}mH_2O$, where M^{2+} (e.g., Mg^{2+}, Ca^{2+}, Mn^2, Fe^{2+}) and M^{3+} (e.g., Al^{3+}, Cr^{3+}, Mn^{3+}) denote divalent and trivalent metal cations, respectively, situated within the "bread layers," while A^{n-} (e.g., NO^{3-}, $CO_3{}^{2-}$, Cl^-) represents interlayer anions (Fig. 1a) [1, 5, 6, 10, 22]. The chemical formula of LDHs is critical for their biomedical applications. The physical and chemical properties of LDHs, such as composition, structure, interlayer distance, can be modified by altering parameters like anion and cation types, cation ratio, anion charge, and water content. Thus, LDHs can exhibit various biological functions to meet the requirements of different tissue repair processes.

Various LDHs have been developed for regenerative medicine and can be categorized into pristine LDHs, LDHs drug delivery systems, and LDHs-based composites based on their their forms of action. Pristine LDHs are further divided into binary, ternary, and quaternary types depending on their cationic composition. For instance, MgAl-LDH belongs to the binary class, while the incorporation of a third or fourth cation produces ternary (e.g., MgAlEu-LDH) or quaternary (e.g., MgAl-GdYb-LDH) variants [10, 27]. Different metal ions in

Table 1 The comparison of LDHs with traditional tissue engineering materials

Types of material	Sample names	Advantages	Disadvantages	Applications of tissue regeneration	Ref.
LDHs	MgFe-LDH MnFe-LDH	Good biocompatibility; Diverse bio-functions; High drug-carrying & release control ability	Low biostability	Potential for regeneration of bone, cartilage, blood vessels, skin, nerves, etc.	[1, 4–8]
Natural polymer	Collagen Chitosan	Biocompatible; Degradable; Facilitate cell adhesion	Poor mechanical properties; Possible immunogenicity	Suitable for soft tissue regeneration, nerve repair, skin wound healing	• [12–14]
Synthetic polymer	PMMA PCL	Precisely adjustable performance; Easy to machine & mold	Poorly biodegradable; Poor cells adhesion	Commonly used to construct 3D scaffolds in bone & cartilage tissue engineering	• [15–17]
Ceramic	HAp BG	Good biocompatibility & stability	Highly brittle; Difficult to mold	Mainly for bone repair	• [18, 19]
Metals	Titanium alloy	High strength; Good mechanical properties	Low bio-activity; High modulus of elasticity	Commonly used for bone repair in areas with high load bearing(e.g., artificial joints, dental implants)	• [20, 21]

PMMA, polymethyl methacrylate; PCL, polycaprolactone HAp, hydroxyapatite;
BG, bioactive glass

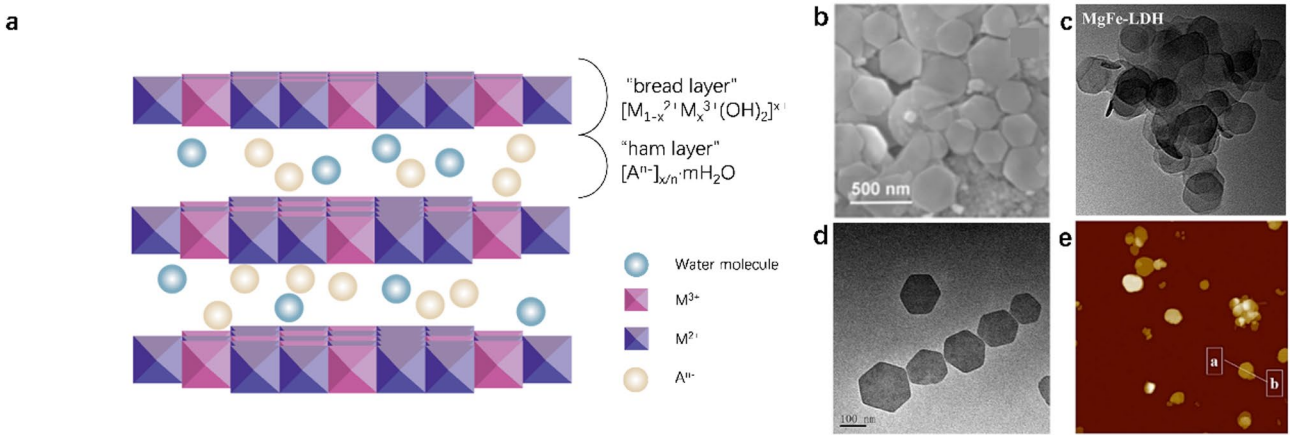

Fig. 1 (**a**) Layered structure of LDHs: Positively charged metal hydroxide layers (M^{2+}/M^{3+}) intercalated with anions (A^{n-}) and water molecules. (**b**) SEM image of ZnAl-LDH. Reprinted with permission from Ref [23]. Copyright (2024) Elsevier. (**c**) SEM image of MgFe-LDH. Reprinted with permission from Ref [24]. Copyright (2023) BMC. (**d**) TEM image of MgFe-LDH. Reprinted with permission from Ref [25]. Copyright (2023) Elsevier. (**e**) AFM image of MgFe-LDH. Reprinted with permission from Ref [26]. Copyright (2024) Elsevier

Table 2 Preparation methods of LDHs

Types	Preparation methods	Synthetic procedure	Advantages	Disadvantages	Refs.
Pristine LDHs	Co-precipitation	At 60–80 °C, pH 6–11, add metal cation salt solution to target anion solution, stir for precipitation	Simple; High yield; One-step drug loading	Low-crystalline; Uneven-sized precipitate	[31, 33]
	Hydrothermal synthesis	Put alkaline metal salts in hydrothermal reactor for high-temperature & high-pressure treatment	High crystallinity & purity; Good size & morphology control	Strict conditions; Complicated operation; High cost	[34, 35]
	Anion-exchange	Add pre-synthesized LDHs precursors to concentrated target anion solution, stir at 50–70°	Suitable for target anions prone to decomposition in strong alkali or reacting with main cations	Time-consuming	[36, 37]
	Separate nucleation and aging steps	add alkaline metal salt solution to colloid mill for uniform nucleation first, then high-temperature & high-pressure aging	More uniform nucleation, narrower particle size than hydrothermal	—	[38, 39]
	Atom economy method	Precisely control reaction components, time & temperature for ful-reaction products or water	Remove by-products; Save water	—	[10]
LDHs nanocomposites	Exfoliation-reassembly	Pretreat pristine LDHs with formamide to get monolayers, then add to target-anion solution and stir	Short reaction time; Mild conditions; High drugs loading rate	—	[40, 41]
	In situ growth	Generate LDHs on substrates (metals, oxides, carbon materials, etc.) via electrodeposition, hydrothermal or etching	Wide substrate range; Ordered nano-arrays	Strict conditions	[32, 42, 43]

pristine LDHs contribute to distinct tissue repair functions, for example, Mg^{2+} and Ca^{2+} promote osteogenesis, while Cu^{2+} and Ni^{2+} facilitate angiogenesis, and Zn^{2+} exhibits antimicrobial activity. LDHs drug-delivery systems are formed by incorporating drugs, nucleic acids, and other therapeutic molecules within the interlayer spaces of pristine LDHs [2, 10]. They not only exert physiological effects via their inherent metal ions but, more importantly, also promote tissue regeneration by delivering therapeutic agents. LDHs-based composites are created by combining pristine LDHs with other materials, such as carbon nanomaterials, metals, and organic compounds. They are defined by synergistic interactions among distinct materials, which compensate for individual shortcomings and enhance overall benefits.

LDHs are derived from abundant, cost-effective raw materials and can be synthesized through relatively simple processes. Common preparation methods include co-precipitation, hydrothermal synthesis, and ion exchange [1, 4, 7]. Additionally, advanced techniques such as the memory effect, exfoliation-reorganization, and in situ growth have been employed to engineer LDHs-based composites with tailored structures and functions, further broadening their application scope. Table 2

highlights the key preparation methods and their characteristics.Table 3 briefly summarizes the influence of the main synthesis parameters on the properties of LDHs. To support the development and optimization of LDHs for biomedical applications, comprehensive characterization of their chemical composition, surface morphology, microstructure, crystallinity, and particle size distribution is essential. X-ray diffraction (XRD) remains the most widely used technique for analyzing the crystal structure of LDHs. Variations in XRD peak positions and intensities reveal microstructural defects. For example, in the hydrothermal synthesis of NiFe-LDHs, diffraction peak asymmetry in the (110) and (113) planes is observed when the hydrothermal reaction time is less than 6 h, indicating lattice mismatch. As synthesis duration increases to 6 h, these peaks become more symmetric and the (003) peak shifts leftward, signifying reduced interlayer defects and an expansion of the interlayer spacing [28]. Transmission electron microscopy and selected area electron diffraction are frequently employed in tandem to further investigate the morphology of LDHs [29]. Raman spectra and infrared absorption spectroscopy can be used to detect the types of foreign anions intercalated in the layers of LDHs, the bonding types, and the orientation of arrangement [30]. However, given that the primary focus of this work is not material synthesis or characterization, these aspects are only briefly addressed here.For a more in-depth discussion on nanoscale characterization strategies, readers are referred to studies by Mallakpour et al. [31] and Tonelli et al. [32].

Several review articles have summarized the recent advancements of LDHs in the entire field of biomedical applications [1, 2, 10], spanning fields such as biosensing, cancer therapy, and medical imaging. However, tissue engineering has received comparatively limited attention in these reviews, resulting in a lack of comprehensive and focused analysis in this specific domain. The two existing reviews dedicated to the role of LDHs in tissue engineering were published several years ago [5, 46], and primarily emphasized composite materials, with a strong focus on bone regeneration. They did not provide a systematic classification of regenerative applications across different tissue types, nor did they delve into the underlying mechanisms of LDH functionality. Given these gaps, a thorough and updated review of LDH-based strategies for tissue regeneration is urgently needed. Such a review could elucidate common mechanisms, foster further research, and clarify current limitations. This article seeks to address that need by presenting a comprehensive overview of the latest developments in LDHs as bio-nanomaterials for regenerative medicine and tissue engineering. It begins with a discussion of LDH structure, classification, and synthesis methods, followed by a detailed examination of their unique advantages in regenerative contexts. The review then explores the recents applications of pristine LDHs, LDHs drug delivery systems, and LDHs-based composites across various tissue types—including bone, cartilage, vasculature, skin, and nerve. Finally, it outlines current key challenges facing the field, such as synthesis complexity, biosafety concerns, stability, drug-loading efficiency, and barriers to clinical translation. It also proposes future directions this rapidly evolving field. The novel contributions of this review are threefold: (1) it focuses exclusively on regenerative medicine, offering a systematic summary of LDH applications across multiple tissue types through three principal modes of action; (2) it incorporates the latest application research and explores the mechanistic basis of LDHs activity; and (3) it addresses both tissue-specific considerations and broader translational challenges, offering a forward-looking perspective on clinical application.

Table 3 The effect of synthesis parameters on the performance of LDHs

Synthesis parameter	Physical and chemical properties	Biological characteristics	Refs.
Cation species and molar ratio	Affects interlayer distance and charge density	Metal ions provide different biological functions	[1, 2, 10, 31, 44, 45]
Reaction solvent	Water slows formation; Ethanol-water adjusts particle size, reduces agglomeration; Alcohol-thermal synthesis promotes crystallization	Solvent choice optimizes hydrophilicity, dispersion, and cytocompatibility	
pH value	Optimal pH (6–11) improves crystallinity; Low pH causes incomplete precipitation, uneven grains; High pH increases particle size, non-lamellar oxides	Optimal pH ensures uniform spacing and good drug loading; High pH can reduce biocompatibility	
Reaction temperature	Suitable range (50–80 °C) improves crystallinity and uniform structure; Low temp (< 50 °C) leads to poor crystallinity; High temp (> 100 °C) can collapse structure	High temp reduces stability, affecting drug loading/release	
Reaction time	Optimal time (12–24 h) produces regular structure; Too short (< 6 h) results in incomplete crystallization; Too long (> 48 h) causes agglomeration and reduces surface area	Prolonged time causes agglomeration, reducing dispersion and drug loading capacity	

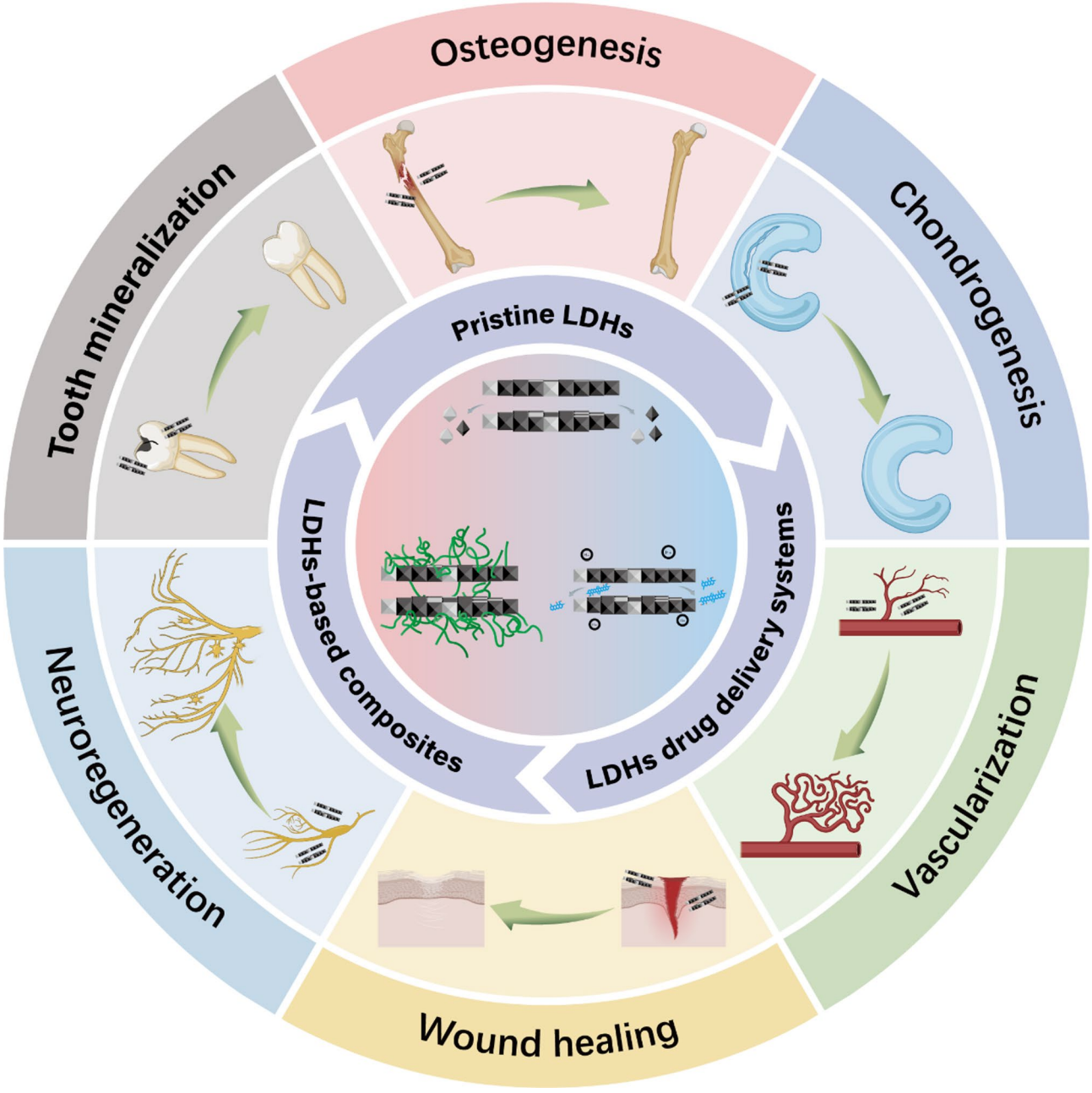

Fig. 2 LDHs promote tissue regeneration through three forms of action: pristine LDHs, LDHs drug-loading systems, and LDHs composites

Advantages of LDHs applied to tissue regeneration

The significant potential of LDHs for tissue regeneration applications primarily arises from their excellent biocompatibility, compositional tunability, and robust drug-loading and controlled-release capabilities [1, 6–10].

High biocompatibility

High biocompatibility is a key factor in the application of LDHs for tissue regeneration(Fig. 3a, b). Clinical applications, in vivo studies, and cytotoxicity assays have confirmed the high safety of LDHs. MgAl-LDH has been employed as a primary component in commercial antigastric agents since the early 21st century [46, 47]. Moreover, the success of ibuprofen (IBU)-loaded LDHs in clinical trials further demonstrates their excellent biosafety [48]. Oral administration of 2000 mg/kg ZnAl-LDH reportedly causes no mortality or acute toxicity in Sprague-Dawley (SD) rats [6]. Additionally, LDHs with various compositions were implanted into the abdominal wall muscles of SD rats. No significant inflammatory response was observed after 28 days. Likewise, no damage to the microcirculation network, including bleeding

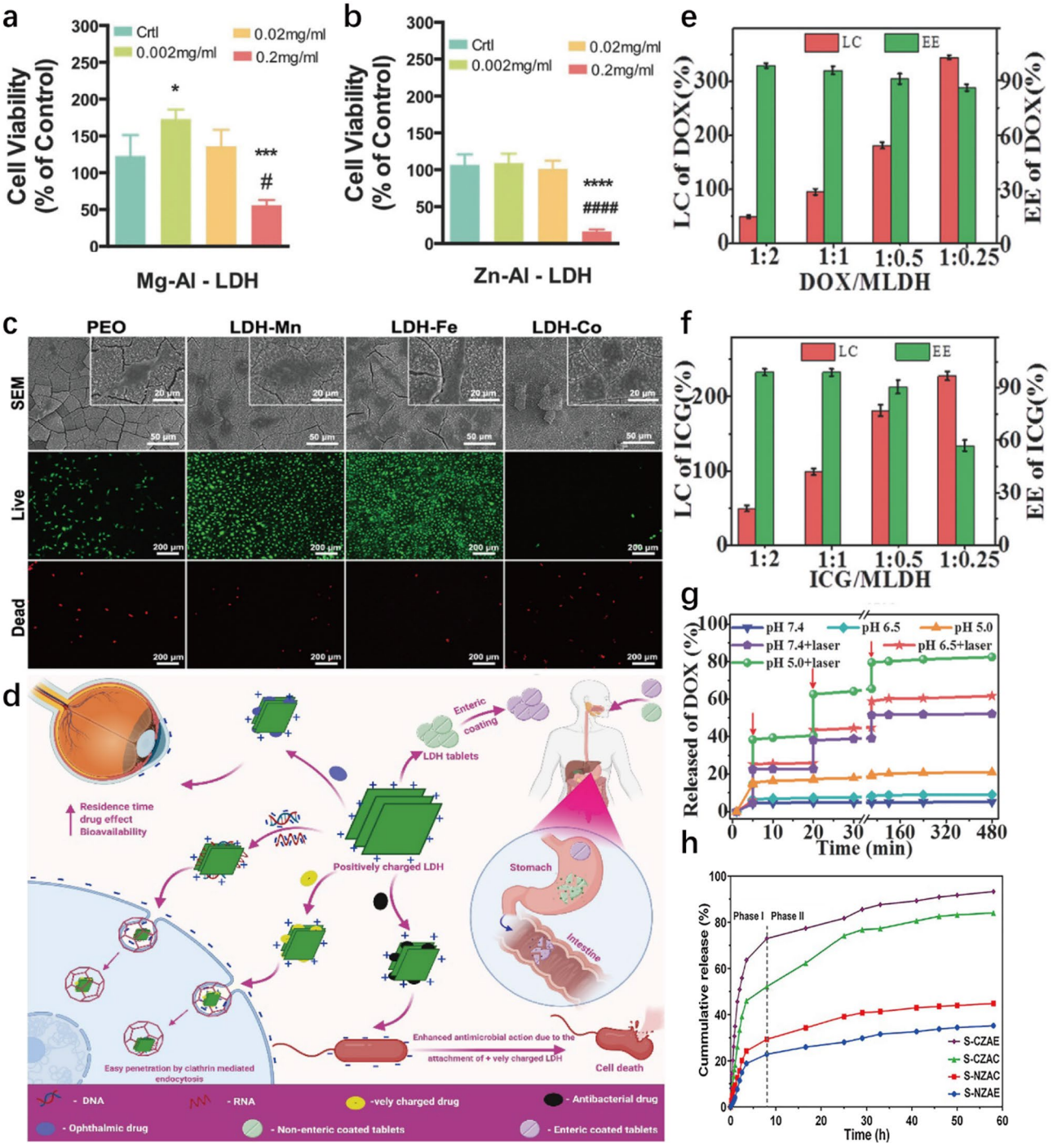

Fig. 3 Cytotoxicity evaluation of MgAl-LDH (**a**) and ZnAl-LDH (**b**) at varying concentrations (0.002–0.2 mg/mL) in healthy cells (cell viability > 95%). Reprinted with permission from Ref [100]. Copyright (2017) John Wiley and Sons. **c**) SEM and live-dead staining plots of MC3T3-E1 cells after 4 days of culture on each set of samples. Reprinted with permission from Ref [51]. Copyright (2022) John Wiley and Sons. **d**) Schematic representation of the targeting role of LDHs during drug delivery. Reprinted with permission from Ref [6]. Copyright (2021) Elsevier. Loading content (LC) and encapsulation efficiency (EE) of MgAl-LDH for **e**) DOX and **f**) ICG. **g**) pH/NIR-triggered DOX release: 4× enhancement under acidic laser irradiation. Reprinted with permission from Ref [75]. Copyright (2018) John Wiley and Sons. **h**) Sustained simvastatin release via ZnAl-LDH ion exchange (Two-stage kinetics). Reprinted with permission from Ref [37]. Copyright (2019) Elsevier

or endothelial adhesion, was detected [5]. Studies in mice also confirm the in vivo safety of LDHs [49]. However, relevant studies in large animals and additional human trials remain limited, posing a major challenge to clinical translation. This issue will be further discussed in the Challenges and Prospects section.

In terms of cytotoxicity, LDHs have demonstrated high cytocompatibility on various human and animal cell lines. For example, ZnAl-LDH, even at concentrations up to 500 μg/mL, has shown no significant toxicity across a broad range of healthy cells, with cell viability remaining close to 100% after co-culture [46]. Likewise, CoMo-LDH has maintained over 95% cell viability at a concentration of 200 μg/mL [50]. The cytotoxicity of LDHs is influenced by several factors: ① Cation type: For instance, MgFe-LDH exhibits a higher safety profile for MC3T3-E1 cells than MgCo-LDH (Fig. 3c) [51]. In the same cell type, Fe-containing LDHs (MgFe-LDH, ZnFe-LDH) show superior compatibility compared to MgAl-LDH and ZnAl-LDH [2].②Anion type: Cl^- accelerates degradation and reduces cytotoxicity, while CO_3^{2-} enhances solution stability but may increase cytotoxicity due to intracellular accumulation [52].③Concentration: At low concentrations, LDHs demonstrate superior cytocompatibility compared to other nanoparticles, such as carbon nanotubes. However, prolonged exposure to high LDHs concentrations can induce toxic effects on cells [53].④Size: Smaller LDHs (< 50 nm) exhibit significantly higher cytotoxicity than larger particles (100–400 nm), likely due to increased cellular uptake [2, 54]. ⑤Target cell type: At concentrations below 250 μg/mL, MgAl-LDH does not affect the proliferation or activity of normal lung epithelial cells (L-132), lung epithelial carcinoma cells (A549), cervical adenocarcinoma cells (HeLa), or osteosarcoma cells (HOS). However, at concentrations up to 500 μg/mL, MgAl-LDH exhibited negligible toxicity toward normal L-132 cells, but induced toxicological effects, including membrane damage and oxidative stress, in tumor cells (A549, HeLa, and HOS) [54]. These findings underscore the importance of carefully tailoring the composition, concentration, size, and other parameters of LDHs based on specific target tissues or cells to optimize therapeutic outcomes.

Chemical composition tunability

Pristine LDHs are chemically versatile and can be modified by altering their cationic and anionic components. Their role in tissue engineering is largely derived from their diverse elemental compositions, as summarized in Table 4. Certain elements impart specialized functionalities to LDHs. For instance, LDHs containing photocatalytic elements like Zn and Ti can function as photocatalysts, while those with transition metals such as Fe and Ni exhibit electrocatalytic activity. Additionally, LDHs incorporating elements like Cu, Mn, and Co demonstrate enhanced photothermal conversion properties. These photosensitive, electrosensitive, and thermosensitive effects are expected to play a pivotal role in tissue regeneration [51, 55]. Beyond their intrinsic functionalities, the compositional tunability of LDHs facilitates the creation of multifunctional composites through chemical modification.

Powerful drug-carrying capacity

The efficient drug-loading capability of LDHs distinguishes them from other two-dimensional nanomaterials [6, 10]. Firstly, LDHs have a strong loading content. The layered structure of LDHs provides a high specific surface area of up to 600 m^2/g, and the tunability of their interlayer spacing (ranging from 0.73 to 2.28 nm) allows

Table 4 Role of LDH components in tissue regeneration

Types of ions	Ions	Biological functions	Refs.
Cation	Mg^{2+}	Regulates osteogenic-osteoblastic balance; Cntributes to vascularization; Improves immune microenvironment	[11, 56–58]
	Zn^{2+}	Promotes bone differentiation; Helps wound healing; Antimicrobial	[59–62]
	Ca^{2+}	Promote bone regeneration & osseointegration	[63]
	Fe^{2+}/ Fe^{3+}	Photothermal effect; High paramagnetism	[57, 64]
	Cu^{2+}	Vascularization; Photothermal effect; Antimicrobial; Generation ROS	[50, 65–67]
	Mn^{2+}	Osteogenic differentiation; Vascularization; Antibacterial	[51, 68, 69]
	La^{3+}	Promote bone regeneration; Inhibit bone resorption	[70]
	Eu^{3+}	Promotes bone repair; Promotes blood vessel regeneration	[27, 51]
	Sr^{2+}	Accelerated bone mineralization	[57, 71, 72]
	Co^{2+}	Stimulates angiogenesis	[73, 74]
	Ni^{2+}	Electrocatalytic effect; Vascular regeneration; Antibacterial	[50, 64, 75]
	Gd^{3+}	High paramagnetic for MRI imaging	[76]
	Yb^{3+}	Bone regeneration	[77]
Anion	F^-/PO_4^{3-}	Enhancement of enamel remineralization	[78–80]
	$Cl^-/NO_3^-/CO_3^{2-}$	Adjusts drug release rate	[81, 82]

the accommodation of various drug molecules or biologically active components such as peptides and nucleic acids [83–85].Peng et al. [86] prepared MgAl-LDH loaded with doxorubicin (DOX) and indocyanine green (ICG). The drug loading capacity (mass ratio of drug to carrier) reached 797.36%, the highest reported among 2D nanocarriers at the time.The drug loading content for DOX and ICG were 344.56% and 227.88%, respectively. Zhang et al. [87] developed DOX-LDH with a drug loading capacity of 734%. The drug-loading capacities of nanocarriers with DOX as the target are summarized in Table 5, highlighting the remarkable drug-loading ability of LDHs.Secondly, LDHs exhibit diverse drug-loading mechanisms. Drugs or functional molecules can be loaded onto LDHs via methods such as ion exchange, physical adsorption, or co-precipitation [6, 10]. For instance, the positively charged "bread layers" of LDHs adsorb negatively charged drugs through electrostatic interactions. For another example, negatively charged DNA can be incorporated into MgAl-LDH through ion exchange with anions(NO_3^-, CO_3^{2-}) in the interlayers [88]. Thirdly, LDHs protect encapsulated molecules by minimizing drug exposure to complex physiological environments, thereby preventing degradation [10]; and the abundant hydroxyl groups in LDHs interact with drug molecules to enhance stability.

Special drug release properties

LDHs enable targeted drug release through electrostatic interactions. Meanwhile, they can also control drug release by degradation in acidic environments or via ion exchange under physiological conditions(Fig. 3d) [6, 97].

The positively charged layered structure of LDHs allows them to bind negatively charged substances via electrostatic attraction [1, 2, 6, 10, 97]. For example, LDHs can adhere to the negatively charged conjunctiva, extending their residence time in the eye [6, 98]. Additionally, the negative charge of phosphomimetic acids and lipopolysaccharides on bacterial surfaces allows LDHs to effectively target bacteria, enhancing antimicrobial activity during tissue repair [46].

Table 5 The loading content of different nanomaterials for DOX

Nano carriers	Loading content	Refs.
MgAl-LDH	734%	[87]
h-BN	309%	[89]
MoS2	239%	[90]
GO	213%	[91]
BP	187%	[92]
g-C3N4	185%	[93]
B NSs	114%	[94]
rGO	98%	[95]
MSN	80.48%	[96]

h-BN, hexagonal boron nitride; MoS2, molybdenum sulfide; GO, graphene oxide

BP, black phosphorus; g-C3N4,graphitic carbon nitride; B NSs, boron nanosheets

rGO, reduced graphene oxide; MSN, mesoporous silica nanospheres

As hydroxides, LDHs undergo hydrolysis in acidic environments, facilitating the release of encapsulated drugs [1, 2, 7, 10, 97]. Their pH responsiveness depends on their chemical composition and particle size. For instance, MgAl-LDHs exhibit greater sensitivity to pH changes compared to ZnAl-LDHs, and larger LDH nanosheets degrade more rapidly under acidic conditions. Exogenous stimuli such as light and heat can further regulate LDHs drug release. Peng et al. [86] demonstrated that loading DOX and ICG into MgAl-LDH nanosheets resulted in a fourfold increase in drug release when exposed to near-infrared laser(NIR) in an acidic environment (Fig. 3e, f,g).

LDHs can achieve sustained drug release through ion exchange with phosphate ions under physiological conditions. Simvastatin-loaded ZnAl-LDH was synthesized via co-precipitation, enabling controlled release to promote osteogenesis [37]. Similarly, ibuprofen was intercalated into MgAl-LDH, significantly slowing its release in simulated intestinal fluids through ion exchange [99].

In summary, LDHs offer biocompatibility, chemical composition versatility, and controlled drug loading and release capabilities, establishing a strong foundation for their application in regenerative medicine and tissue engineering. On this basis, the following sections explore recent advancements in LDHs for tissue regeneration.

Repair of bone defects

Engineered scaffolds are frequently employed in bone defect repair to provide structural support and promote new bone formation [10, 101]. To be effective, these scaffolds must exhibit mechanical properties that offer adequate support while avoiding stress-shielding effects. Pristine LDHs exhibit mechanical characteristics well-suited for bone tissue engineering [7], with elastic moduli closely matching that of human cortical bone (7–30 GPa). Specific measurements for MgAl-LDH, MgFe-LDH, ZnAl-LDH, and ZnFe-LDH are 18.9, 9.6, 27.7, and 34.5 GPa, respectively (Fig. 4a). Importantly, these properties remain stable even after prolonged immersion in body fluids [59].

Leveraging their intrinsic mechanical suitability, pristine LDHs are often incorporated into bone scaffold composites to enhance mechanical performance. For instance, polymethyl methacrylate (PMMA) bone cement—commonly used to fill bone defects—possesses an excessively high elastic modulus, which can contribute to osteolysis and aseptic loosening. To mitigate this, Wang et al. [102] developed a PMMA cement modified with MgAl-LDH nanosheets. This modification significantly reduced the elastic modulus and improved interfacial bone integration compared to unmodified PMMA. Conversely, in cases where scaffold materials exhibit

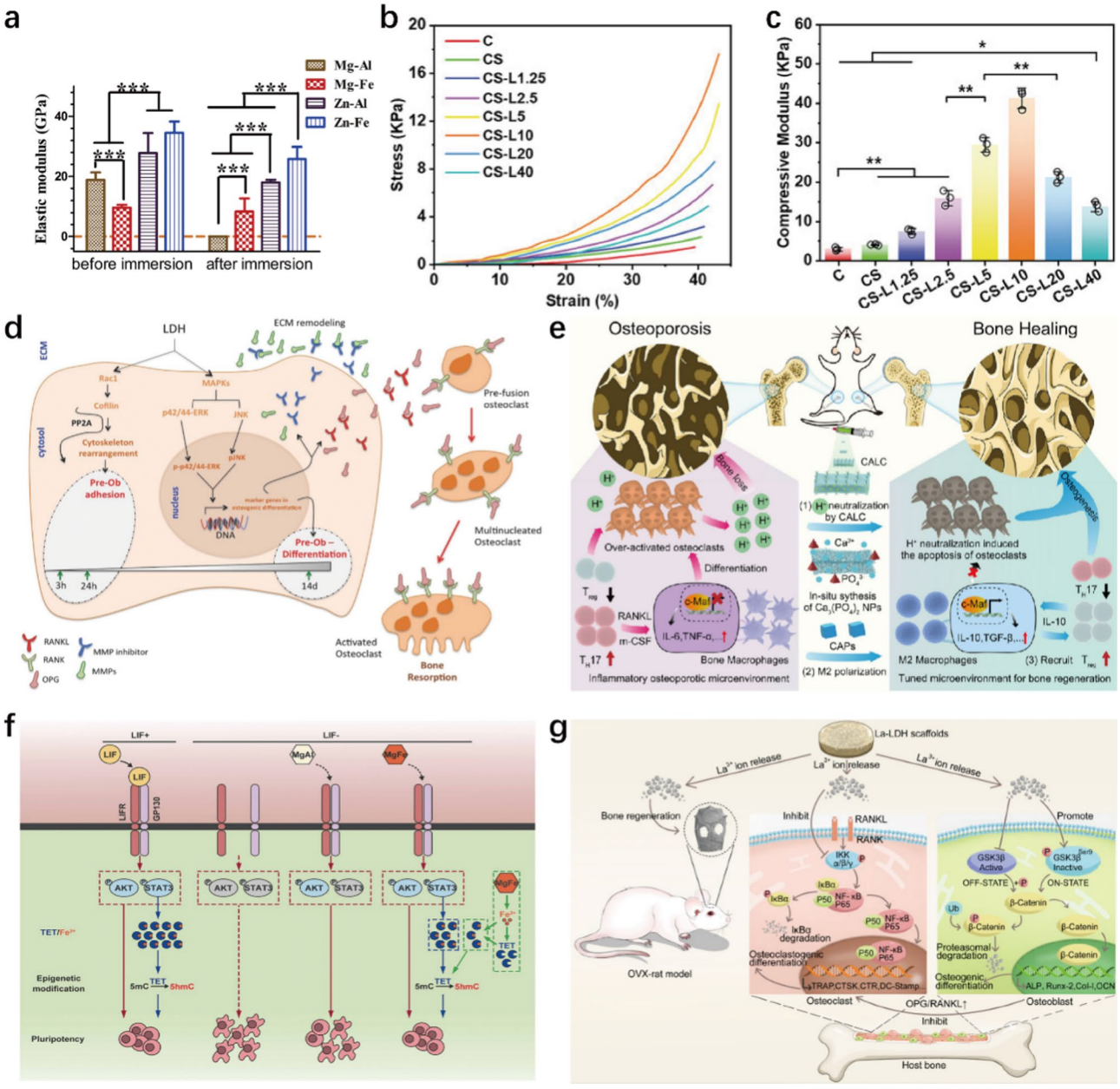

Fig. 4 (**a**) Mechanical stability of LDHs in simulated body fluids: Elastic modulus of MgAl-LDH (18.9 GPa) matches cortical bone (7–30 GPa). Reprinted with permission from Ref [59]. Copyright (2018) Elsevier. (**b**) Compressive stress-strain curves and (**c**) compressive modulus for C, CS and CS-L composite scaffolds with different concentrations of LDH added. Reprinted with permission from Ref [104]. Copyright (2022) John Wiley and Sons. (**d**) MgAl/ZnAl-LDH regulate osteoblast-osteoclast balance via MAPK & Wnt pathways. Reprinted with permission from Ref [100]. Copyright (2017) John Wiley and Sons. (**e**) CaAl-LDH promotes M2 macrophage polarization via PI3K-AKT-mTOR. Reprinted with permission from Ref [63]. Copyright (2022) American Chemical Society. (**f**) MgFe-LDH maintains stem cell pluripotency via LIFR/JAK/STAT3 signaling. Reprinted with permission from Ref [106]. Copyright (2021) John Wiley and Sons. (**g**) La-LDH enhances osteogenesis (Wnt/β-catenin) and inhibits osteoclastogenesis (NF-κB). Reprinted with permission from Ref [70]. Copyright (2021) Ivyspring International Publisher

insufficient strength, LDHs can reinforce mechanical performance (Fig. 4b, c). For example, poly(L-lactic acid) (PLLA), widely used in 3D-printed bone scaffolds, suffers from limited mechanical strength [103]. Zhu et al. [65] addressed this by incorporating LDHs into PLLA scaffolds, achieving a 21% increase in compressive strength and a 13.8% improvement in elastic modulus. Similarly, the addition of MgFe-LDH to chitosan/sericin composites enhanced their elastic modulus by a factor of 10.2 [104]. In another case, the tensile strength and elongation at break of polycaprolactone/gelatin nanofiber scaffolds were markedly improved with MgAl-LDH doping [105]. These examples underscore the dual utility of LDHs: their favorable intrinsic mechanical properties and their

capacity to enhance the mechanical behavior of composite materials, making them highly promising for the development of tailored scaffolds in bone regeneration.

Osteogenesis of pristine LDHs

LDHs exhibit a wide range of chemical compositions, endowing them with remarkable intrinsic osteogenic potential [1, 6]. Their mechanisms of action vary depending on both elemental composition and the target cell type. Traditional LDHs incorporating magnesium, zinc, or iron are known to enhance bone formation. For example, MgAl-LDH upregulates osteogenic gene expression and increases alkaline phosphatase activity in human bone marrow mesenchymal stem cells (BMSCs)[13–17]. ZnAl-LDH promotes osteogenic differentiation by modulating key signaling pathways such as MAPK, PI3K/Akt, and Wnt/β-catenin (Fig. 4d) [100]. Similarly, MgFe-LDH supports osteogenesis in embryonic stem cells (ESCs) by maintaining self-renewal and pluripotency through activation of the LIFR/JAK/STAT3, p-STAT3/TET, and related pathways [106] (Fig. 4f).Manganese-containing LDHs (Mn-LDHs) have also demonstrated potent bone regenerative capacity [69].

Certain rare earth elements contribute to bone repair as well. For instance, La-LDH enhances the proliferation and differentiation of rat BMSCs by activating the Wnt/β-catenin pathway, while simultaneously inhibiting osteoclastogenesis through suppression of NF-κB signaling (Fig. 4g) [70]. Yb-doped MgAl-LDH monolayer nanosheets (MgAlYb-LDHs) significantly improved in vivo bone regeneration, with a 2.77-fold increase in bone volume compared to the negative control, and a 1.41-fold increase relative to autologous bone grafts [51, 77].

The osteogenic performance of LDHs can vary considerably with their elemental makeup. In Zhang et al. [51], Fe-LDH outperformed Mn-LDH in both in vitro and in vivo settings, whereas MnFe-LDH yielded the highest osteogenic efficacy by co-releasing Mn^{2+} and Fe^{3+}. Similarly, Kang et al. [100] reported that ZnAl-LDH induced stronger in vitro osteogenic differentiation than MgAl-LDH under identical conditions. Although direct comparisons of osteogenic efficacy under standardized conditions remain limited, preliminary evaluations can be made based on the inherent properties of the constituent metal ions. For example, calcium-based LDHs may excel in promoting matrix mineralization but exhibit limited early-stage osteogenic activity. Zinc-based LDHs provide antimicrobial benefits alongside osteogenic promotion. Iron-based LDHs show strong osteogenic potential, though the effects of Fe^{3+} concentration on cellular iron metabolism warrant consideration. These insights, however, require further validation through extensive experimental data.

Beyond direct osteogenesis, LDHs also modulate the bone regenerative microenvironment through immunoregulatory mechanisms. Leveraging the bioactivity of divalent cations such as Mg^{2+}, MgAl-LDH exhibits potent immunomodulatory properties. It promotes anti-inflammatory responses by inducing M2 macrophage polarization and recruiting regulatory T cells (Tregs) [107, 108]. Fu et al. [109] applied MgAl-LDH in osteoarthritis therapy, demonstrating its capacity to attenuate local inflammation, inhibit osteoclastogenesis by preventing monocyte fusion, and activate osteoblasts, thereby enhancing bone healing. Similarly, CaAl-LDH releases Ca^{2+}, which reacts with endogenous phosphate to generate calcium phosphate nanoparticles. These particles promote M2 macrophage polarization via the c-Maf transcription factor pathway. M2 macrophages secrete anti-inflammatory cytokines such as IL-10 and TGF-β, recruit and activate Tregs, and suppress T helper 17 (Th17) cell function, collectively creating a favorable immune milieu for bone regeneration (Fig. 4e) [63, 110].

Osteogenesis of LDHs drug delivery systems

LDHs also act as carriers for delivering endogenous biomolecules (e.g., active factors, miRNAs, DNA), exogenous drugs, and other materials [6, 7, 111], effectively transmitting osteogenic signals.

Biologically active molecules, essential for growth and metabolism, benefit from LDH carriers that enhance their effects via tailored delivery. Lv et al. [104]loaded bone morphogenetic protein-2 (BMP-2) into MgFe-LDH nanosheets, incorporating them into CS hydrogels containing platelet-derived growth factor-BB(PDGF-BB; CSP-LB; Fig. 5b). Through controlled electrostatic interactions, BMP-2 achieved sustained release while PDGF-BB exhibited a burst release (Fig. 5a), resulting in enhanced bone regeneration. In another study, Kang et al. [112] encapsulated adenosine (Ado) within MgFe-LDH via electrostatic equilibrium. The co-release of Ado and Mg^{2+} ions synergistically activated adenosine A_{2b} receptors, significantly improving bone defect repair compared to Ado alone (Fig. 5e). Similarly, MgAl-LDH, with its positive surface charge and proton sponge effect, facilitates efficient localized delivery of miRNAs, promoting mesenchymal stem cell (MSC) differentiation and improved transfection efficiency (Fig. 5g) [113, 114].

LDHs are effective carriers for exogenous chemical drugs, addressing challenges such as poor bioavailability, short duration of action, and low solubility. For example, alendronate (AL), an osteoporosis drug, suffers from limited cellular uptake. LDH carriers enhance its delivery through endocytosis and transport to the perinuclear region, thereby improving efficacy [6, 115]. The strong electrostatic interaction between LDHs and AL's phosphate groups facilitates sustained and stable drug release

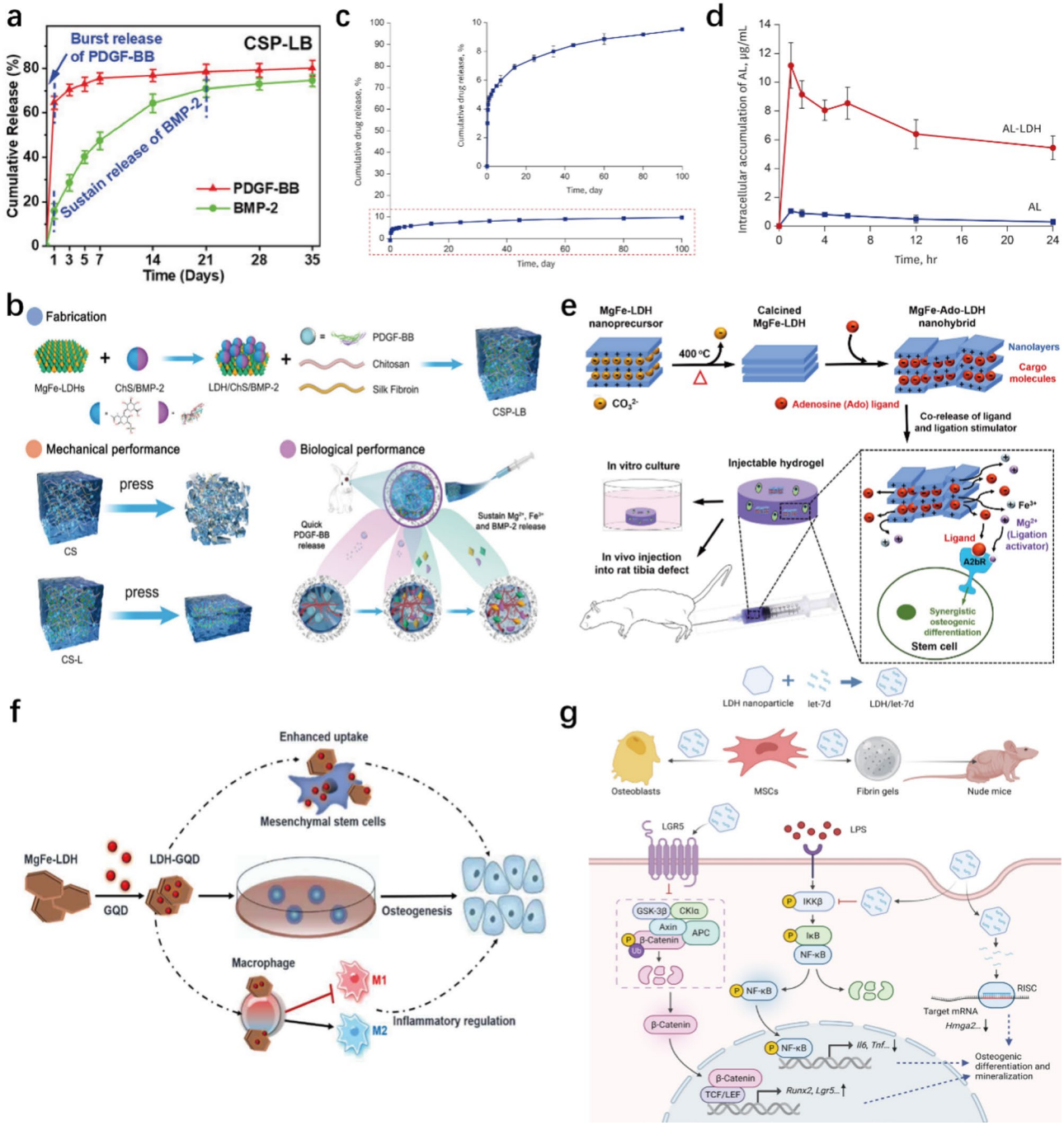

Fig. 5 (**a**) Release kinetics of PDGF-BB with burst release (more than 70%) within 3 days and BMP-2 with continuous release (cumulative release up to 60%) within 35 days from CSP-LB hydrogel. Reprinted with permission from Ref [104]. Copyright (2022) John Wiley and Sons. (**b**) Schematic representation of CSP-LB hydrogel preparation with enhanced mechanics and excellent drug and ion release.Reprinted with permission from Ref [104]. Copyright (2022) John Wiley and Sons.**c**) In vitro cumulative AL release profile of AL-LDH in pH 7.4 PBS. Reprinted with permission from Ref [116]. Copyright (2019) Korean Academy of Medical Sciences. **d**) The intracellular accumulation of AL molecules in the AL-LDH treatment group increased by more than 30% within 12 h compared to the intact AL group. Reprinted with permission from Ref [116]. Copyright (2019) Korean Academy of Medical Sciences. **e**) Synergistic assembly mechanism of MgFe-Ado-LDH and injectable hydrogel: Promote osteogenic differentiation of bone marrow mesenchymal stem cells and repair bone defects through the release of Mg^{2+}/Fe^{3+} ions and the activation of A2bR receptor by adenosine ligand. Reprinted with permission from Ref [112]. Copyright (2017) Elsevier. **f**) LDH: GQD nanocomposite synergistically promotes osteogenic differentiation of rBMSCs by enhancing cell uptake efficiency and regulating the inflammatory microenvironment through polarization of M1 macrophages to M2. Reprinted with permission from Ref [124]. Copyright (2022) IOP Publishing. **g**) The LDH/let-7d nanocomposite regulates osteogenic differentiation and mineralization of BMSCs by activating the Wnt/β-catenin signaling pathway and inhibiting the NF-κB signaling pathway. Reprinted with permission from Ref. Copyright (2021) American Chemical Society

(Fig. 5c, d) [77, 116]. Similarly, atorvastatin's osteogenic potential is limited by its poor solubility, which LDHs overcome through their lamellar structure, improving water solubility and bioavailability [117]. Comparable improvements have been reported for naproxen (NAP) [118, 119], IBU [120], thymoquinone (TQ) [121], calcineurin [26], pifithrin-α (PFTα) [122, 123], and other drugs, all of which benefit from LDH-mediated delivery in bone repair.

LDHs also enhance the delivery of other nanomaterials. For example, graphene quantum dots (GQDs) loaded onto LDHs exhibit superior uptake and osteogenic differentiation in BMSCs compared to physical mixtures of the materials (Fig. 5f) [124], highlighting new research possibilities for biomaterial interactions.

Overall, LDHs are widely recognized for their efficacy as drug carriers in osteogenesis. We believe that the following directions still warrant attention in future research. In drug loading, LDHs are better suited for anionic drugs due to their positively charged lamellar structure, but their use for non-anionic drugs remains limited. Employing intermediate storage media, such as hydrogels, to encapsulate non-anionic drugs before loading into LDHs could expand their application. In terms of drug release, the release control mechanisms of LDHs need to be explored in greater depth. For example, the number and arrangement of molecules in the intermediate layer, as well as the type of interlayer anions, influence drug release. A clear understanding of the drug release mechanism of LDHs will facilitate the optimal selection or design of LDH compositions and structures according to clinical needs and drug types, ultimately achieving more desirable osteogenic effects.

Osteogenesis of LDHs-based composites

LDHs not only exhibit inherent osteogenic properties and the ability to carry osteogenic drugs for bone repair but can also be combined with various materials to create composite bone scaffolds that enhance bone regeneration [125, 126]. These composite scaffolds are typically classified as LDHs-based inorganic, organic, or hybrid scaffolds, depending on the materials incorporated.

Traditional inorganic scaffolds such as hydroxyapatite (HAp), bioactive glass (BG), and β-tricalcium phosphate (β-TCP) are extensively used for treating large bone defects. Each material possesses unique osteogenic properties (Table 6), and their combination with LDHs offers a strategy to offset individual limitations while enhancing overall performance. HAp, despite being a widely accepted scaffold material, suffers from limited osteoinductive capacity and suboptimal cell adhesion, resulting in slower bone regeneration [127]. To address these limitations, Wang et al. [27] synthesized MgAlEu-LDH (MAE-LDH) nanosheets in situ on porous HAp scaffolds using a hydrothermal technique (Fig. 6a). This modification significantly increased surface roughness, specific surface area, and hydrophilicity. In vivo, the resulting composite scaffolds yielded a 3.18-fold increase in new bone formation and a 2.21-fold increase in mineral density, attributable to the sustained release of Mg^{2+} and Eu^{3+} ions. Similarly, while BG is a classical scaffold material, its homogenous composition limits its biological functionality, particularly in addressing complex bone defects. To overcome this, Bian et al. [128] employed an in situ reduction method to assemble MgFe-LDH nanosheets and selenium nanoparticles (LDH/Se) onto bioactive glass scaffolds, forming BGS@LDH/Se composites (Fig. 6b). These scaffolds surpassed the performance of BGS alone in promoting extracellular matrix (ECM) mineralization and suppressing bone resorption

Table 6 The comparison of LDHs with inorganic bone scaffold materials

Category	Crystal structure	Mechanical property	Degradability	Osteogenesis	Functional extensibility	Clinical application	Refs.
LDHs	Nanolayer structure	Medium, adjustable	Adjustable (weeks- months)	Good	Excellent: • easy drug-load & modifications • some have anti-inflammatory, antibacterial, angiogenic	Emerging materials, lack of clinical applications	[1, 4–8]
HAp	Nano/micron hexagonal crystal	High hardness & brittleness	Difficult to degrade (years)	Excellent	General: • surface-adsorb drugs; • Alone has no antimicrobial, anti-inflammatory	Mature	[144–146]
BG	Amorphous	Medium hardness, brittle	Adjustable (weeks- months)	Excellent	General: • Functional extension by surface modification or component doping; • Alone has some angiogenic	Medium	[147, 148]
β-TCP	Tripartite crystal	Relatively low hardness	Rapid (1–3 months)	Good	General: • Alone has very weak antibacterial, anti-inflammatory, angiogenic	Medium	[149–151]

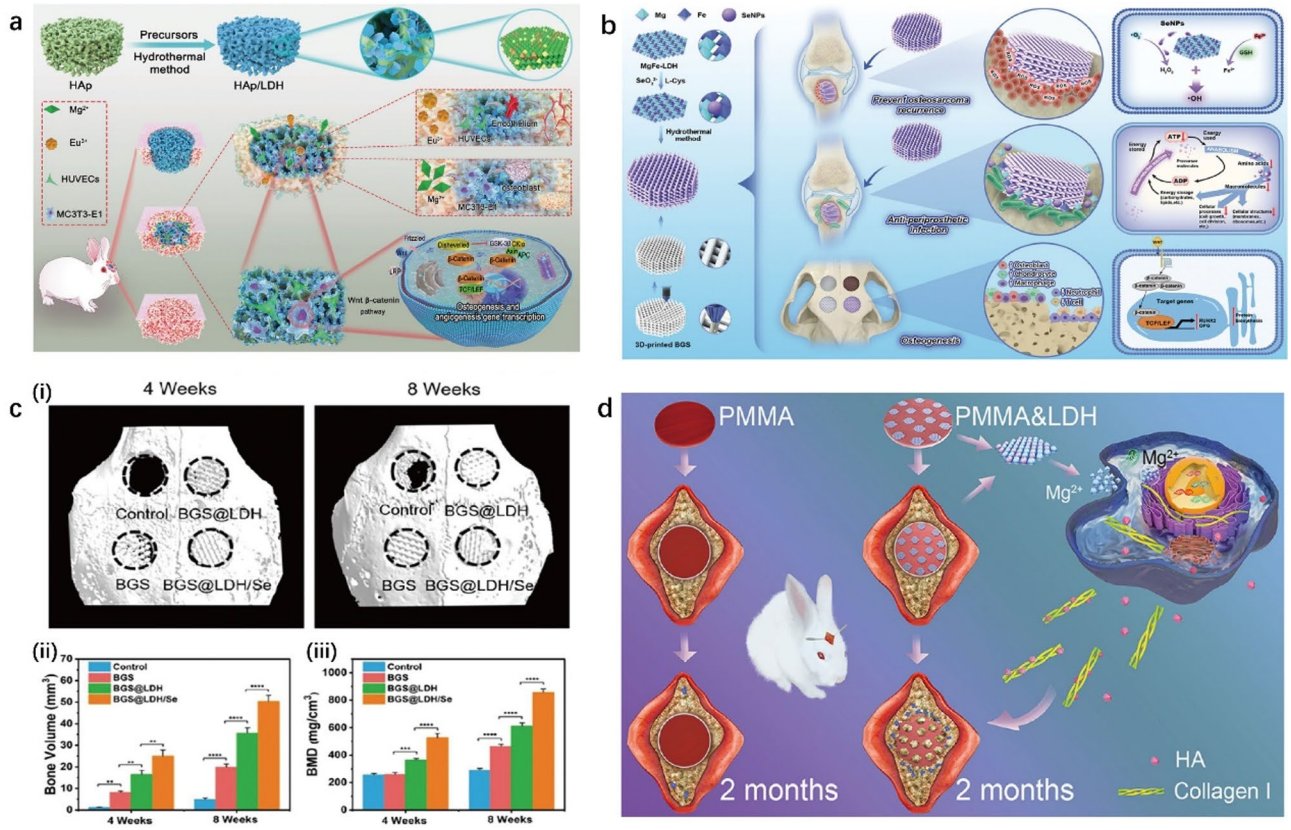

Fig. 6 (**a**) The MAE-LDH nanosheet-modified hydroxyapatite scaffold activates osteogenesis-related gene expression by regulating the Wnt/β-catenin signaling pathway, and at the same time promotes angiogenesis to improve the bone repair microenvironment. Reprinted with permission from Ref [27]. Copyright (2022) John Wiley and Sons. (**b**) Multifunctional mechanism of SeNPs-embedded MgFe-LDH nanosheet platform: Antibacterial, anti-inflammatory, promoting angiogenesis, and osteogenic differentiation synergistically act on bone defect repair. Reprinted with permission from Ref [128]. Copyright (2024) John Wiley and Sons. (**c**) Micro-CT quantitative analysis and three-dimensional reconstruction images of BGS@LDH/Se showing a 2.5-fold increase in bone volume and an 1.8-fold increase in bone mineral density compared to the control group at 8 weeks. Reprinted with permission from Ref [128]. Copyright (2024) John Wiley and Sons. (**d**) Schematic diagram of the bone formation mechanism of PMMA and PMMA&LDH. Reprinted with permission from Ref. Copyright (2021) American Chemical Society

(Fig. 6c(i)-(iii)). Additionally, LDH/Se inhibited bacterial energy metabolism, thereby preventing the proliferation of drug-resistant strains and creating a more favorable microenvironment for bone repair. In another case, β-TCP, a material frequently used in oral and orthopedic surgeries due to its excellent bioabsorbability, is limited by its rapid degradation and weak mechanical strength. Eskandari et al. [129, 130] utilized polyurethane sponge replication to fabricate β-TCP scaffolds integrated with MgAl-LDH. Incorporating 10% LDHs improved the mechanical integrity of β-TCP, slowed its biodegradation, and enhanced its capacity to support bone regeneration.

Among LDHs-based organic scaffolds, chitosan is the most extensively studied. Ge et al. [57] developed multifunctional nanoscaffolds by embedding strontium iron oxide nanoparticles ($SrFe_{12}O_{19}$) and MgAl-LDH into a chitosan matrix. The released Mg^{2+} ions reduced osteoclastic bone resorption by inhibiting the NF-κB pathway, while Sr^{2+} ions accelerated bone mineralization through activation of the BMP-2/SMAD pathway. The hydrostatic magnetic field effect of $SrFe_{12}O_{19}$ further enhanced bone regeneration. Similarly, Cao et al. [71] constructed Ag^{+}-containing ternary MgSrFe-LDH/CS porous scaffolds, which featured interconnected pores (100–300 μm) conducive to new bone formation and osseointegration. The sustained release of Mg^{2+}, Sr^{2+}, and Fe^{3+} ions acted synergistically to promote osteogenesis, while Ag^{+} provided antimicrobial properties. Shi et al. [131] created biomimetic nacre-mimetic scaffolds by embedding MgAl-LDH and graphene oxide (GO) into a chitosan matrix. The LDHs improved mechanical strength, while the released Mg^{2+} and Al^{3+} ions, in conjunction with GO, promoted osteoblast differentiation and M2 macrophage polarization. Beyond chitosan, other polymers such as PMMA(Fig. 6d) [102], PLLA [65, 132], polycaprolactone (PCL) [125, 133, 134], alginate (ALG) [135] have been incorporated with LDHs to form bone scaffolds.

Hybrid scaffolds, combining both inorganic and organic materials, offer further versatility. Fayyazbakhsh et al. [136, 137] fabricated composite bone scaffolds by

integrating LDHs, HAp, and gelatin through layer solvent casting, freeze drying, and lamination techniques. The resulting scaffold had porosity levels of 82–92%, mimicking natural cancellous bone. Vitro and vivo studies confirmed its superior bone defect repair compared to control groups. Similarly, Wang et al. [138] developed poly N-isopropylacrylamide (PNIPA)/LDHs/nano-HAcomposite hydrogel scaffolds using in situ free radical polymerization. The scaffold exhibited excellent hemocompatibility and osteogenic activity. The incorporation of two oppositely charged nanocrosslinkers (positively charged LDHs and negatively charged HA) imparted mechanical toughness and reversible thermosensitive swelling properties, expanding its potential clinical applications.

In conclusion, LDHs-based composites have shown great promise in repairing bone defects efficiently. However, most research has primarily centered on their direct osteogenic effects, with limited focus on vascularized osteogenesis and immune microenvironment modulation. Moreover, studies investigating the neurogenic osteogenic strategy of LDHs-based composites remain scarce. As the critical role of innervation in bone metabolism and regeneration is now widely recognized [139, 140], and given LDHs' notable potential in promoting nerve formation [141–143], developing LDHs-based composites with pro-nerve regeneration capabilities for bone defect repair presents an exciting and valuable research avenue.

LDHs coating modified bone implants

Due to their excellent biocompatibility and ion-exchange capacity, LDHs have been extensively explored as coatings for bone implant materials, enhancing both osteogenic performance and corrosion resistance [69, 152–154].This is particularly important for magnesium-based implants, where magnesium-based LDHs can be synthesized and grown in situ, creating a robust, tightly adhered coating through magnesium sharing. Wang et al. [153] developed composite coatings laser-treated-LDHs-octadecyl-trimethoxy-silane (L-LDHs-OTS) on magnesium alloys via laser treatment, in situ growth of MgAl-LDH, and OTS modification. These coatings demonstrated outstanding corrosion resistance, reducing corrosion current density by five orders of magnitude compared to bare magnesium alloys. LDHs' remarkable ion exchange and lamellar structure enable self-healing: when corrosion-dissolved Mg^{2+} and Al^{3+} ions accumulate locally, LDHs recrystallize to repair defective regions and maintain prolonged corrosion resistance (Fig. 7a). Similarly, Cheng et al. [58] fabricated MgAl-LDH coatings on pure magnesium using hydrothermal treatment. Compared to bare Mg and $Mg(OH)_2$ coatings, MgAl-LDH coatings offered superior corrosion resistance, osteogenic potential, and immune microenvironment modulation(Fig. 7b). PEO/MgZnAl-LDH composite coatings were further developed on magnesium alloys through plasma electrolytic oxidation (PEO) and hydrothermal treatment [155]. In addition to enhanced corrosion resistance, these coatings leveraged the synergistic effects of Zn^{2+} and Mg^{2+} ions to promote osteogenic differentiation.

For titanium-based implants, researchers have also employed LDH coatings to improve biological properties. Liao et al. [72] synthesized SrFe-LDH coatings on titanium implants using a hydrothermal process. The coatings downregulated CTSK and TRAP gene expression, inhibited osteoclast fusion and maturation, and significantly enhanced osseointegration in osteoporotic rats.

Similarly, Li et al. [156] prepared MgFe-LDH films on acid-etched titanium surfaces through hydrothermal treatment. By adjusting the Mg/Fe ratio, the authors effectively controlled the local pH, mitigating corrosion-induced pH increases and promoting osteoblast growth and differentiation.

In summary, LDHs have emerged as promising materials for bone implant coatings due to their biocompatibility, corrosion resistance, and tissue regeneration capabilities. Among them, research on constructing magnesium-based LDHs on the surface of magnesium-based implants is the most extensive. This is because the two components, by sharing magnesium elements, achieve dense coating coverage and strong adhesion. However, when LDHs do not contain the same metal element as the substrate, it is difficult to achieve the desired results, thus limiting the use of LDHs as a coating for universal bone implant materials. A potential solution involves layer-by-layer assembly with intermediate substances, such as polydopamine (PD), to bridge LDHs and the implant matrix [157]. Moreover, the tunable chemical composition and excellent drug-delivery capabilities of LDHs may enable bone implant materials to play a more practical role in bone defect repair. For example, the incorporation of antimicrobial elements such as Ag, Cu, and Zn into LDH coatings can confer antimicrobial properties to the implants, preventing or mitigating infections in the surrounding tissues. Additionally, by loading various functional drugs into the coated LDHs, multifunctional bone implant coatings can be developed to locally exert specific therapeutic effects and promote osseointegration.

Cartilage reconstruction

Mature cartilage lacks vascular and neural tissues, severely limiting its capacity for selfrepair following injury [157]. The emergence of cartilage tissue engineering offers a promising solution for cartilage reconstruction [158, 159]. Leveraging the exceptional properties of LDHs, researchers have increasingly explored their application in cartilage regeneration. This chapter summarizes

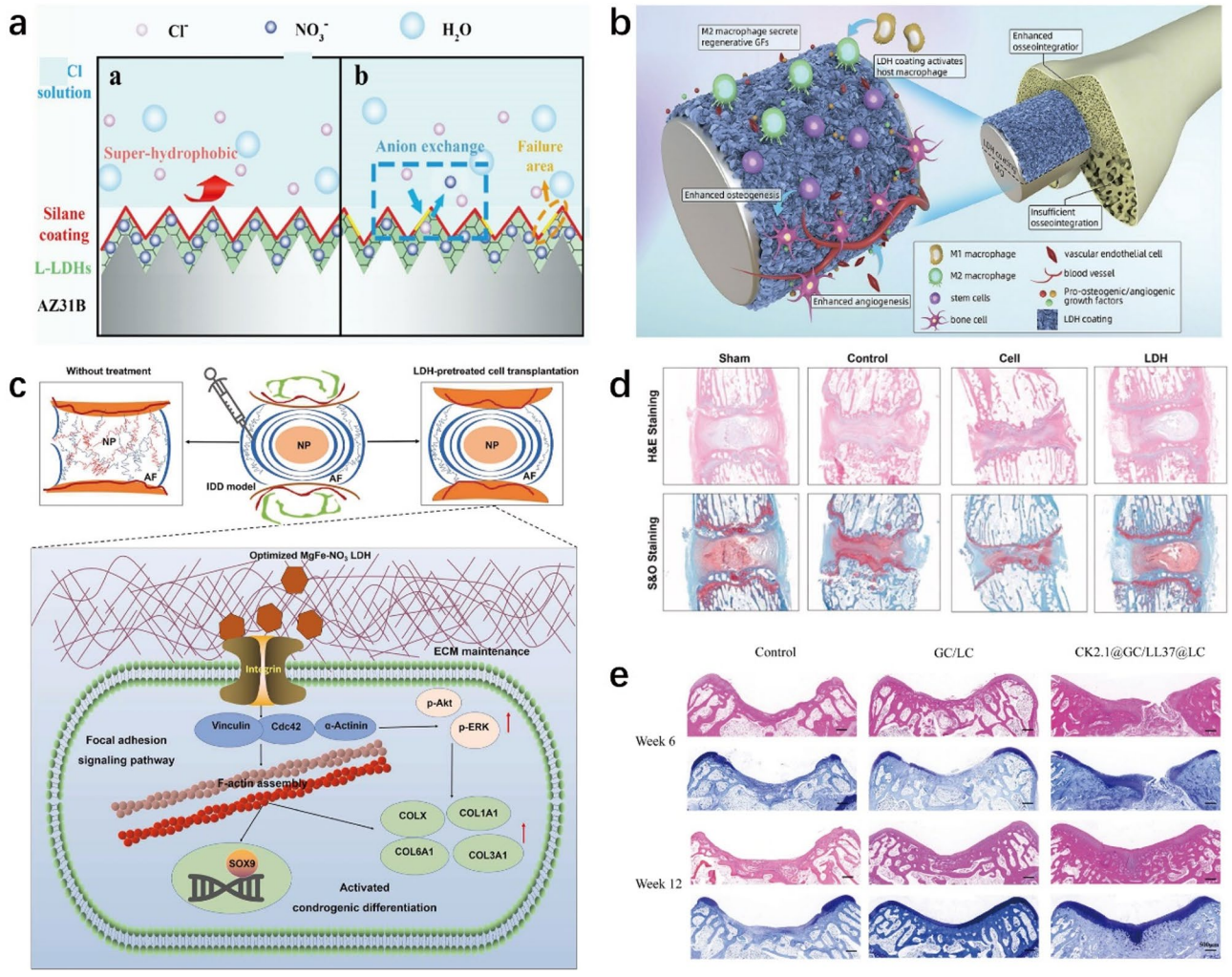

Fig. 7 (**a**) The L-LDHs-OTS composite coating adsorbs Cl^- ions through cation exchange and simultaneously releases NO_3^- ions to achieve self-healing. The superhydrophobic property with a contact angle greater than 150° of the coating further enhances the anti-corrosion performance. Reprinted with permission from Ref [153]. Copyright (2021) American Chemical Society. (**b**) LDH coating promotes osteoblast mineralization by releasing Mg^{2+}/Fe^{3+} ions. At the same time, it activates M2 macrophage polarization, and synergistically enhances bone integration efficiency. Reprinted with permission from Ref [58]. Copyright (2021) Elsevier. (**c**) LDH-pretreated cell transplantation enhanced cartilage differentiation and in situ disc regeneration through the focal adhesion signaling pathway. Reprinted with permission from Ref [25]. Copyright (2023) Elsevier. (**d**) H&E and S&O staining of different treatments after 12 weeks. Reprinted with permission from Ref [25]. Copyright (2023) Elsevier. (**e**) Histologic analysis of HE and toluidine blue staining of osteochondral repairs in different groups at 6 and 12 weeks postoperatively. Reprinted with permission from Ref [166]. Copyright (2021) Elsevier

the latest progress of LDHs in cartilage regeneration in three forms: pristine LDHs, LDHs drug delivery systems, and LDHs-based composites.

The biological functions of pristine LDHs vary depending on their elemental composition. Wang et al. [25] synthesized four types of LDHs with different anions and cations: MgAl-Cl LDH, MgFe-Cl LDH, MgAl-NO_3 LDH, and MgFe-NO_3 LDH. Among them, MgFe-NO_3 LDH exhibited the highest efficiency in cell compatibility and promoting chondrogenic differentiation of human umbilical cord mesenchymal stem cells (hUCMSCs). It significantly stimulated cells to produce the largest amount of glycosaminoglycan (GAG) and up-regulated the expression of cartilage-specific genes SOX9 and COL2A1. To study its in vivo effect, the authors established a rat intervertebral disc injury model using acupuncture needle puncture. Transplantation of hUCMSCs treated with MgFe-NO_3 LDH restored both the intervertebral disc height and the overall cartilage structure. Transcriptome sequencing revealed that activation of the focal adhesion signaling pathway was crucial for promoting the chondrogenic differentiation of hUCMSCs by LDHs. Specifically, LDHs promoted the expression of Integrin, Vinculin, and Actinin, and up-regulated p-Akt and p-ERK expression (Fig. 7c, d).

Beyond directly promoting cartilage regeneration, LDHs also serve as carriers for chondropromoting drugs. Boswellia serrata extract (BSE) alleviates osteoarticular

inflammation and slows the degradation of articular cartilage. However, its poor water solubility limits its use in tissue regeneration [160]. Cometa et al. [161] loaded BSE onto MgAl-LDH and incorporated the drug-loaded LDHs into gellan gum for local administration. LDHs facilitated the delivery of hydrophobic BSE while improving the mechanical properties of the resulting cold gels. After adding LDHs, the compressive Young's modulus of the sample increased threefold compared to bare gellan gum. This is likely due to LDHs forming a network within the hydrogel polymer. LDHs also increased the fracture strain and elastic deformation ability of the hydrogel, which is crucial for tissue engineering of soft tissues, such as cartilage, requiring high deformability. The BSE released from LDHs promotes chondrogenesis and alleviates local inflammation by down-regulating COX2 and PGE2, and up-regulating IL10.It is worth mentioning that, due to its good biocompatibility and the cartilage-like structure formed by glucuronic acid residues [162], gellan gum primarily functions as a scaffold support and does not directly promote chondrogenesis. Furthermore, small interfering RNA (siRNA) applications have shown promise in addressing cartilage tissue degeneration [163]. To enhance siRNA stability and activity, MgAl-LDH and MgFe-LDH serve as protective carriers, shielding siRNAs from enzymatic degradation and improving their cellular uptake to target negative regulators involved in cartilage homeostasis [164]. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an endogenous model gene to assess silencing efficiency in this study. After 6 days of culture, GAPDH expression in the LDHs vector system group decreased by 82–98%, confirming the enhancement of cellular uptake and siRNA delivery by LDHs.

LDHs-based composites have also demonstrated potential in cartilage regeneration.The stem cell therapy for damaged cartilage is challenged by low retention, survival, and differentiation rates at the target site. Lee et al. [165] developed a novel 2D/3D composite nanoscaffold combining tonsil-derived mesenchymal stem cells (TMSCs), RGD-encapsulated LDHs, and kartogenin (KGN)-doped PEG-PA-PD thermogel. The inclusion of LDHs increased matrix stiffness and provided a 2D anchoring surface for cells, enhancing cell-material interactions and regulating KGN release. This composite scaffold significantly elevated the expression of cartilage biomarkers, including type II collagen and SOX9, compared to the pure PEG-PA-PD thermogel system.PEG-PA-PD mainly serves to provide the convenience of drug administration in this context. In another study, Liu et al. [166] designed a biomimetic bilayer scaffold incorporated with LDHs to simultaneously repair articular cartilage and subchondral bone. The upper layer contained CK2.1 peptide-coated β-glycerophosphate chitosan hydrogel (CK2.1@GC) for cartilage repair, while the lower layer comprised an MgAl-LDH/chitosan (LL37@LC) scaffold loaded with LL37 peptide for subchondral bone repair. An ideal cartilage scaffold should possess mechanical properties comparable to those of human cartilage. The study found that the upper layer, CK2.1@GC, exhibits excellent ductility, with compressive strength exceeding 2.5 MPa and minimal fracture risk. The lower layer, LL37@LC, can withstand forces of at least 2.0 MPa, satisfying the requirements for cartilage repair [167].The CK2.1 and LL37 peptides promoted cartilage and vascular regeneration, respectively. LDHs regulate the differentiation balance between osteoblasts and osteoclasts, maintaining bone metabolism through $Mg2+$ release. Chitosan hydrogel serves as a scaffold in the defect area. To evaluate the in vivo effect, the authors created a condylar osteochondral defect model (5 mm depth, 5 mm diameter) in New Zealand white rabbits. At week 12, a small amount of new tissue appeared at the boundary of the control group. In contrast, the bilayer scaffold group showed near-complete defect repair, with a distinct boundary between the repaired cartilage and subchondral bone (Fig. 7e).

In summary, LDHs offer innovative solutions for cartilage reconstruction. Several future research directions merit attention. First, precision medicine using gene therapy could be transformative for repairing cartilage defects. To address the immunogenicity and cytotoxicity issues linked to viral vectors, the development of safe, efficient LDHs gene delivery systems targeting key cartilage-related genes present an attractive avenue. Second, given the frequent association of cartilage defects with inflammatory conditions like osteoarthritis and rheumatoid arthritis, effective inflammation control is critical for successful regeneration [168]. While single-component LDH materials may have limitations, combining nanomaterials, cells, and growth factors into multifunctional LDHs-based composites—offering anti-inflammatory and regenerative properties—is a promising strategy. Third, LDHs' exceptional lubrication properties could reduce friction within articular cartilage, facilitating automatic surface smoothing and minimizing damage [169, 170]. Consequently, investigating LDHs as a lubricating medium for cartilage repair represents another key research area.

Angiogenesis

Most tissues rely on blood vessels to support their metabolic functions, with few exceptions, such as cartilage and the cornea, which are avascular. Promoting angiogenesis has become a major strategy in tissue engineering to accelerate tissue regeneration and remodeling [171]. Thanks to their adaptable chemical composition and unique lamellar structure, LDHs can play a vital role in vascular tissue regeneration by releasing angiogenic

components (e.g., Mg^{2+}, Fe^{3+}) or delivering angiogenic drugs [27, 51, 131].

Magnesium-based LDHs are the most prevalent LDHs. Cheng et al. [58, 172] developed MgAl-LDH coatings on the surfaces of pure magnesium and the magnesium alloy AZ31.Compared with the uncoated group and the $Mg(OH)_2$ coating group, MgAl-LDH prevents the excessive accumulation of local Mg^{2+} concentrations, which may otherwise impair cell activity. In vitro studies show that MgAl-LDH significantly promotes the proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs). Further investigation revealed that MgAl-LDH promotes angiogenesis through several mechanisms: First, the controlled release of Mg^{2+} upregulates angiogenesis-related genes and proteins, such as EGF, KDR, and HIF-1α. Second, MgAl-LDH induces macrophages to polarize into the M2 phenotype. The secreted factors in the macrophage culture medium of the MgAl-LDH group promote angiogenesis. Additionally, the slight pH increase induced by LDHs enhances endothelial cell adhesion, spreading, and proliferation.

Beyond conventional magnesium-based LDHs, the inclusion of less common vasculogenic elements such as Mn^{2+}, Eu^{2+}, Cu^{2+}, and Ni^{2+} can further improve vascular regeneration. For instance, Zhang et al. [51] synthesized MnFe-LDH using a two-step method combining submerged and hydrothermal treatments, yielding significant in vitro angiogenic potential. In this system, iron ions promote angiogenesis primarily by increasing the level of endothelial nitric oxide synthase in endothelial cells, while manganese ions promote angiogenesis mainly by upregulating angiogenesis-related genes, such as HIF-1α and KDR. KDR, also known as vascular endothelial growth factor receptor 2 (VEGFR2), is the primary receptor that regulates angiogenesis [173]. Similarly, Wang et al. utilized a hydrothermal approach to grow MgAlEu-LDH nanosheets (HAp/MAE-LDH) on HAp surfaces [27].Compared to HAp and HAp/MgAl-LDH, HAp/MAE-LDH significantly enhanced the proliferation, adhesion, migration, and tube formation of HUVECs. The vasculogenic capacity increased with higher MAE-LDH content, highlighting crucial role of Eu^{3+} in promoting angiogenesis (Fig. 8a). In the in vivo implantation experiment, the expression of the neovascular marker CD31 increases with the MAE-LDH content. Gross photographs of the chick chorioallantoic membrane (CAM) experiment show significantly more neovascular vessels in the groups with higher MAE-LDH content. Transcriptome sequencing and KEGG analysis revealed that among the top 20 signaling pathways, the HIF1 and Notch signaling pathways play crucial roles in the angiogenesis promoted by LDHs. Additionally, Ingenuity Pathway Analysis based on a specific algorithm revealed that the Wnt/β-catenin pathway was significantly activated. This classical signaling pathway plays a key role in the remodeling of the vascular plexus.

Photothermal therapy (PTT) has emerged as a promising strategy for tissue regeneration. Zhu et al. [65] synthesized copper-doped LDHs (Cu-LDHs) that elevated cellular HSP90 protein levels, activated the PI3K/Akt pathway, and upregulated hypoxia-inducible factor (HIF-1α) under PTT, thereby promoting angiogenesis (Fig. 8b). Yao et al. [75] synthesized NiTi-LDH on NiTi alloys and constructed a cost-effective photothermal film by reducing NiTi-LDH in a H_2 atmosphere. The released Ni^{2+} ions simulated a hypoxic microenvironment by affecting heme-containing oxygen-sensing molecules, leading to the expression of VEGF and HIF-1α and promoting vascular regeneration. Near-infrared light irradiation further enhanced its tube-forming capacity.

While LDHs demonstrate pro-angiogenic effects through the release of metal ions, maintaining a controlled, long-term release remains challenging. Gallic acid (GA), a naturally occurring polyphenol, can bind stably to metal ions and modulate their release kinetics [174, 175]. Based on this concept, Chen et al. [176] synthesized MgCoAl-LDHs on Ti alloy substrates using a hydrothermal reaction and modified the surface with GA (Ti-LDH/GA). GA chelation significantly slowed the release of Co^{2+} and Mg^{2+} ions, extending the release period to nearly a month. Co^{2+}, due to its larger net negative charge, formed a more stable complex with GA, resulting in a slower release rate compared to Mg^{2} + and providing prolonged angiogenic stimulation(Fig. 8c) [73, 74].

While LDHs containing transition metal ions, as shown in the examples above, have demonstrated good biocompatibility, it is important to note that transition metal ions (e.g., Mn^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}) can have a "double-edged sword" effect during angiogenesis. Therefore, it is crucial to properly control their concentrations. For instance, when the Cu^{2+} concentration exceeds 5 μM, the survival rate of HUVECs decreases significantly. At concentrations above 10 μM, Cu^{2+} can induce endothelial cell death through cuproptosis [177]. High concentrations of Co^{2+} (> 50 μM), Mn^{2+} (> 20 μM), and Ni^{2+} (> 20 μM) can also impair blood vessel network formation [178–180]. To address these issues, efforts should focus on studying the dose-effect relationship of ions released by LDHs and precisely controlling their concentrations. Additionally, leveraging the compositional diversity of LDHs, one can consider replacing them with elements that offer higher biosafety.

Beyond their intrinsic angiogenic properties, the superior drug-loading capabilities of LDHs have been explored in angiogenesis research. Liu et al. [166] incorporated the antimicrobial peptide LL37 into MgAl-LDH.

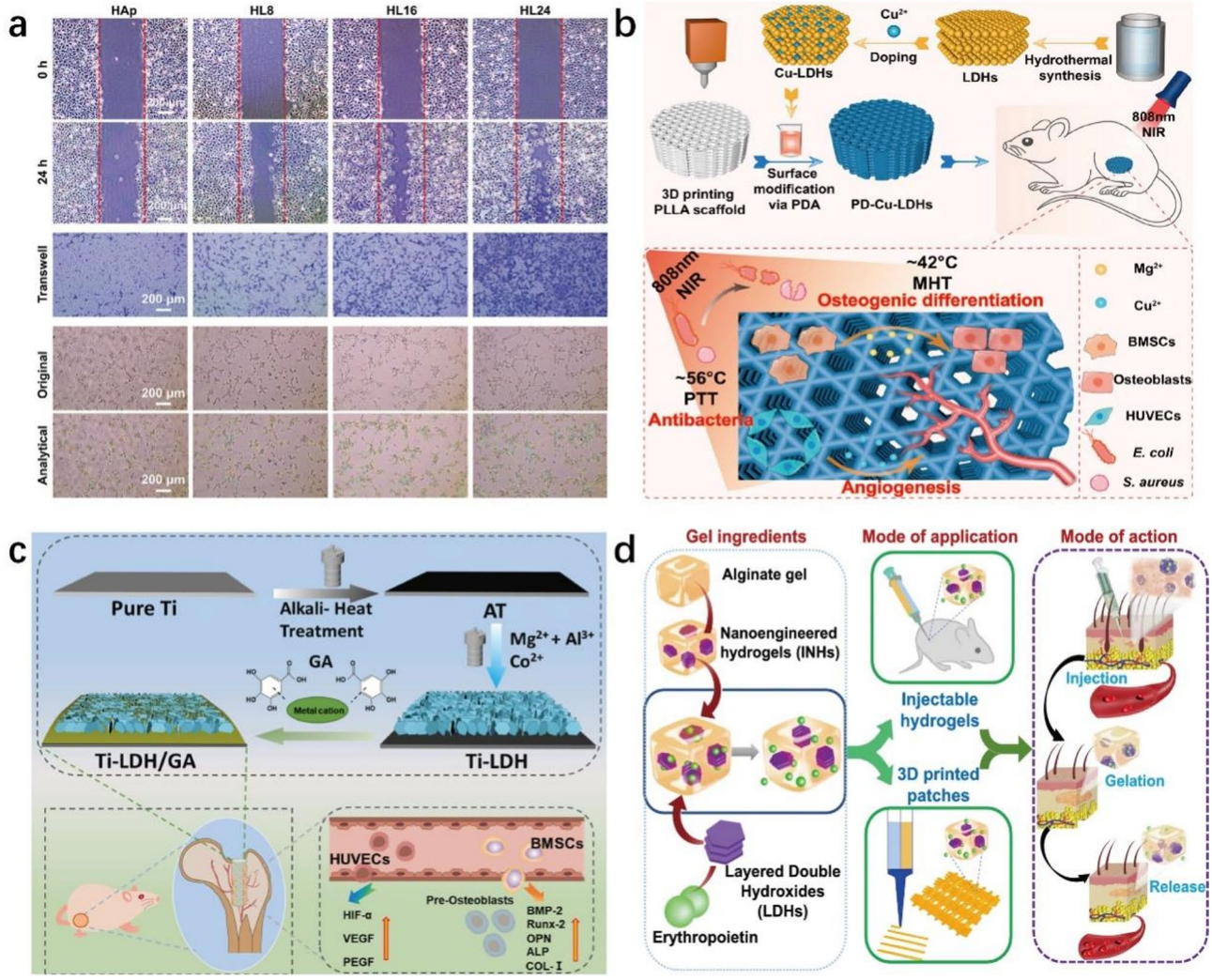

Fig. 8 (**a**) Optical microscope images of HAp and HL scaffolds cultured with different concentrations of LDH, results of Transwell assay and Matrigle assay. Reprinted with permission from Ref [27]. Copyright (2022) John Wiley and Sons. (**b**) Schematic structure of PU-Cu-LDHs. The scaffold effectively promotes angiogenesis through the MHT effect, PTT effect and the released Cu^{2+} and Mg^{2+}. Reprinted with permission from Ref [65]. Copyright (2023) American Chemical Society. (**c**) GA coating realizes a synergistic mechanism of improving osteogenesis efficiency and avoiding acute toxicity by regulating the release rate of Mg^{2+} and Co^{2+} ions. Reprinted with permission from Ref [176]. Copyright (2024) Elsevier. (**d**) Schematic diagram of the operation of INHs. EPO-loaded INHs and their utilization, and the effect of slow release of INHs implanted in situ in the mouse subcutaneous tissue on tissue regeneration. Reprinted with permission from Ref [181]. Copyright (2023) Springer Nature

The post-loaded LDHs exhibited greater efficacy in promoting HUVECs migration and tube formation compared to pre-loaded LDHs. Similarly, Pang et al. [181] embedded erythropoietin (EPO) within the interlayer space of MgAl-LDHs and integrated the drug-loaded LDHs into alginate hydrogels (Alg-Gel) to create nanoengineered injectable hydrogels (EPO-INHs)(Fig. 8d). Compared to EPO-loaded Alg-Gel (EPO-Alg-Gel), EPO-INHs released only one-fourth of the drug over the same period, avoiding an initial burst release and ensuring sustained action. In a chicken chorionic allantoic membrane (CAM) assay, EPO-INH implantation resulted in 43 neovessels after 15 days, compared to 28 in the EPO-Alg-Gel group.

In conclusion, LDHs have demonstrated significant potential in promoting angiogenesis. However, their underlying mechanisms remain unclear. Future research should explore their effects on endothelial cell proliferation, migration, and differentiation. ①Proliferation: Endothelial cells require rapid activation of mitochondrial oxidative phosphorylation during early proliferation stages [182]. It remains unclear whether LDHs influence this process by modulating mitochondrial function. Notably, metabolic reprogramming induced by 2D nanomaterials offers a novel perspective on angiogenic regulation. While pathways such as MAPK and PI3K/Akt are well-established in endothelial proliferation, emerging mechanisms involving the Notch pathway and

autophagy may also play roles in mediating LDH effects on endothelial dynamics [183, 184]. ②Migration: LDHs may influence endothelial migration via integrin/focal adhesion signaling or by activating mechanosensitive membrane proteins during endocytosis, thereby regulating F-actin polymerization and filopodia extension. However, these mechanisms remain speculative and require further experimental validation. Additionally, reactive oxygen species (ROS), traditionally regarded as cytotoxic, are now recognized as key modulators of cell signaling. At low concentrations, ROS can enhance endothelial migration [185]. The dual regulatory role of ROS in angiogenesis has been exploited by other nanomaterials, and it remains to be seen whether LDHs exhibit similar properties. ③ Differentiation: Certain 2D nanomaterials can mimic microenvironmental cues—such as low substrate stiffness and dynamic shear stress—present during embryonic development, thereby inducing stem cell differentiation toward the endothelial lineage. These materials activate transcription factors such as ETV2, ERG, and FLI1, effectively reinitiating developmental gene programs [186, 187]. This conceptual framework could be leveraged to investigate LDH-mediated endothelial differentiation. Nevertheless, all proposed mechanisms require extensive experimental validation to elucidate the specific roles of LDHs in angiogenic modulation.

Skin wound healing

The skin, serving as the body's primary defense against external stimuli, is highly susceptible to injury and damage [188]. While common skin wounds typically heal through natural processes, larger full-thickness defects, infected wounds, and inflammatory injuries often experience delayed or prolonged healing [189]. Developing bioactive tissue regeneration dressings is an effective strategy to accelerate the healing process. This section highlights recent advances in the application of LDHs for both normal and infected wound treatments.

LDHs on common skin wounds

Certain LDHs promote skin soft tissue repair due to their inherent composition. Fibroblasts play a key role in wound repair. Fernandes et al. [190] studied the effects of LDHs with different compositions on fibroblasts. ZnAl-LDH can significantly promote the proliferation of fibroblasts. After being treated with it, the expressions of the cyclin-dependent kinases CDK2 and CDK6 increase by approximately 30 times. At the same time, ZnAl-LDH has been demonstrated to induce the rearrangement of the cytoskeleton and enhance the adhesion and migration of fibroblasts. This is achieved by inhibiting the activity of PP2A, thus promoting the phosphorylation of the filament-cutting protein cofilin at the Ser03 site. While MgAl-LDH was found to be able to affect the remodeling of the extracellular matrix (ECM). The remodeling of the ECM plays an important role in wound healing [191, 192]. The potential mechanisms by which MgAl-LDH regulates the ECM mainly include the following three aspects. Firstly, LDHs can directly regulate the components of collagen in the ECM, thereby affecting the structure and function of the ECM. After treating fibroblasts with MgAl-LDH, the expression of Col-1a1 is down-regulated, while the expression of Col-3a1 is up-regulated. Secondly, matrix metalloproteinases (MMPs) and their inhibitors play a crucial role in the degradation and remodeling of the ECM. MgAl-LDH can promote the activity of MMP2. At the same time, it up-regulates the gene expressions of MMP-related inhibitors (such as TIMP1, TIMP2 and RECK). This enables the degradation and synthesis of the ECM to reach a balance, which is beneficial for wound healing. Third, during the early phases of healing, MgAl-LDH upregulates pro-inflammatory factors such as TNF-α and NF-κB, facilitating ECM degradation and the clearance of pathogens and necrotic debris. In the later stages, it activates the Sonic Hedgehog signaling pathway, which exerts anti-inflammatory effects, promotes fibroblast migration and proliferation, stimulates ECM secretion, and accelerates wound closure.

LDHs can also enhance skin healing through drug loading. For example, Mohammadi et al. [193]intercalated curcumin into MgAl-LDH and developed nanocomposite dressings by incorporating LDHs into polyurethane films. LDHs significantly improved the bioavailability and sustained release of curcumin, promoting essential processes such as fibroblast proliferation, migration, and re-epithelialization(Fig. 9c, d,e). Furthermore, Figueiredo et al. [60] intercalated NAP between Mg_4FeAl-LDH and Zn_4FeAl-LDH layers and integrated these LDHs into an elastomeric block copolymer, polyether-block-amide (PEBA). The LDHs enhanced PEBA's mechanical properties, modulated NAP release, and provided Mg^{2+}, Zn^{2+}, and Al^{3+} ions to aid wound healing (Fig. 9a). Additionally, Shiny et al. [194]designed a MgAl-LDH loaded with arginine and bacitracin within a nanofibrous poly-3-hydroxybutyric acid (P) and sodium alginate (S) matrix featuring a core-shell structure. This design allowed for the controlled delivery of biomolecules, facilitating wound contraction and collagen deposition.

The development of LDHs-based multifunctional composite dressings offers a promising strategy for enhanced wound healing. Zhang et al. [195] modified gelatin with MgFe-LDH and dopamine (DA) to create a composite hydrogel (G/DA@LDH) with adhesive, anti-inflammatory, and pro-healing properties (Fig. 9f). MgFe-LDH improved the hydrogel's mechanical strength by promoting polymer chain entanglement and established an alkaline environment conducive to healing. The composite

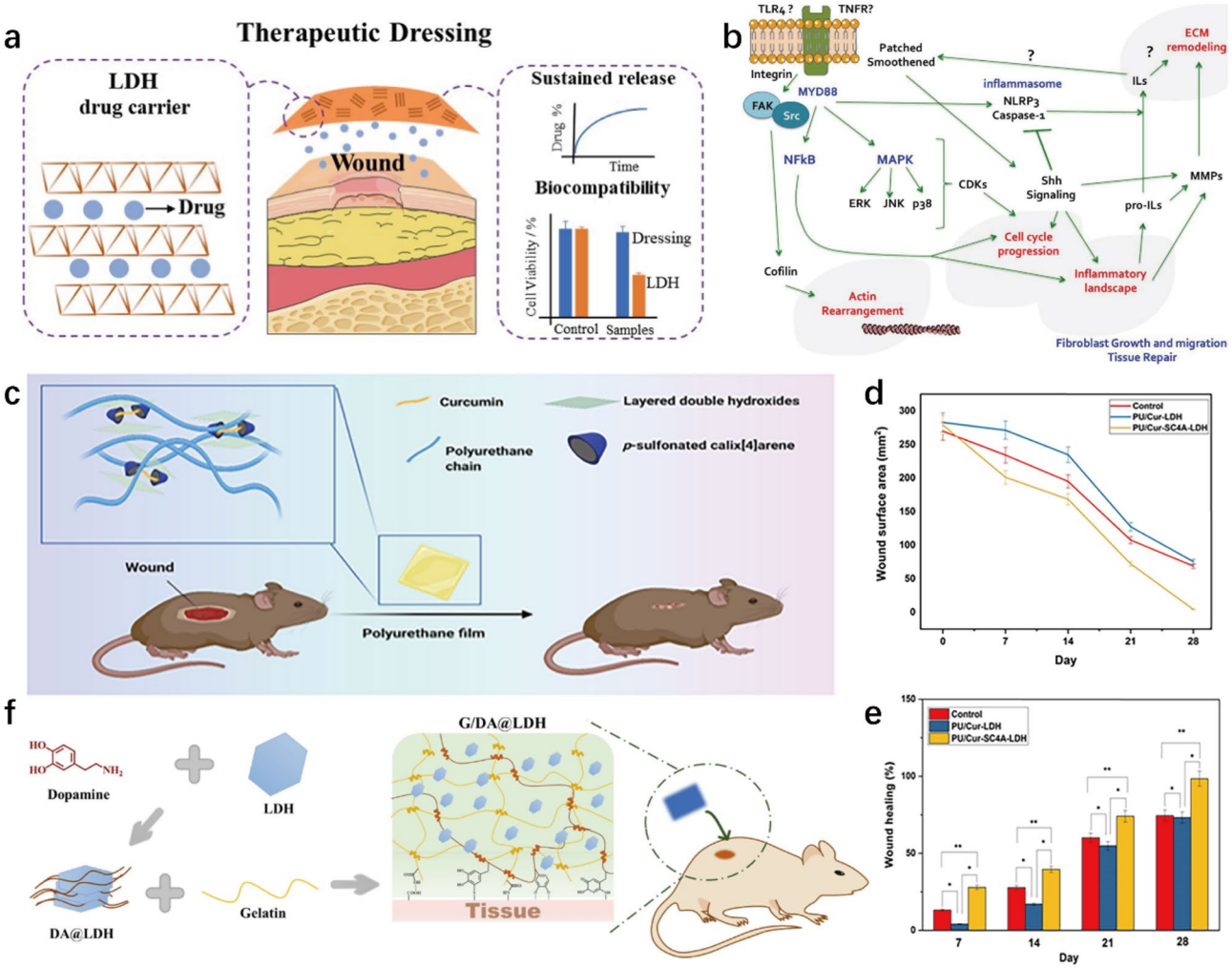

Fig. 9 (**a**) NAP-loaded MgFe-LDH/polymer composite accelerates wound closure by 40% through sustained Mg^{2+} release and ECM remodeling. Reprinted with permission from Ref [60]. Copyright (2020) MDPI. (**b**) Schematic diagram of the mechanism of LDH promoting wound healing by regulating NF-κB and MAPK signaling pathways. Reprinted with permission from Ref [190]. Copyright (2019) John Wiley and Sons. Schematic representation of the (**c**) wound healing process, (**d**) wound surface area, and (**e**) percent wound healing for PU/Cur-LDH and PU/Cur-SC4A-LDH treatments. Reprinted with permission from Ref [193]. Copyright (2022) American Chemical Society. (**f**) Schematic representation of G/DA@LDH formation. Reprinted with permission from Ref [195]. Copyright (2024) MDPI

hydrogel group containing LDHs significantly enhanced L929 cell migration compared to the control group. Additionally, in the full-thickness skin wound model of SD rats, this group exhibited a faster wound healing rate. The regenerated tissue had a thicker keratinized layer, with more organized collagen fibers. In studying anti-inflammatory properties, the author used nitric oxide (NO) production by RAW264.7 cells upon stimulation as a key inflammatory indicator. The addition of MgFe-LDH significantly reduced NO production, with a reduction exceeding 50%. The mechanisms through which LDHs exert their inflammatory regulatory effects include the following: First, certain metal ions in LDHs possess anti-inflammatory properties. For example, Mg^{2+}, Zn^{2+}, and others effectively inhibit pro-inflammatory factors while up-regulating anti-inflammatory factors, thereby inhibiting inflammation at the molecular level. Second, some LDHs exhibit antioxidant effects, inhibiting chronic inflammation induced by oxidative stress [196]. Additionally, the immunomodulatory effect of LDHs promotes M2 polarization of macrophages, exerting anti-inflammatory effects.

In conclusion, LDHs exhibit significant promise as biomedical nanomaterials for skin soft tissue regeneration. However, skin wound healing progresses through four stages: hemostasis, inflammation, proliferation, and remodeling. A single LDH material is unlikely to be effective across all stages, making the combined use of multiple materials to create multifunctional LDH-based dressings a strategic approach for comprehensive healing. Additionally, as living standards improve, wound treatments increasingly prioritize restoring skin function and

aesthetics. Future studies could investigate areas such as sensory restoration, hair follicle regeneration, scar reduction, and pigmentation control.

LDHs acting on infected wounds

Infections in skin wounds can significantly hinder the healing process [197], making infection control essential for recovery. Research on LDHs in wound healing has primarily centered on their antimicrobial applications. LDHs possess multiple antibacterial mechanisms. These mechanisms will be discussed from three aspects: (1) LDHs utilize the metal ions in their composition for antibacterial activity; (2) LDHs exploit their nanozyme properties to generate reactive oxygen species (ROS) for antibacterial effects; and (3) antibacterial effects are achieved through drug delivery via LDH systems.

Certain LDHs possess inherent antibacterial properties. Their positively charged surfaces target negatively charged bacteria and hydrolyze in the acidic microenvironment of infected sites, releasing antimicrobial metal ions. These ions inhibit bacterial growth by disrupting surface charge distribution, inducing protein denaturation, or inactivating bacterial DNA [10, 11, 56, 198]. Examples include CuAl-LDH, NiAl-LDH, CoAl-LDH, and MnAl-LDH, which exhibit bacteriostatic effects against *E. coli* and *S. aureus* (Fig. 10a) [50]. However, the exact mechanisms of action remain unclear. Further research is needed to elucidate how LDHs interact with bacterial membranes, proteins, enzymes, and genetic material. In particular, the resistance mechanism of LDHs to pathogen biofilms should be elaborated using more stable in vivo and in vitro models.

Nanoenzyme-driven ROS therapy has emerged as a promising approach for treating wound infections. Although most ROS production requires external stimuli, certain LDHs exhibit intrinsic nanoenzymatic properties that enable them to generate high ROS concentrations without modifications or external energy input. For instance, CuFe-LDH demonstrates oxidase-like activity, producing ROS such as singlet oxygen ($^1O_2$), superoxide radicals ($\cdot O_2^-$), and hydrogen peroxide (H_2O_2), while its peroxidase-like function converts H_2O_2 into hydroxyl radicals ($\cdot OH$). This dual activity effectively inhibits methicillin-resistant *Staphylococcus aureus* (MRSA) in mice and accelerates wound healing (Fig. 10e) [67]. Similarly, hollow MnNi-LDHs, developed by Zhang et al. [68], generate ROS without needing external H_2O_2 and exhibit strong antibacterial effects against *E. coli* and *S. aureus*. Their hollow structure and layered surface enhance bacterial capture. In vivo studies demonstrated that MnNi-LDHs could clear infections without drug loading (Fig. 10d). Future designs integrating hollow structures with drug delivery systems may further enhance their antimicrobial and healing capabilities.

LDHs also serve as efficient carriers for antibiotic delivery, improving drug internalization and controlling infections at the wound site. Yoosefi et al. [199] developed composite nanofiber dressings LDH-VAN/IBU/CMC-PEO(LICs) by electrospinning vancomycin (VAN) intercalated into MgAl-LDH (LDH-VAN) and blending it with IBU and carboxymethylcellulose-polyethylene oxide (CMC-PEO). The LDH component enhanced the mechanical properties of LICs and prevented the rapid release of VAN. In vivo experiments showed that LICs significantly promoted wound healing with optimal re-epithelialization. Similarly, Li et al. [200]loaded enoxacin (ENO) into MgAl-LDH and incorporated the resulting LDH-ENO nanoparticles into polyurethane-polyvinyl alcohol (PU-PVA) hydrogels. This dual-carrier system improved both the mechanical properties and biocompatibility of the hydrogel, while delaying ENO release. Another example is the intercalation of silver sulfadiazine (SDZ) into MgAl-LDH, followed by embedding it in either a polylactic acid (PLA) scaffold or a sodium ALG matrix. Both dressings demonstrated strong antibacterial activity against *E. coli* and *S. aureus* and good compatibility with fibroblasts [201, 202]. Additionally, Du et al. [203] developed triboelectric nanogenerator patches (TENGs) by combining minocycline-loaded MgAl-LDH with polytetrafluoroethylene (PTFE) and flexible polymer substrates. The patches generate mild electrical stimulation at the wound site while releasing antibiotics, promoting wound repair (Fig. 10b, c).

In summary, LDHs play a versatile role in treating infected skin wounds. They exhibit antimicrobial effects through metal ion release, ROS generation, and targeted drug delivery with controlled release, enhancing overall efficacy. However, most studies have focused on single-pathogen infections, whereas real-world wound infections often involve multiple microorganisms with synergistic effects that complicate treatment. To address this, future research should assess LDHs' effectiveness in mixed infections. In addition, although some studies indicate that specific LDHs possess antifungal properties, in vivo research on fungal wound infections remains limited due to the challenges in developing reliable animal models. Developing LDHs-based comppsites with well-defined antifungal effects is crucial for treating fungal infections, which often require prolonged treatment and are costly. Moreover, as bacterial resistance evolves, using LDHs as drug carriers alone may not fully mitigate antibiotic resistance. Innovative approaches, such as loading non-antibiotic bioactive agents—including tetrahedral framework nucleic acids (tFNAs), defensins, bacteriophages, and probiotics—may provide effective alternatives [204].Finally, there is concern over the potential risks of microbial mutations induced by LDHs as nanomaterials, which could cause DNA damage and epigenetic changes, possibly altering drug resistance.

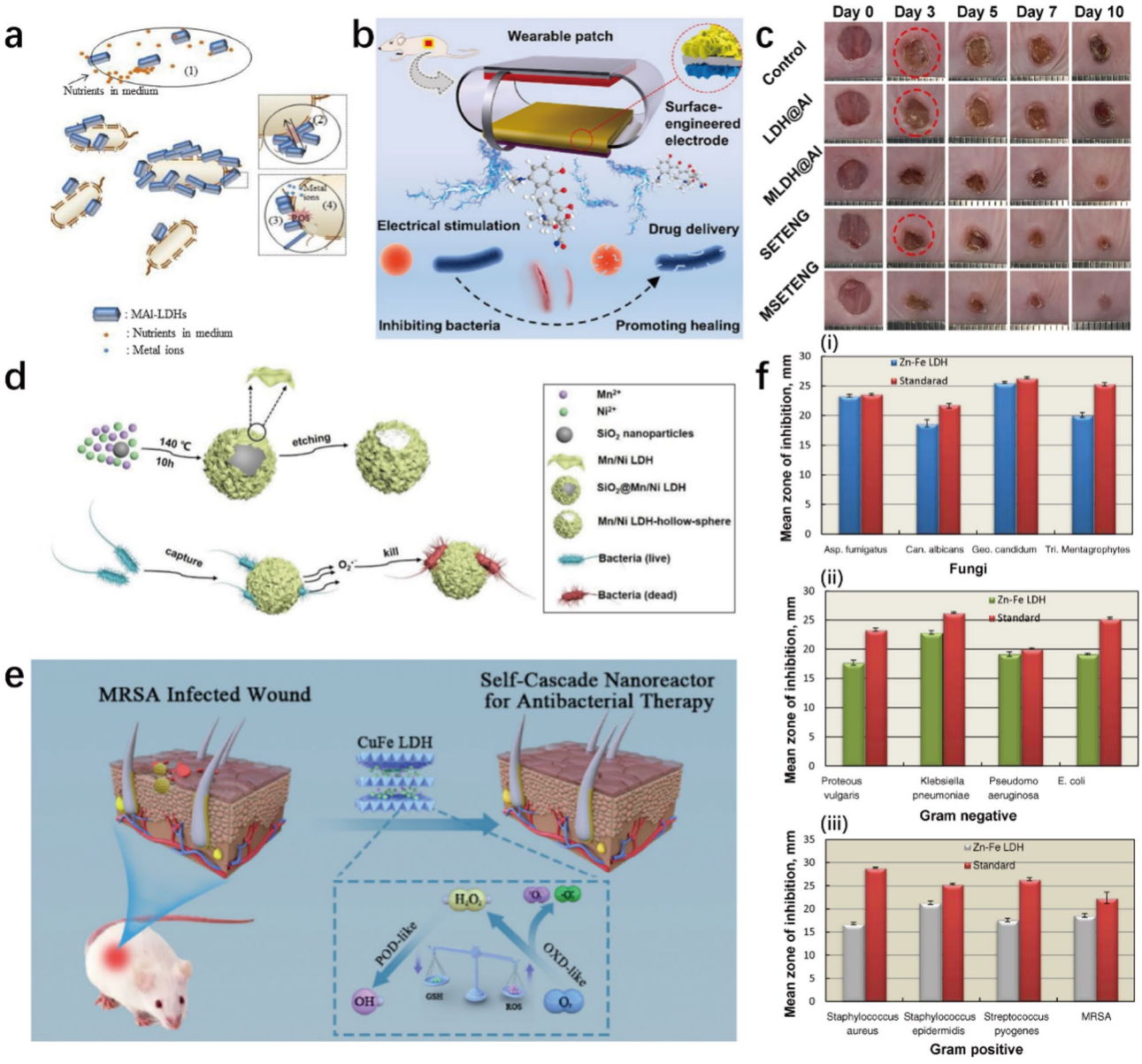

Fig. 10 (**a**) Schematic representation of the possible antimicrobial mechanism of MAl-LDHs against *E. coli*. Reprinted with permission from Ref [50]. Copyright (2020) Elsevier. (**b**) TENG patch promotes vascular endothelial cell proliferation and antimicrobial drug delivery through electrical stimulation, achieving a synergistic mechanism for improving the healing efficiency of infected wounds.Reprinted with permission from Ref [203]. Copyright (2021) Elsevier. (**c**) Representative photographs of skin wounds at different time periods after wearing different patches and quantification of the wound area. Reprinted with permission from Ref [203]. Copyright (2021) Elsevier. (**d**) Schematic representation of synthesis strategy of nanoenzymes and antimicrobial properties of nanoenzymes. Reprinted with permission from Ref [68]. Copyright (2020) John Wiley and Sons. (**e**) CuFe LDH as a self-cascading nanoreactor for MRSA-infected wound therapy. Reprinted with permission from Ref [67]. Copyright (2023) American Chemical Society. (**f**) ZnFe-LDH exhibits broad-spectrum antibacterial activity against E. coli and S. aureus (90% inhibition rate) via ROS generation and membrane disruption. Reprinted with permission from Ref [61]. Copyright (2016) Elsevier

Addressing this risk is critical to ensuring the long-term safety and efficacy of LDHs-based treatments.

Nerve regeneration

Exogenous injuries, degenerative lesions, and other factors can damage nerve tissue, posing significant challenges for autonomous repair and regeneration [205]. LDHs have shown potential in addressing these challenges by regulating stem cell fate, promoting neurogenesis, and reducing neuroinflammation. Their exceptional physicochemical properties—such as a high surface area-to-thickness ratio and flexible compositional tunability—offer promising avenues for treating neurological damage. This section highlights recent advances in using

LDHs for nerve repair and regeneration, focusing on pristine LDHs, LDHs drug delivery systems, and LDHs-based composites.

Pristine LDHs mainly contribute to nerve regeneration through two primary mechanisms: modulating stem cell neural differentiation and remodeling the local immune microenvironment. Regarding stem cell differentiation, LDHs exhibit component-dependent functional specificity. For instance, MgAl-LDH has been shown to promote the differentiation of embryonic stem cells (ESCs) into neural progenitor cells (NPCs) [142], indicating strong potential in neuroregenerative applicationsMechanistically, MgAl-LDH upregulates the methyltransferase METTL3, which leads to an increase in the m6A level in the mRNA of the NPCs marker Sox1. This results in increased Sox1 gene and protein expression, which in turn enhances the transcription of other NPCs markers and significantly drives ESCs differentiation into NPCs(Fig. 11e). Notably, this regulatory effect exhibits size dependence; 100 nm LDHs demonstrate a stronger capacity to induce NPC differentiation compared to 30 nm and 50 nm variants. MgAl-LDH has also been implicated in facilitating the differentiation of ESCs into motor neurons [141]. Compared with untreated controls, LDH treatment produced a higher number of mature motor neurons and increased expression of motor neuron-specific markers. The pro-differentiation effect of LDHs begins with enhanced cell adhesion and is governed by several signaling pathways, including the Itga10/Itgb8-mediated focal adhesion pathway, the Htr2b-mediated neuroactive ligand-receptor interaction pathway, and the Cacna1-mediated calcium signaling pathway. These pathways collectively influence neural development and support the formation of functional neural networks. In addition, MgFe-LDH has been shown to promote neural stem cell differentiation into neurons while limiting astrocyte formation.When integrated into nanofiber scaffolds and transplanted into a mouse model with spinal cord transection, MgFe-LDH significantly enhanced neuronal regeneration, axonal growth, and neural circuit remodeling [206]. Transcriptome analysis further highlighted the key roles of the RhoA/Rock/Myosin II pathway and the neuroactive ligand-receptor interaction pathway in spinal cord injury repair by the material. Additionally, apart from promoting neural stem cell differentiation, LDHs can overcome obstacles to neuron and axon regeneration by enhancing the immune microenvironment [207]. For instance, in the study of Zhu et al. [143], MgAl-LDH exhibits excellent properties in suppressing the inflammatory response and accelerating nerve regeneration. MgAl-LDH implantation has demonstrated improved motor and electrophysiological recovery in spinal cord-injured mice. The transforming growth factor β receptor 2 (TGFBR2) may serve as the target receptor for LDHs. LDHs activate TGFBR2, downregulate Smad2/3 expression, and promote the M2 polarization of microglia and bone marrow-derived macrophages. This reduces TNF-α expression and increases IL10 expression, creating a favorable immune microenvironment for neural stem cell proliferation and differentiation, thereby promoting neurogenesis.

LDHs drug delivery systems offer controlled release and enhanced stability of neurotrophic factors and neuroprotective agents. The neurotrophic factor NT3, crucial for neuronal growth and synaptic formation [208], faces challenges related to low concentration and instability at injury sites. To address this, Zhu et al. [143] loaded NT3 into MgAl-LDH, protecting its structure and function through the LDH's nanosize and bilayer characteristics while enabling slow, pH-responsive release over three months (Fig. 11a, b). Compared to MgAl-LDH alone, LDH-NT3 exhibited superior motor recovery and neuronal regeneration. Similarly, Zhang et al. [24] incorporated NT3 into MgFe-LDH and paired it with ultrasound (US) therapy. This combination, likely mediated by Piezo1 downregulation, promoted spinal cord repair (Fig. 11c). In another study, Wang et al. [209] utilized MgAlGd-LDH to deliver atorvastatin (ATO) and a blood-brain barrier transporter (ferritin heavy subunit, FTH), forming AFGd-LDH. This system demonstrated biocompatibility, blood-brain barrier penetration, antioxidant activity, and neuroprotective effects, significantly reducing neuronal apoptosis and oxidative damage in a mouse ischemia-reperfusion model. A major highlight of this study is the application of FTH. FTH binds to transferrin receptor 1 (TfR1) on endothelial cells, facilitating the LDH carrier system's passage through the blood-brain barrier. In vivo fluorescence labeling revealed strong fluorescence signals in the brain regions of mice 3 and 5 h after AFGd-LDH injection. However, no fluorescence signal was detected in the brain regions of mice treated with the LDH carrier without FTH (AGd-LDH). This suggests that LDHs alone cannot cross the blood-brain barrier and must be modified with other substances.Meneses et al. [76] developed another LDH complex (LDH-INDO) by loading indomethacin (INDO), an anti-inflammatory agent, to minimize side effects during neurodegeneration.

LDHs-based composite scaffolds represent an emerging approach to nerve injury repair. Zhang et al. [210] developed a gelatin-chitosan(GC)-LDH/A scaffold by combining MgFe-LDH, gelatin, and chitosan, using anisotropic freeze-drying to achieve a microchannel structure. These scaffolds serve three key functions: promoting neurogenesis, guiding axonal growth, and improving the local inflammatory microenvironment. Mechanistically, LDHs enhance neuronal differentiation and inhibit inflammation by regulating TGFBR2 activity (Fig. 11d). In vivo studies demonstrated partial motor

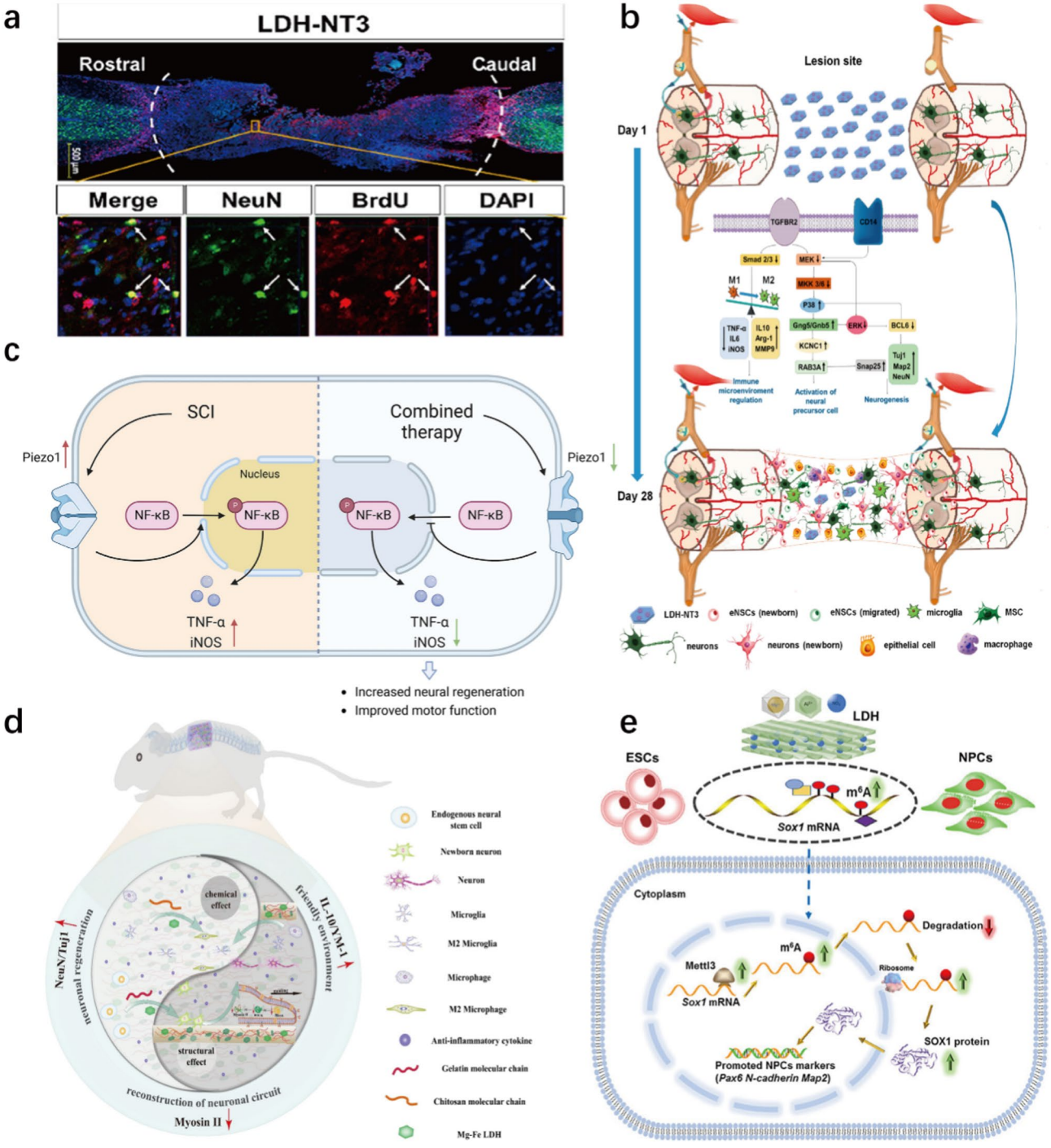

Fig. 11 **a**) LDH-mediated NT3 delivery enhances spinal cord repair: axonal regeneration and functional recovery in a murine model. Reprinted with permission from Ref [143]. Copyright (2021) American Chemical Society. **b**) Flowchart of LDH-NT3 transplantation promoting nerve regeneration and neural circuit reconstruction after spinal cord injury by activating eNSCs differentiation and inhibiting microglia inflammatory response. Reprinted with permission from Ref [143]. Copyright (2021) American Chemical Society. **c**) Piezo1 inhibits TNF-α release by regulating the NF-κB signaling pathway, realizing a dual mechanism of reducing inflammation in vitro and increasing the efficiency of nerve regeneration in vivo. Reprinted with permission from Ref [24]. Copyright (2023) BMC. **d**) The GC-LDH/A scaffold promotes neural stem cell proliferation and the formation of an anti-inflammatory microenvironment by releasing Mg^{2+} and Al^{3+} ions, realizing a synergistic mechanism for neural function recovery. Reprinted with permission from Ref [210]. Copyright (2023) Elsevier. **e**) LDH regulates the directional differentiation of embryonic stem cells into neurons through m^6A modification of Sox1 mRNA, promoting the expression of neural progenitor cell differentiation markers. Reprinted with permission from Ref [142]. Copyright (2024) Dove Medical Press Ltd

function restoration in mice with spinal cord injuries. Ahmadi et al. [105] advanced this concept by incorporating MgAl-LDH into a PCL/GEL composite, creating nanofibrous scaffolds (PCL/GEL/LDH) through electrospinning. The inclusion of LDHs significantly improved the mechanical properties of the scaffolds and enhanced neuronal growth and differentiation compared to PCL/GEL alone.

In summary, LDHs exhibit considerable potential in promoting nerve regeneration. However, further in-depth research is required in several key areas. First, a primary challenge in targeted central nervous system (CNS) repair is the restricted transport across the blood–brain barrier (BBB). LDHs alone cannot traverse this barrier, but functional modifications offer a promising solution: ① Receptor-Mediated Transport: Ligands can be designed to target specific receptors on the surface of endothelial cells—such as transferrin receptors (TfR), lactoferrin receptors (LfR), and the low-density lipoprotein receptor family—and conjugated to LDHs to facilitate translocation across the BBB [211]. ②Carrier-Mediated Transcytosis: Transport proteins like glucose transporter (GLUT) and large neutral amino acid transporter 1 (LAT-1) may be employed to carry LDHs across the BBB [212]. ③Transcellular Lipophilic Transport: Nanoplatforms with high lipophilicity show favorable BBB permeability. Accordingly, liposomes or nano-lipid carriers encapsulating LDHs could provide an effective delivery route [213]. ④Nasal Delivery: Intranasal administration via the olfactory epithelium is an emerging strategy for CNS drug delivery and has been increasingly applied in the treatment of neurological disorders [214, 215]. ⑤Physical Strategies: Recent advances in physical modulation—such as magnetic fields, lasers, and focused ultrasound—have demonstrated the ability to transiently enhance BBB permeability. These techniques may also be applied to facilitate LDHs delivery across the barrier. Second, while research on LDHs has predominantly focused on CNS repair, studies exploring their role in peripheral nerve regeneration remain limited. Addressing long-gap peripheral nerve injuries with LDH-based composite materials represents a significant avenue for innovation. Thirdly, the potential neurotoxicity of metal ions in LDHs should be considered. LDHs generally exhibit good compatibility with nerve tissues. For example, at 40 μg/mL, MgAl-LDH shows no cytotoxicity to neural stem cells [142]. After 72 h of MgFe-LDH treatment, no significant difference in viability was observed in NSCs and mouse microglia cells (SIM-A9) [24]. Treatment with 50 μg/mL AFGd-LDH maintained over 90% viability in pheochromocytoma 12 cells(PC12) [209]. However, certain metal ions (e.g., Mn^{2+}, Cd^{2+}, Cu^{2+}) have been reported to exhibit neurotoxicity [216–218]. When using LDHs containing these ions, their concentrations must be carefully controlled. Furthermore, the integration of multiple nanotechnologies holds strong potential in nerve regeneration. For instance, nanofibers offer excellent biocompatibility, controlled biodegradability, and a structural resemblance to the extracellular matrix, promoting cell adhesion and proliferation. These properties make them highly suitable for regenerative applications such as nerve repair and wound healing [219–221]. However, their mechanical properties may require enhancement; and they lack the characteristics such as ion exchange and pH degradation that LDHs possess. By integrating LDHs with nanofiber systems, it is possible to synergize their respective strengths and achieve superior regenerative outcomes.

Other tissue regeneration applications

The application of LDHs in tissue regeneration extends beyond aforementioned fiels and demonstrates significant promise in dentistry and ophthalmology, offering versatile solutions for regenerative medicine.

In dentistry, maintaining low fluoride concentrations in the oral environment inhibits enamel demineralization, enhances remineralization, and suppresses bacterial growth, effectively preventing or treating dental caries [222]. Conventional fluoride treatments, such as toothpaste and mouthwash, often fail to provide sustained, low-dose fluoride release [223]. MgAl-LDH and CaAl-LDH overcome this limitation by enabling long-term, controlled fluoride ion release through their anion-exchange properties(Fig. 12a) [223, 224]. This capability has led to the development of fluoride reservoirs, including LiAl-F LDH [78] and LDH-F/MA [79] (Fig. 12b), which are incorporated into light-curing resin materials to create composite resins with enhanced mechanical properties and long-term fluoride release and reuptake, promoting sustained tooth remineralization. Researchers have also explored combining LDHs with other ions to boost remineralization. For instance, Bernardo et al. [80] incorporated phosphate into ZnAl-LDH through structural modification, creating a smart dental material capable of slowly releasing phosphate ions in response to environmental cues, further promoting enamel repair. LDHs not only facilitate remineralization of dental tissues but also find application in oral antibacterial treatments and enhancing soft tissue sealing around implants. Luo et al. [225] demonstrated that CuAl-LDH eliminates oral bacteria through Fenton-like catalytic activity, promoting mucosal healing and periodontal remodeling. Yin et al. [226] observed that MgFe-LDH enhances gingival fibroblast adhesion and proliferation around implants by modulating local pH.

In ophthalmology, LDHs have primarily been studied for corneal regeneration and drug delivery. The corneal stroma plays a crucial role in maintaining corneal

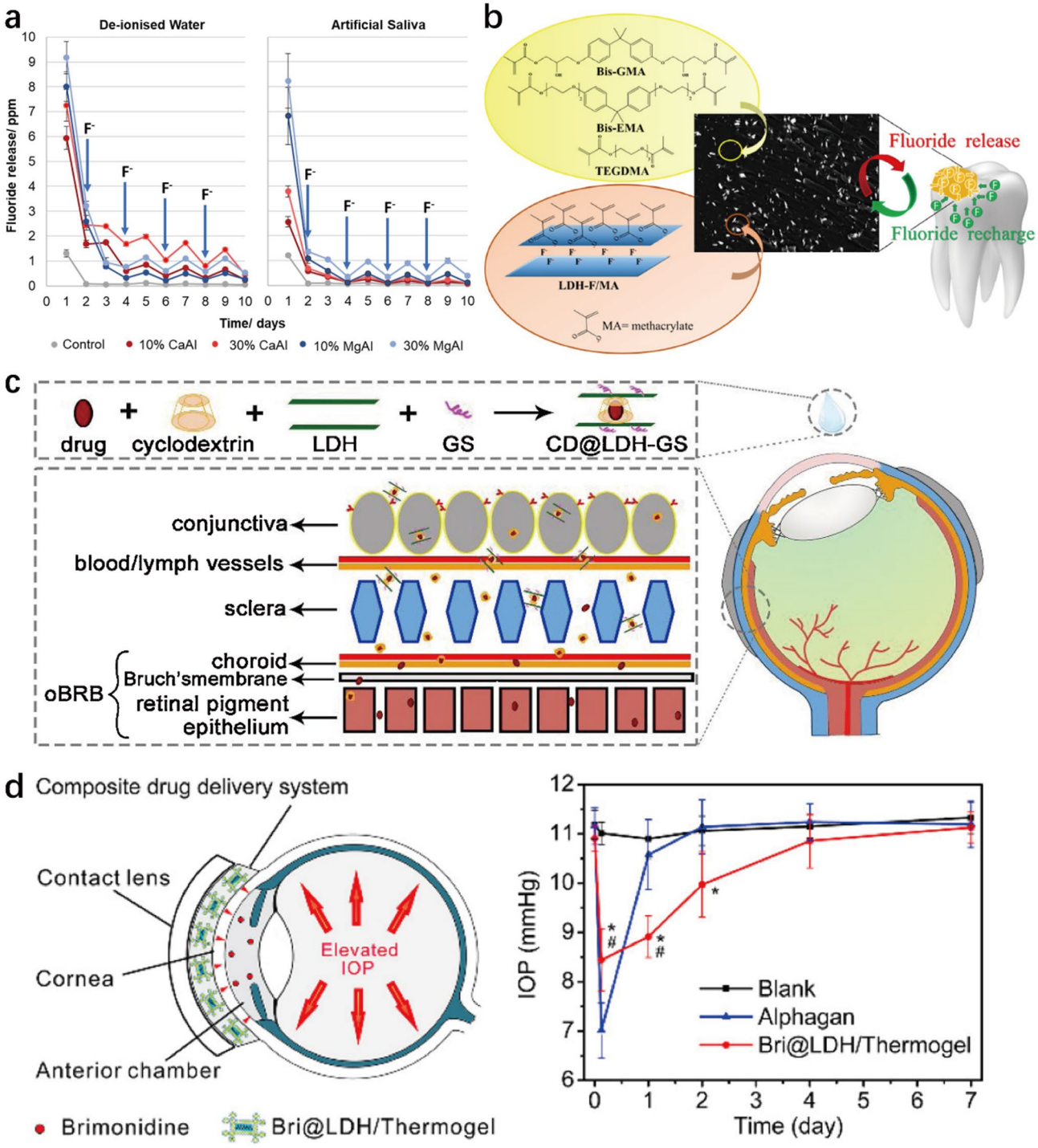

Fig. 12 (**a**) Quantitative analysis of MgAl-LDH dental resin continuously releasing fluoride ions (0.05–0.15 mg/L/day) within 10 days and reducing enamel demineralization. Reprinted with permission from Ref [224]. Copyright (2020) Elsevier. (**b**) Schematic diagram of the specific structure of LDH-F/MA and its fluorine release characteristics. Reprinted with permission from Ref [79].Copyright (2020) Elsevier. (**c**) Schematic design of multifunctional dexamethasone-carboxymethyl-β-cyclodextrin@laminar double hydroxide-glycine carnosine(DEX-CM-β-CD@LDH-GS) and schematic drug diffusion pathway of DEX-CM-β-CD@LDH-GS nanocomposite eye drops. Reprinted with permission from Ref [230]. Copyright (2021) Elsevier. (**d**) Quantitative analysis of Bri@LDH/Thermogel Drug delivery system reducing intraocular pressure (IOP) by 2.3 mmHg within 7 days compared to the Alphagan group (from 11.5 mmHg to 9.2 mmHg), with a drug sustained-release period of up to 5 days. Reprinted with permission from Ref. Copyright (2017) American Chemical Society

transparency and mechanical integrity, with severe stromal damage potentially leading to blindness. While corneal transplantation is the primary treatment [227], the shortage of suitable donors has spurred research into functional biomaterials. For instance, nanocomposite scaffolds (PUU-VC-LDH) were developed by incorporating vitamin C-loaded ZnAl-LDH into poly(urethane-urea) (PUU) scaffolds through electrospinning [228]. The slow-release capability of LDHs enables prolonged vitamin C delivery, stimulating extracellular matrix synthesis by corneal keratocytes. PUU-VC-LDH scaffolds upregulate key proteins, including ALDH3A1, and promote the proliferation and alignment of corneal stromal fibroblasts, offering promising prospects for corneal tissue engineering. LDHs are also gaining attention in ocular drug delivery. Conventional drug delivery to the posterior segment of the eye faces challenges such as short residence time and low drug concentrations at the target site [229]. Xu et al. [230] designed nanocomposite eye drops using LDHs as drug carriers, leveraging the proton sponge effect to deliver dexamethasone (DEX) through the conjunctival-scleral pathway, maintaining effective therapeutic levels in the choroidal retina for up to 3 h. This novel approach improves drug delivery from the ocular surface to the posterior eye segment(Fig. 12c). Similarly, Sun et al. [231] developed a sustained-release system by loading Brimonidine (Bri), a first-line glaucoma treatment, into MgAl-LDH and dispersing it in a thermogel (Bri@LDH/Thermogel). The thermogel forms a soft lens on the ocular surface, allowing controlled drug release for at least 7 days, effectively reducing intraocular pressure and minimizing dosing frequency (Fig. 12d).

In addition, LDHs have been explored for adipose tissue engineering. Uniform, bead-free PCL-MgAl-LDH composite fibers were fabricated using electrospinning [232]. LDHs enhanced the tensile strength, elongation at break, hydrophilicity, and degradation rate of the PCL scaffolds. Importantly, PCL-LDH scaffolds promoted the adhesion, proliferation, and adipogenic differentiation of mouse adipose-derived stem cells (mADSC), highlighting their potential in adipose regeneration applications.

Limitations and perspectives

Optimization of synthetic methods

The synthesis and preparation of LDHs are pivotal in determining their functional properties and ultimately their clinical efficacy [233]. Several challenges must be addressed to advance their biomedical application.

Foremost is the development of standardized synthesis protocols. Although numerous methods exist for LDH synthesis, the absence of harmonized standards hampers reproducibility and therapeutic consistency in tissue engineering. Establishing unified guidelines for synthesis and characterization would facilitate cross-study comparisons during the research and development phase, while also ensuring product safety and efficacy during clinical translation.

Second, existing synthesis techniques often suffer from issues such as low yield, limited purity, and heterogeneity in particle size, all of which constrain biomedical utility. Overcoming these limitations requires a comprehensive understanding of how key synthesis parameters—such as pH, temperature, reaction time, and metal ion ratios—affect the physicochemical characteristics of LDHs. Optimizing these variables is essential to achieving high-quality LDHs with enhanced structure and function.

Additionally, innovative synthesis methods are necessary. For example, an expandable microreactor with adjustable shear rates was developed, offering a novel method for precise control over crystallinity and particle size—a significant advancement in LDH synthesis [234].

Moreover, because biomedical materials are intended for human use, stringent quality control must be applied throughout the synthesis process. This includes strict regulation of raw materials, critical process parameters, and production conditions to ensure the consistency and stability of LDHs, particularly after clinical translation.

Enhancement of biosafety

The biosafety of nanomaterials is a fundamental prerequisite for their clinical adoption [235, 236]. LDHs generally exhibit favorable biocompatibility and low immunogenicity. Importantly, once their therapeutic functions are fulfilled, LDHs are gradually degraded and excreted via hepatic and renal pathways, minimizing the risk of long-term accumulation and toxicity [86, 237, 238]. To elucidate the degradation process, Cao et al. [239] utilized real-time transmission electron microscopy to observe the hydrolysis of FeAl-LDH at pH 5. The nanosheets began decomposing within 30 min, exhibited structural collapse after 2 h, and showed no residual particles at 4 h. This inherent degradability supports the in vivo safety profile of LDHs and reinforces their promise as a clinically translatable nanomaterial.

Despite significant advancements, the long-term in vivo safety assessment of LDHs remains inadequate, posing a challenge to their clinical translation. We identify the following key research gaps: ① There is a lack of systematic and continuous studies tracking the full biological "journey" of LDHs, including their biodistribution, degradation pathways, metabolism, and clearance. Notably, LDHs with varying compositions may exhibit distinct in vivo behaviors, underscoring the need for in-depth mechanistic understanding. ② Current analyses of LDH activity in vivo are largely dependent on discrete sampling methods and lack real-time monitoring capabilities. The development and application of advanced dynamic imaging and detection technologies are critical

for capturing the spatiotemporal interactions of LDHs with biological systems. ③ Most toxicity evaluations focus on short-term outcomes, with insufficient investigation into the effects of chronic exposure and long-term accumulation, both of which are crucial for establishing a comprehensive safety profile. ④ Although some studies have confirmed the complete degradation of LDHs in vivo, the potential adverse effects of high-concentration degradation byproducts on local tissues remain unclear and require further experimental validation. ⑤ Toxicological assessments should be aligned with standardized protocols, such as those recommended by the American Society for Testing and Materials (ASTM), to enhance consistency and regulatory relevance [240].

Improvement of stability

Stability is a critical determinant of the biological performance of two-dimensional nanomaterials, including LDHs, under both in vitro and in vivo conditions [241]. The primary challenges affecting LDHs stability in physiological environments are aggregation and degradation [242, 243]. Due to their positively charged surface and abundant hydroxyl groups, LDHs tend to aggregate, which impairs their biomedical applicability and translational potential. Surface functionalization and predispersion in hydrogels are two promising strategies to mitigate this issue. Among functionalization approaches, coating LDHs with bioactive molecules or organic polymers via non-covalent interactions (e.g., hydrogen bonding, van der Waals forces) has emerged as a mainstream method to enhance colloidal stability. For instance, serum albumin-functionalized LDHs have been developed as long-acting nanopharmaceuticals, which not only improve nanoparticle stability but also evade premature immune clearance, thereby prolonging systemic circulation time [244, 245]. Similarly, modification with polyethylene glycol (PEG) and its derivatives effectively reduces aggregation under physiological conditions, while enhancing both biocompatibility and therapeutic efficacy [242, 246]. Emerging materials such as alginate, mannose, and hyaluronic acid (HA) also hold promise for future surface engineering applications. In addition to surface modifications, uniformly dispersing LDHs within biodegradable hydrogels represents another viable strategy to enhance stability. These hydrogels can be applied to physiological sites such as bone defects or skin wounds, where they provide sustained release and support tissue regeneration—either through the intrinsic bioactivity of LDHs or the controlled delivery of encapsulated therapeutics.

The acidic sensitivity of LDHs further complicates their stability profile. While their pH-responsive degradability is advantageous for tissue regeneration, excessively rapid degradation can compromise therapeutic efficacy. Strategies to modulate degradation rates include increasing the thickness (number of layers) and particle size of LDHs [247], as well as secondary encapsulation using organic polymers (e.g., PVA, PCL), inorganic materials (e.g., silica), or bioactive carriers (e.g., liposomes). Nevertheless, achieving an optimal balance between degradability and structural stability remains a critical challenge, necessitating extensive experimental validation to optimize therapeutic outcomes.

Enhancement of drug-carrying capacity

The ability of LDHs to facilitate drug loading through electrostatic and hydrogen bonding interactions provides a key advantage over other nanomaterials used in tissue regeneration. However, there is still significant potential for improvement in aspects such as drug loading and delivery by LDHs.

In terms of loading capacity, one limitation is the restricted interlayer spacing of LDHs, which often confines them to loading small molecules and limits applications involving large molecules, such as therapeutic proteins. Exploring methods to regulate interlayer spacing for loading larger drugs is a promising direction. Additionally, while LDHs are typically used for anionic drug delivery, expanding their capacity to carry non-anionic drugs could broaden their application range. Achieving uniform drug distribution within layers and ensuring long-term stability also require further innovation.

In terms of drug delivery, targeted transport is a growing focus. Effective strategies may include packaging LDHs with cell membranes or exosomes, or hybridizing them with magnetic nanoparticles for directional transport via external magnetic fields. Another emerging approach involves the in situ synthesis of drugs at the target site using double orthogonal chemical reactions, offering a novel path for selective therapy [248].

Exploration of multifunctional composite materials

In recent years, significant efforts have been directed toward designing LDHs-based composites to integrate complementary functionalities and broaden their applicability in regenerative medicine. We believe several future research directions merit attention in this evolving field.

The integration of personalized medicine with tissue engineering is rapidly advancing regenerative medicine from a "one-size-fits-all" approach toward precision treatment. LDHs, with their tunable chemical compositions and structural versatility, offer promising potential for the customized design of tissue engineering scaffolds. ①The incorporation of different metal cations into LDHs imparts distinct tissue-repair functionalities. By tailoring the LDH composition to match a patient's specific tissue defect, more effective therapeutic outcomes can

be achieved. ② Surface functionalization of LDHs with polypeptides, polymers, or antibodies can facilitate the selective recognition of target cells or tissues, thereby enhancing therapeutic specificity. For instance, while pristine LDHs exhibit inherent immunomodulatory properties, conjugation with a CD68-targeting peptide enables them to specifically target macrophages. This targeted interaction promotes more efficient regulation of the local microenvironment and accelerates tissue regeneration. ③LDHs can also be integrated into 3D-printed bioinks, injectable hydrogels, or electrospun fibers to fabricate scaffolds tailored to the shape and dimensions of individual defect sites—further advancing the goals of personalized medicine. ④Additionally, LDH-based composites can serve as delivery platforms for genetic agents such as siRNA, miRNA, or CRISPR components, paving the way for individualized gene therapy strategies.

Secondly, beyond the photothermal effect, advanced stimulus-responsive LDHs-based composites, such as photodynamic, electric, magnetic, and ultrasound-responsive systems, are expected to enable precise control of tissue regeneration.

In addition, despite these advancements, systematic investigations into the effects of fabrication processes and material combinations on the performance of LDH-based composites remain limited. The integration of LDHs with organic polymers, biomolecules, or inorganic substrates may alter their inherent physicochemical properties, potentially impacting biocompatibility, mechanical integrity, and degradation profiles [249, 250]. A deeper understanding of these interfacial interactions is essential to optimize composite design for clinical use. Moreover, processing conditions can significantly influence critical attributes such as material homogeneity, functional stability, and overall efficacy. These interdependencies warrant further exploration to inform rational material development.

Promotion of clinical translation

The ultimate objective in this field is the clinical translation of LDHs for tissue regeneration. Although extensive in vitro and in vivo studies have demonstrated the therapeutic potential of LDHs, real-world applications, clinical trials, and intellectual property filings remain relatively limited.

In terms of clinical applications, commercial antacids represent the most established clinical application of LDHs. For example, Talcid® (Bayer), composed of MgAl–CO_3 LDH, is widely used to treat conditions such as peptic ulcers and gastroesophageal reflux disease.

In terms of clinical trials, some early-phase clinical trials have also been conducted. Fermagate, an MgFe-LDH based agent developed to treat hyperphosphatemia in patients with chronic renal failure, completed a Phase II trial but was discontinued in Phase III due to unspecified reasons [251]. Another candidate, an ibuprofen–LDH formulation designed to mitigate gastrointestinal side effects of NSAIDs, successfully completed a Phase I trial, which evaluated the influence of the LDH carrier on the pharmacokinetics of ibuprofen [48].

Regarding intellectual property, most patents involving LDHs pertain to their synthesis, functionalization, or industrial applications, with relatively few focused on biomedical uses. Notable exceptions include a U.S. patent covering the use of LDHs in cartilage regeneration, which demonstrated that LDHs enhanced the chondrogenic differentiation of human umbilical cord mesenchymal stem cells [252]. Another patent was granted for an LDH-based rechargeable fluoride delivery system designed for dental restoration, highlighting the expanding potential of LDHs in clinical applications [253].

In general, despite notable advancements in the basic experimental research of LDHs, a substantial gap remains between these findings and their clinical translationFirstly, the issues mentioned above, such as those in the aspects of synthesis methods, biosafety, stability, drug-loading capacity, and personalized medicine, are all factors hindering the clinical translation of LDHs. In addition, so far, the animal models used in LDHs-based tissue regeneration research mainly focus on small animals such as mice, rats, and rabbits. There have been no reports on the use of large animals like dogs, pigs, and monkeys. Comprehensive preclinical evaluation in large live animals and the establishment and improvement of the clinical trial framework are also indispensable.

Conclusion

In summary, as a novel nanobiomaterial, LDHs possess adjustable compositions and variable structures, good biosafety, diverse biological functionality, excellent drug-delivery capabilities, and convenience in constructing composite materials. Researchers have demonstrated the good application value and prospects in the regeneration applications of tissues such as bone, cartilage, blood vessels, skin, nerves, conjunctiva, and teeth. Few bio-nanomaterials exhibit such broad regenerative potential. Nevertheless, the application potential of LDHs in this field remains underexplored. Meanwhile, the specific molecular mechanisms underlying their functions also await further in-depth elucidation. Extensive research efforts still need to be carried out in this field to fully realize their clinical potential and address actual therapeutic challenges.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
Ado	Adenosine
AL	Alendronate

ALG	Alginate
ALP	Alkaline phosphatase
ASTM	American Society for Testing and Materials
ATO	Atorvastatin
β-TCP	β-tricalcium phosphate
BG	Bioactive glass
BMP-2	Bone morphogenetic protein-2
Bri	Brimonidine
BSE	Boswellia serrata extract
CAM	Chorionic allantoic membrane
CNS	Central Nervous System
CS	Chitosan/sericin
DA	Dopamine
DEX	Dexamethasone
DOX	Doxorubicin
ECM	Extracellular matrix
EE	Encapsulation efficiency
ENO	Enoxacin
eNSCs	Endogenous neural stem cells
EPO	Erythropoietin
ESC	Embryonic stem cell
FTH	Ferritin heavy subunit
GA	Gallic acid
GAG	Glycosaminoglycan
GC	Gelatin-chitosan
GEL	Gelatin
GLUT	Glucose transporter
GO	Graphene oxide
GQDs	Graphene quantum dots
HAp	Hydroxyapatite
hUCMSCs	Human umbilical cord mesenchymal stem cells
hBMSCs	Human bone marrow mesenchymal stem cells
HUVECs	Human umbilical vein endothelial cells
IBU	Ibuprofen
ICG	Indocyanine green
INDO	Indomethacin
KGN	Kartogenin
LC	Loading content
LDL	Low-density lipoprotein
mADSC	Mouse adipose-derived stem cells
MRSA	Methicillin-resistant Staphylococcus aureus
MSC	Mesenchymal stem cell
NAP	Naproxen
NIR	Near-Infrared laser
NPCs	Neural progenitor cells
PCL	Polycaprolactone
PD	Polydopamine
PEBA	Polyether-block-amide
PEG	Polyethylene glycol
PEO	Plasma electrolytic oxidation
PFTα	Pifithrin-α
PLA	Polylactic acid
PLLA	Poly(L-lactic acid)
PMMA	Polymethyl methacrylate
PNIPA	Poly (N-isopropylacrylamide)
PTFE	Polytetrafluoroethylene
PTT	Photothermal therapy
PU-PVA	Polyurethane-polyvinyl alcohol
PUU	Polyurethane-urea
rBMSCs	Rat bone marrow mesenchymal stem cells
ROS	Reactive oxygen species
SDZ	Silver sulfadiazine
siRNA	Small interfering RNA
TENGs	Triboelectric nanogenerator patches
tFNAs	Tetrahedral framework nucleic acids
TMSCs	Tonsil-derived mesenchymal stem cells
TQ	Thymoquinone
US	Ultrasound
VAN	Vancomycin
XRD	X-ray diffraction

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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