REVIEW

Electrospun Fibers Control Drug Delivery for Tissue Regeneration and Cancer Therapy

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Abstract

Versatile strategies have been developed to construct electrospun fiber-based drug delivery systems for tissue regeneration and cancer therapy. We first introduce the construction of electrospun fiber scaffolds and their various structures, as well as various commonly used types of drugs. Then, we discuss some representative strategies for controlling drug delivery by electrospun fibers, with specific emphasis on the design of endogenous and external stimuli-responsive drug delivery systems. Afterwards, we summarize the recent progress on controlling drug delivery with electrospun fiber scaffolds for tissue engineering, including soft tissue engineering (such as skin, nerve, and cardiac repair) and hard tissue engineering (such as bone, cartilage, and musculoskeletal systems), as well as for cancer therapy. Furthermore, we provide future development directions and challenges facing the use of electrospun fibers for controlled drug delivery, aiming to provide insights and perspectives for the development of smart drug delivery platforms and improve clinical therapeutic effects in tissue regeneration and cancer therapy.

Keywords Electrospinning · Electrospun fibers · Drug delivery · Stimuli-responsive · Tissue engineering · Cancer therapy

Introduction

Living systems are based around complex and precise regulatory rules that modulate the on-demand release or alteration of important biologically active substances in a spatiotemporally controlled manner to maintain normal metabolic balance [1]. However, the limited capability of many human tissues to perform self-regulation and/or self-repair can cause the occurrence of many diseases [2]. In these cases, the assistance of biologically active substances or drugs is necessary to inhibit or eliminate the internal and external factors that are unfavorable to health, effectively treating diseases and promoting regeneration of damaged tissues [3]. As a key component of drug delivery systems (DDSs), drugs play pivotal roles and are responsible for achieving satisfactory therapeutic effects [4, 5]. However, most drugs are administered systemically, require frequent administration and are characterized by short-term effectiveness, potentially leading to adverse cytotoxic side effects and the development of drug resistance. In addition, drug concentration and therapeutic effects at targeted tissues cannot be guaranteed [6]. Meanwhile, the tissue regeneration and cancer treatment involve complex physiological processes [7], so it is difficult for a single type of drug to achieve an ideal therapeutic effect; rather, effective treatment usually requires multiple types of drugs to be released in a coordinated and periodically controlled manner.

With the rapid development of nanotechnology, various DDSs have been developed to address problems such as burst and discontinuous drug release, unsatisfactory drug loading efficiency, and low drug stability and utilization

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efficiency in vivo [8–10]. Compared with DDSs based on liposomes, micelles, nanoparticles and hydrogels, electrospun fibers have attracted increasing attention as promising drug carriers [11]. DDSs based on electrospun fibers have been studied and explored due to the maneuverability of the electrospinning process and the subsequent customizable design of the fiber-based scaffolds [12, 13]. Electrospun fiber scaffolds have characteristics that include simple preparation, high material universality, and favorable surface chemical properties for drug adsorption [14, 15]. In addition, the high porosity and large specific surface area of electrospun fiber scaffolds make them beneficial to increasing drug-loading efficiency and the response speed of stimuli-delivered drugs [16]. The extracellular matrix (ECM)-like morphology of electrospun fibers inherently guides cellular drug uptake [1]. These advantages allow multifunctional electrospun fiber scaffolds to support customizable drug delivery platforms that can achieve the sustained and programmed release of multiple drugs for tissue regeneration and cancer therapy.

In principle, almost all polymers and many additional functional components can be integrated into the electrospun fiber platform [13, 17]. As for drug delivery, a variety of technologies derived from electrospinning, including coaxial electrospinning [18], multiaxial electrospinning [19], electrospraying [20], etc., have been developed to prepare drug-loaded electrospun fiber platforms. In addition, electrospinning can be used to fabricate porous micro- and nanofibers, as well as various types of hierarchically controlled fibrous structures, ranging from 1 to 3D fibrous scaffolds. A growing number of customized electrospun fiber scaffolds have been used for drug delivery to facilitate tissue regeneration and cancer therapy. By modifying loading strategies, drugs can be released in a fast, sustained, heterogeneous or controlled manner by being combined with polymers, adsorbing on the fiber surface, or indirectly encapsulating onto electrospun fibers [21, 22]. Similarly, multifunctional electrospun fiber scaffolds that allow the sequential release of multiple drugs or in a spatiotemporally controllable manner, can be created to meet a variety of in vivo needs [23, 24].

Critically, a combination of strategies is needed for tissue engineering and cancer therapy, including the development of multifunctional scaffolds to provide biomimetic topographical cues and mechanical support, as well as the simultaneous delivery of small molecule drugs, growth factors, and other biochemical signals [25–27]. In addition to serving as a drug carrier, electrospun fibers can also be engineered to manipulate cell morphology and migration, neurite elongation, and stem cell differentiation by controlling their structure and array. Given that the realization of multiple functions in the body requires high levels of temporal and spatial precision, electrospun fiber scaffolds that enable the precise delivery of

drug doses with spatiotemporal control have received great attention [28, 29]. It is well known that responsive DDSs can exploit intrinsic endogenous stimuli in living systems to develop new strategies for drug delivery with electrospun fiber scaffolds based on factors such as drug sensitivity to pH [30], reactive oxygen species (ROS) [31], enzymes [32], and glucose [33]. Likewise, external stimuli such as temperature [34], light [35], electricity [36], magnetic fields [37], and ultrasound [38] have also been used to modulate cellular behaviors, inducing tissue regeneration, and to remotely control drug delivery [39]. Based on this, stimuli-responsive electrospun platforms can serve as precise on-demand drug release repositories to mimic the function of living systems as much as possible and develop new tissue regeneration methods via the design of fiber structural features, thereby expanding the application of electrospun fibers for drug delivery in the fields of tissue regeneration and disease treatment.

Herein, we summarize the recent progress on controlling drug delivery from electrospun fiber scaffolds for tissue engineering, including soft tissue engineering (such as skin, nerve, cardiac, blood vessels) and hard tissue engineering (such as bone, cartilage, musculoskeletal, dental), as well as for cancer therapy. Meanwhile, emerging strategies for combining drugs with electrospun fibers and the resultant mechanism of drug delivery are discussed, and the effects of endogenous and external stimuli on drug release are emphasized (Fig. 1). Typically, "drugs" refer not only to traditional small-molecule drugs but also to bioactive components with specific therapeutic and regenerative functions, which can be divided into small molecular drugs and bioactive substances (e.g., growth factors, protein polypeptides, gene nucleic acids, and liposomes), as well as nanoparticles with therapeutic effects. Finally, the future directions of electrospun fibers for controlled drug delivery in tissue regeneration and cancer therapy are prospected, providing insights and perspectives for the development of smart drug release and highlighting the challenges to accelerate clinical translation.

## Construction of Electrospun Fibers for Drug Delivery

The setup of electrospinning consists of a high-voltage power supply, a syringe pump, a spinneret, and a conductive collector. Firstly, the solution is extruded from the spinneret and forms a hanging droplet due to surface tension. When the high voltage power supply is applied, electrostatic repulsion among the same charges formed on the droplet surface turns it into a Taylor cone, from which a charged jet is ejected. Because of the behavior of bending instability, the

jet undergoes a whipping motion after initially extending in a straight line. The jet will get slimmer and solidify quickly when the diameter of jet is optimal under the action of the electric field, then finally deposit on the surface of the conductive collector [17]. To meet various applications, different electrospun fiber sizes and morphologies can be obtained by changing the spinning process and parameters such as the voltage, solution composition, and collector design [40]. Meanwhile, satisfactory fiber structures can also be obtained by post-treatment procedures, such as weaving [41], twisting [42], foaming [43] and others. In this section, electrospun fibers are divided into three categories as follows: 1D pristine fiber (an individual fiber with different morphologies and structures), 2D hybrid fiber (in which material is loaded on the lumen/surface of an individual fiber), and 3D fiber architecture (arrangement and combination of fibers in 3D space).

The morphology and structure of 1D pristine fibers are the most basic units, and the most common and easily obtained morphology is the fiber with a smooth surface (Fig. 2a), however, at the same time, its simpleness makes it unsuitable for many applications. Many emerging structures, such as beaded, grooved, multi-channel, core–shell, and porous structures, have been designed and constructed, with various advantages described. Contrary to previous perception, beaded fibers tend to be produced due to a decrease in surface tension or an uneven distribution of solution concentration (Fig. 2b) [44], which is considered to be a structural defect that needs to be avoided and removed. However,

it has been found that the presence of beads changes the surface roughness of the fiber, and this high surface roughness can have some beneficial effects on cell differentiation [45]. The fabrication of fiber by multi-fluid control technology is a new method in recent years [46]. A porous or grooved structure can be formed by electrospinning and stretching two incompatible polymers, then removing one of the components with a specific solvent [47] (Fig. 2c, d). Compared with the original fibers, both of these structures possess increased surface roughness and area, which are beneficial cell adhesion [48]. In addition, the grooved surface can provide topographic cues to promote the directional migration of cells. Meanwhile, some additional properties can be integrated into the hollow lumen of core–shell structures [46] and multi-channel structures [49] to meet the unique conditions for the regeneration of different tissues (Fig. 2e, f).

Distinct from pristine fibers, 2D hybrid fibers can combine nanoparticles, cells, and bioactive factors to provide some specific effects. For example, embedding bioactive factors in fibers can promote cell migration, proliferation, and differentiation [50] (Fig. 2g). Packing cells in fibers can not only maintain high cellular activity and the ability to secrete immune molecules but can also provide a suitable environment for tissue regeneration [51] (Fig. 2h). In addition, embedding nanoparticles, such as iron oxide nanoparticles [52], graphene and organic materials [53] in fibers, can increase the intensity of external signals, thereby enhancing stimulation to promote tissue repair (Fig. 2i). Attaching specific substances to the fiber surface by post-treatment or
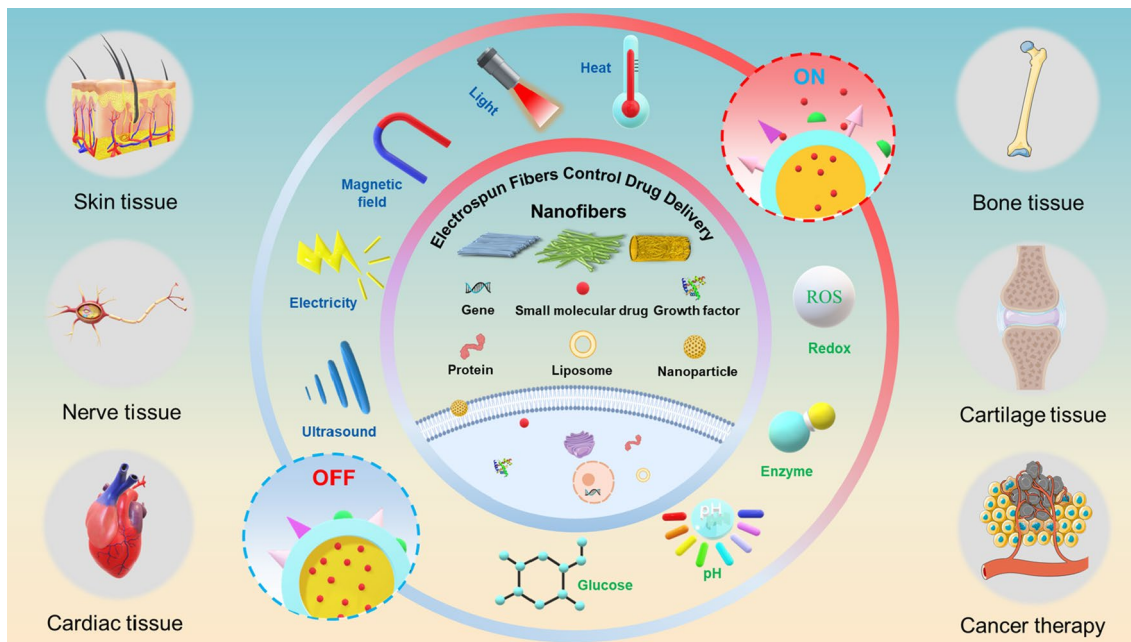

Fig. 1 Schematic illustration showing electrospun nanofiber scaffolds for controlling drug delivery and their biomedical applications in tissue regeneration and cancer therapy

in-situ growth is also a common method for broadening the applications of electrospun fibers [54–56] (Fig. 2j–l). For example, the introduction of polydopamine (PDA) coatings to electrospun nanofiber membrane could provide nucleation sites and active centers for zinc oxide (ZnO) nano-seeds to form nanorod structures, endowing nanofiber membrane

with excellent photocatalysis and antibacterial properties [56].

Compared with the 2D hybrid fibers, the growth, morphology, differentiation, and function of cells in 3D scaffolds are closer to those found in in vivo microenvironments. Using the previously described pristine fibers or hybrid fibers, 3D scaffolds with different structures can be fabricated,
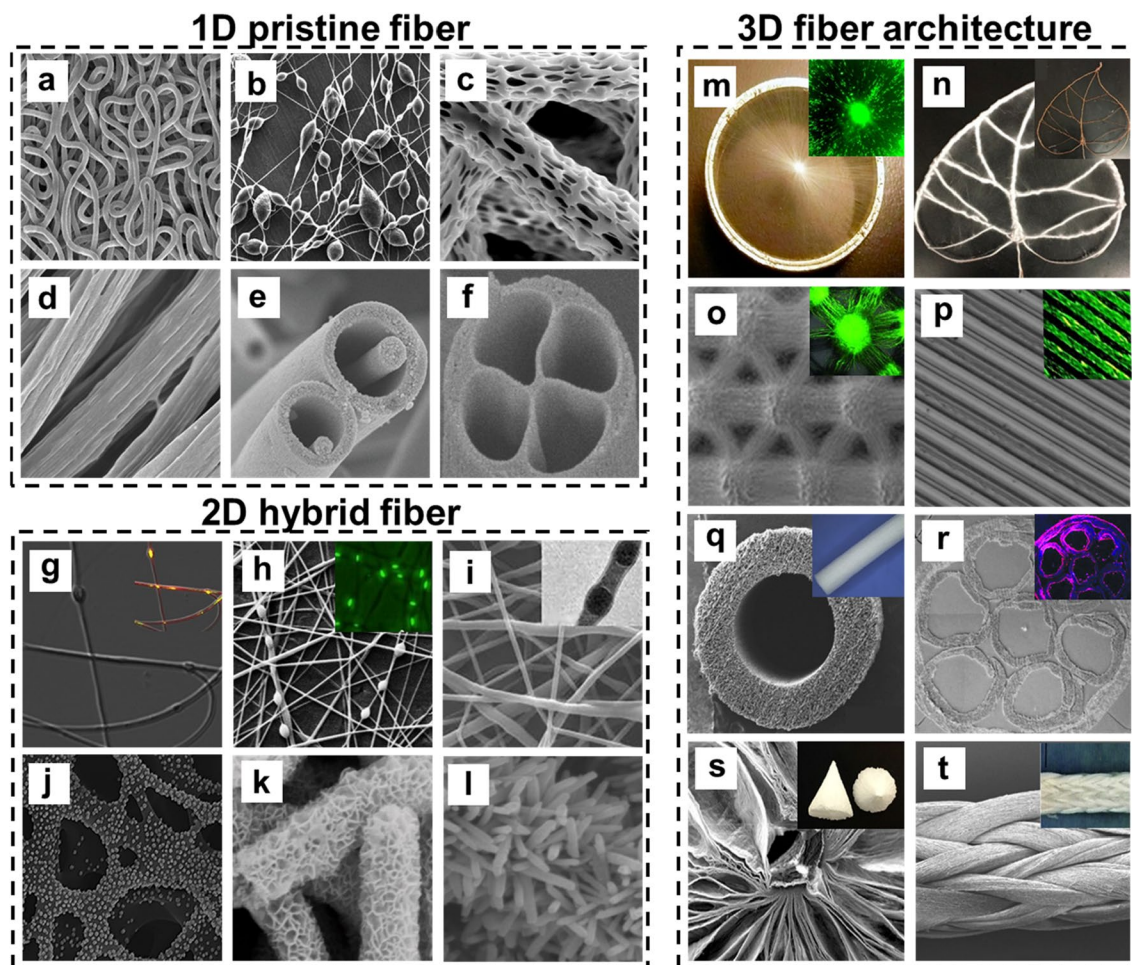
Fig. 2 The versatile structure of electrospun fibers. **a** Solid fiber. Reproduced with permission from Ref. [200]; Copyright 2020, Wiley–VCH Limited. **b** Beaded fiber. Reproduced with permission from Ref. [44]; Copyright 2008, Wiley–VCH Limited. **c** Porous fiber. Reproduced with permission from Ref. [47]; Copyright 2008, Wiley–VCH Limited. **d** Grooved fiber. Reproduced with permission from Ref. [48]; Copyright 2020, Wiley–VCH Limited. **e** Core-sheath fiber. Reproduced with permission from Ref. [46]; Copyright 2010, American Chemical Society Limited. **f** Multi-channel fiber. Reproduced with permission from Ref. [49]; Copyright 2007, American Chemical Society Limited. **g** Fiber loaded with bioactive molecules. Reproduced with permission from Ref. [50]; Copyright 2014, Wiley–VCH Limited. **h** Cell-encapsulated fiber. Reproduced with permission from Ref. [51]; Copyright 2020, Elsevier Limited. **i** Nanoparticles-embedded fiber. Reproduced with permission from Ref. [53]; Copyright 2015, Elsevier Limited. **j** Nanoparticles anchored fiber. Reproduced with permission from Ref. [54]; Copyright 2020, Elsevier Limited. (k) Nanosheet-grown fiber. Reproduced with permission from Ref.

[55]; Copyright 2021, Elsevier Limited. **l** Nanorod-grown fiber. Reproduced with permission from Ref. [56]; Copyright 2018, Elsevier Limited. **m** Radially aligned fiber array. Reproduced with permission from Ref. [57]; Copyright 2010, American Chemical Society Limited. **n** Bionic patterned fiber array. Reproduced with permission from Ref. [41]. Copyright 2020, Wiley–VCH Limited. **o** Complex pattern fiber array. Reproduced with permission from Ref. [58]; Copyright 2011, Wiley–VCH Limited. **p** Fiber mat with grooved surface. Reproduced with permission from Ref. [59]; Copyright 2021, American Association for the Advancement of Science Limited. **q** Tubular conduit. Reproduced with permission from Ref. [60]; Copyright 2017, Wiley–VCH Limited. **r** Multi-tubular conduit. Reproduced with permission from Ref. [61]; Copyright 2018, Wiley–VCH Limited. **s** 3D porous fiber scaffold. Reproduced with permission from Ref. [62]; Copyright 2019, American Chemical Society Limited. **t** Multifilament electrospun fiber yarns. Reproduced with permission from Ref. [42]; Copyright 2018, Elsevier Limited

typically by changing the collector, or by post-processing procedures such as crimping, weaving, molding, and others. By using different collectors, such as rollers and conductive rings [57], fibers arranged in an orderly 3D direction can be prepared (Fig. 2m), and the collector substrate pattern can be changed to fabricate various patterned scaffolds (Fig. 2n, o), making these scaffolds conducive to the development of cells in vivo [41, 58]. In addition, post-treatment methods can be used to change the surface morphology of scaffolds. For example, molding and photoetching can form grooves on the surface, providing topographical cues for cell migration (Fig. 2p) [59]. Another simple method, rolling-up, is often used to fabricate conduits from fiber membrane to connect defective nerves and build a bridge conducive to nerve regeneration (Fig. 2q) [60]. To improve the ability of bionics to simulate physiological cues, several small tubes were sequentially embedded in a larger tube to simulate the multifascicle structure of normal nerves, effectively avoiding misaligned axons growth (Fig. 2r) [61]. Foaming technology is another important method to fabricate 3D scaffolds composed of fibers. Scaffolds with radial arrangement structure can be fabricated through customizable control technology, which can effectively promote the migration of cells from the periphery to the center (Fig. 2s) [62]. Moreover, this 3D structure provides larger porosity and pore size, broadening the applications of electrospun fiber scaffolds in tissue engineering [62, 63]. Yarn can be made of electrospun fibers by weaving and twisting, leading to better permeability and drafting behavior (Fig. 2t), as well as increased suitability for tissue suturing [42].

Electrospun fiber scaffolds have wide application prospects in tissue regeneration and cancer therapy due to their porosity, high loading capability, adjustable mechanical properties, and excellent biocompatibility [64]. The integration of emerging 3D printing technology can support the design of more scaffolds with different structures and patterns, which can play unique roles in specific tissue regeneration processes [65]. Furthermore, advanced 4D electrospun fiber scaffolds can be developed by incorporating shape memory or stimuli-responsive properties for biomedical applications [66]. Accordingly, the optimization of electrospun fiber scaffold-based DDSs has attracted increasing attention. Therefore, it is believed that a wide variety of electrospun fibers will be developed to support better and multifunctional drug delivery platforms.

Drug Delivery for Tissue Engineering and Cancer Therapy

In recent years, the loading of functional therapeutic agents into electrospun fibers has attracted research attention. Functional therapeutic agents can be classified into (i) small molecular drugs, such as ciprofloxacin [67, 68], doxorubicin (DOX) [69], and ibuprofen [70], (ii) bioactive substances, such as peptides [71], proteins [72], nucleic acids [73], and liposomes [74], and (iii) nanoparticles with therapeutic efficacy, such as Ag nanoparticles [75], mesoporous silica nanoparticles (MSNs) [76], nano-enzymes [77, 78], and bioglass [79, 80].

Small molecular drugs are typically signal transduction inhibitors that can treat diseases by blocking corresponding signaling pathways [81–83]. Small molecular drugs are mainly chemically synthesized or derived from natural extracts, and their molecular weights are usually less than 1,000 [84]. They have a wide range of applications due to their low cost, ease of storage and transport, high tissue permeability and minimal immunogenicity [85]. Although small molecular drugs have excellent therapeutic effects, most have poor pharmacokinetics and are easily metabolized into other substances in the body [86]. Therefore, it is essential to effectively deliver small molecular drugs using a suitable platform. Loading small molecular drugs into fibers can significantly overcome the above challenges by improving water solubility and stability, increasing drug concentrations at disease sites, and reducing side effects.

Compared with small molecular drugs, bioactive substances have relatively larger molecular weights, more complex structures, and better water solubility. The immobilization or encapsulation of these bioactive substances onto the surface and into the interior of fibers can overcome limitations associated with systemic administration or local injection. Proteins and growth factors are involved in many physiological processes in the human body. For example, bone morphogenetic protein-2 (BMP-2) and insulin-like growth factor-1 [72, 87] have the ability to promote bone tissue repair, while vascular endothelial growth factor (VEGF) [88], epidermal growth factor (EGF) [89], and nerve growth factor (NGF) [90] can promote skin and nerve tissue repair. Unlike macromolecule proteins, peptides are not specifically absorbed by the reticuloendothelial system or liver, leading to fewer toxic side effects and more mature peptide synthesis technology. Therefore, many types of peptides are widely used in tissue engineering repair, including ε-polylysine peptides with antibacterial properties [91] and peptides for angiogenesis [71], as well as many other types of anti-bacterial peptides. For the delivery of nucleic acids, the key outstanding issue is protecting nucleic acid activity from the surrounding environment [92–95]; currently, commonly used nucleic acids primarily include plasmid DNA, microRNA, and small interfering RNA, among others [96]. Most bioactive molecules are easily damaged by the external environment due to their chemical instability, relatively short half-lives, and vulnerability, so it is often difficult to effectively encapsulate bioactive molecules in nanofibers with conventional electrospinning technology. Therefore,

it is particularly important to develop new technologies to enable the effective encapsulation and delivery of bioactive molecules by nanofibers.

In addition to the above-mentioned drugs, a number of functional nanoparticles have the ability to promote tissue repair and cancer treatments. For example, Ag nanoparticles have excellent antibacterial effects [75], and manganese dioxide nanoparticles can effectively scavenge excess hydrogen peroxide in the body [91]. Similarly, metal–organic framework materials, such as magnesium organic frameworks, can effectively scavenge ROS, slow down the inflammatory response, and promote angiogenesis [97]. Compared with small molecular drugs and bioactive substances, these therapeutic nanoparticles have more stable chemical properties and are easier to load into electrospun fibers. More importantly, they can also act as drug carriers to facilitate the controlled release of drugs from electrospun fibers [76, 98].

## Manipulation of Electrospun Fibers to Control Drug Delivery

Strategies for Encapsulating Drugs in Electrospun Fibers

Due to their ECM-like structure, high specific surface area, high porosity, high drug loading capability, and controlled drug delivery function, electrospun fiber-based scaffolds have outstanding advantages for the delivery of functional therapeutic agents [99–102]. Functional therapeutic agents can be loaded into electrospun fibers by blending electrospinning, second carrier electrospinning, emulsion electrospinning, coaxial electrospinning, electrospraying, physical adsorption, and covalent immobilization. In selecting the fiber matrix for drug loading to achieve a typical drug release profile, the interaction between the drug and the fiber scaffolds should be considered. The composition, molecular weight, hydrophilicity, and degradation rate of the fiber polymer matrix all affect the drug release behavior. In addition, the relative molecular mass, crystallinity and solubility of the drug, and other properties of the drug also affect the release behavior. In addition to hydrogen bonds and electrostatic interactions, covalent bonds can also be used to link the drug with the fibers. Evaluations of the bioactivities of both the drug-loaded scaffolds and the released drug are necessary. Typically, the activities of both the drug-loaded scaffolds and the drug can be evaluated by co-culturing with cells or bacteria to observe the influence of the scaffolds on the adhesion, growth, migration and differentiation of cells or the growth of bacteria, depending on the application direction.

Blend electrospinning is the most straightforward technique for loading drugs into nanofibers (Fig. 3a).

Specifically, a number of drugs or functional nanoparticles with chemical stability and organic solvent resistance can be mixed with polymers to form a homogeneous electrospinning solution. Then, micro- or nanofibers loaded with one or multiple drugs can be fabricated by electrospinning [70, 103]. Due to the random distribution of drugs on the fiber surface and inside the fibers, the release process is generally characterized by an initial burst release and subsequent slow release [104]. Since most fibers have high specific surface area and large porosity, the drug is often completely released from the fibers within a few hours or days, incompatible with long-term administration at the tissue. In these cases, polymers that can form electrostatic adsorption interactions with the drugs can be used to delay drug release. It is difficult to induce interactions between some chemical drugs or biologically active molecules and polymers, so new technologies are urgently needed to prolong release time. One solution is to load chemical drugs and bioactive molecules into a secondary carrier, after which the drug-loaded electrospun fibers can be prepared by blending electrospinning. These secondary carriers can be nanoparticles [105, 106], micelles [107], vesicles [108], microspheres and other forms. For example, drug-loaded halloysite clay nanotubes were doped into polycaprolactone (PCL)/gelatin nanofibers, achieving sustained drug release over 20 days, which was greatly extended compared to directly loading the drugs in pristine electrospun fibers [109].

Chemically unstable and easily inactivated bioactive factors, such as growth factors, proteins and nucleic acids, function only when they are able to enter cells. Therefore, it is important to avoid contact between bioactive factors and organic solvents, as well as to deliver bioactive molecules successfully to the cellular interior without inactivation [110, 111]. The above-mentioned problems can be solved using emulsion electrospinning technology [112]. In emulsion electrospinning, there is no direct contact between the molecules and the dissolved organic matter, as the bioactive substances are partitioned into the aqueous phase, thus greatly enhancing molecular activity. The loading of drugs into the fiber interior by emulsion electrospinning effectively mitigates the explosive release of drugs at early stages. In addition, emulsion electrospinning enables the simultaneous loading of multiple drugs. Furthermore, emulsion electrospinning can realize the simultaneous loading of multiple drugs and alleviate the problem of explosive drug release in early stages [113]. For instance, emulsion electrospinning was applied to fabricate nanofibers loaded with hydrophobic 10-hydroxycamptothecin (HCPT) in the sheath layer and with hydrophilic tea polyphenols in the core layer [114]. In the initial 4 days, the release of HCPT reached about 61.5%, while the release of tea polyphenols was only about 20.4%. Although emulsion electrospinning has significant advantages, it still has some problems, including
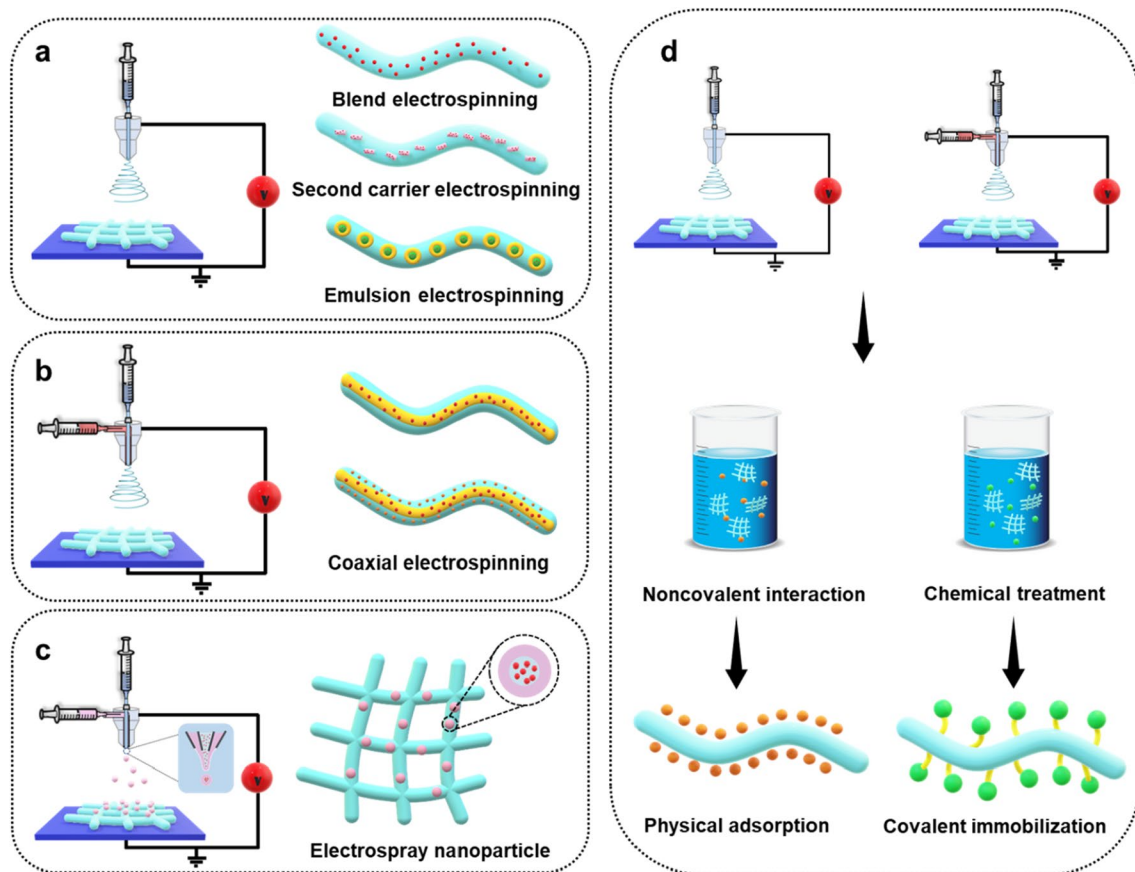
Fig. 3 Schematic illustration showing the different fabrication methods of drug-loaded electrospun fibers, including **a** blend electrospinning, second carrier electrospinning, emulsion electrospinning, **b** coaxial electrospinning, **c** electrospinning combined with electrospraying, and **d** post-processing by physical adsorption and covalent immobilization

poor solution stability and low drug-loading efficiency. In this case, microsol-electrospinning technology can be used to achieve efficient loading and slow release of hydrophilic drugs or easily deactivated biomolecules [115, 116]. For example, when microsol-electrospinning was used to load VEGF in electrospun nanofibers, only 36.8% of VEGF was released in the initial two days, followed by sustained release over 4 weeks [117].

Similar to emulsion electrospinning, coaxial electrospinning can successfully be used to encapsulate bioactive molecules with unstable chemical properties into electrospun fibers (Fig. 3b) [118]. For coaxial electrospinning, a core layer spinning solution composed of biomolecules and a sheath layer spinning solution composed of polymers form two separate jets from the coaxial needle to fabricate core-sheath nanofibers. Compared with commonly used electrospinning methods, coaxial nanofibers are prepared in a way that minimizes interactions between the organic polymer solution and the water-based biomolecules, maintaining the biological activity of unstable biomolecules. Meanwhile, compared with blend electrospinning, coaxial

electrospinning can reduce the explosive early-stage release of drugs, realize the simultaneous loading of hydrophilic and hydrophobic drugs, and avoid the biological toxicity caused by late crosslinking of hydrophilic polymers [18, 119]. Since coaxial electrospinning can be used to prepare core-sheath electrospun fibers, it is feasible to load different drugs or bioactive molecules into the core and sheath layers, respectively. The drug in the core layer needs to pass through the sheath layer to be released, slowing its release rate compared to that of the sheath layer [102]. As an example, an *in vitro* release study showed that the amount of doxorubicin hydrochloride released from the sheath of nanofibers reached 62.2% in the first 200 hours, while the amount of matrix metalloproteinase-2 released from the core layer was only about 50% through 960 hours [120]. To further delay the rate of drug release, the drugs can also be encapsulated into a secondary carrier before preparation of the nanofiber membrane by coaxial electrospinning [121].

Electrospray technology can integrate nanoparticles loaded with bioactive molecules or drugs into and/or onto fibers (Fig. 3c) [122]. For electrospraying, it allows the

deposition of particles loaded with bioactive molecules or drugs on the fibers. It can not only encapsulate drugs with bioactive molecules, microspheres, and micelles to protect their activity and prolong drug release but can also allow the design of on-demand DDSs responsive to external stimuli. Compared with the passive release of drugs from other electrospun fibers, fibers that enable spatiotemporally controlled drug release can be prepared by integrating electrospinning and electrospraying technologies. For example, collagen particles loaded with neurotrophin-3 (NT-3) can be sandwiched between two nanofiber layers using electrospray technology, realizing the sustained and controllable release of NT-3 [123]. In addition, the combination of masked electrospray technology and electrospinning can achieve a gradient distribution of biomacromolecular particles on fibers [124].

In addition to the above methods, a number of drugs can also be loaded onto fibers by physical adsorption (Fig. 3d) [125, 126]. Especially for certain biomolecules, physical adsorption is not only the simplest way to load biomolecules into fibers but can also effectively maintain the activity of the biomaterials. Although this method of drug loading is relatively simple, the drugs cannot be released in a sustained manner [127]. In particular, drugs and bioactive molecules that do not make electrostatic interactions with nanofibers are difficult to load by this method [15]. For example, recombinant human BMP-2 was adsorbed on the surface of poly(D,L-lactide-co-glycolide)/hydroxylapatite composite nanofibers by the physical adsorption method [128]. The in vitro BMP-2 release profile showed that 75% of BMP-2 was released within the first 5 days. In addition, layer-by-layer self-assembly (LBL) is another common physical adsorption method for drug loading onto fibers based on the alternating adsorption of polyelectrolytes on the matrix through electrostatic interactions, hydrogen bonds or other interactions. For example, positively charged chitosan and negatively charged type I collagen can be assembled onto electrospun silk fibroin fiber membrane by LBL technology for scar-free wound repair [129].

In addition to physical absorption, drugs or biomacromolecules that can react with functional groups on the fiber surface can be bound to nanofibers by covalent immobilization [125, 129]. Such drugs and biomacromolecules can also be released in vivo by endogenous stimuli. For example, a polypeptide containing a carboxyl group reacted with the amino group on the surface of chitosan hydrogel nanofibers to form an amide bond; thus, the polypeptide was successfully loaded onto the nanofibers [71].

At present, the development of a multi-functional electrospinning platform is conducive to the delivery of multiple drugs. Sequential electrospinning is a technique used to construct multilayer nanofibers, and a variety of drugs can be loaded into the different nanofiber layers, so as to control the release rates of different drugs [130]. For example,

sequential electrospinning was used to prepare a three-layer nanofiber scaffold in which the inner and middle layers were loaded with microRNA-126 and microRNA-145, respectively, leading to the sequential release of microRNA-126 followed by microRNA-145 [131].
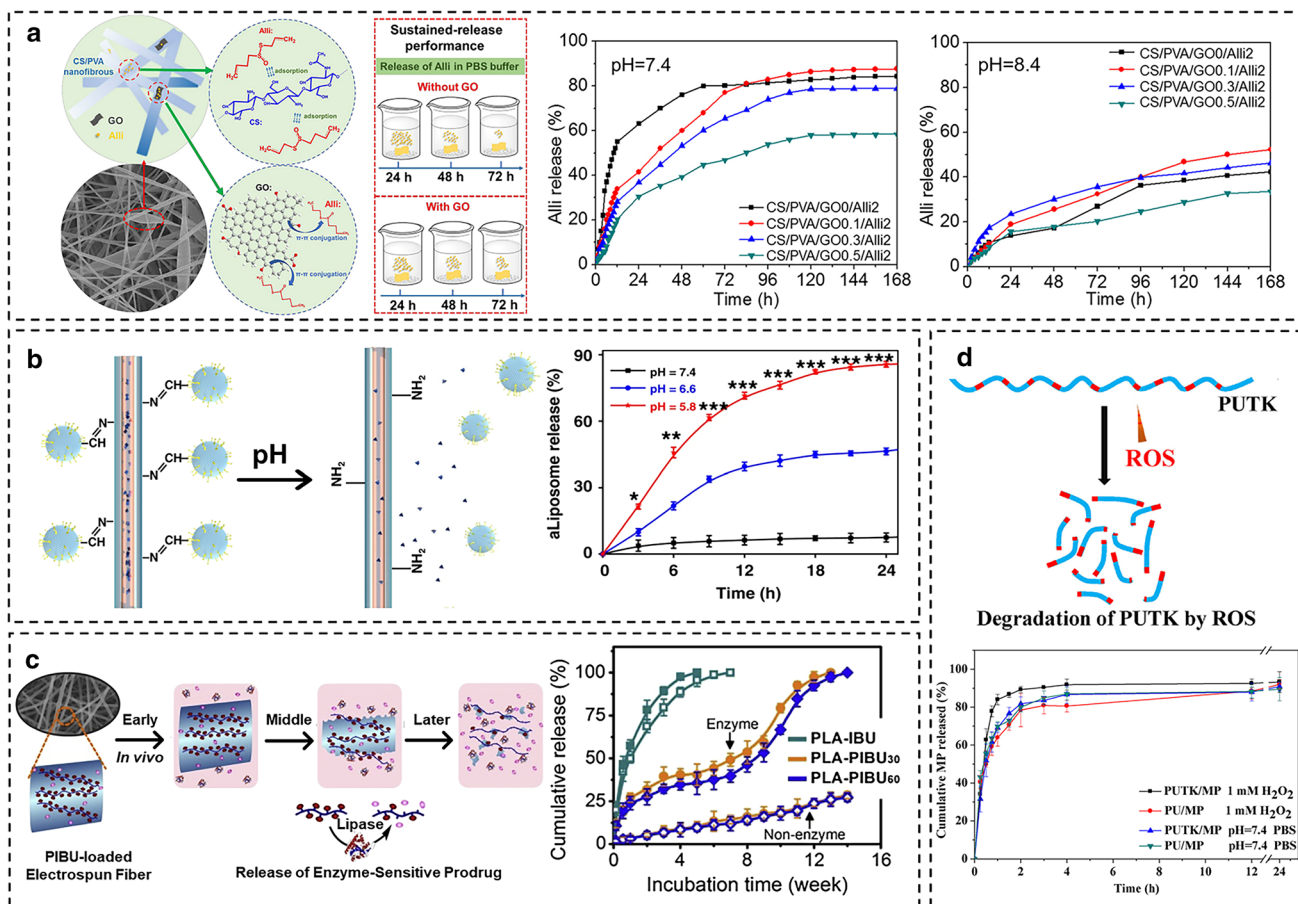
Stimuli-Responsive Drug Delivery Systems

Electrospun fiber platforms incorporating stimuli-response are emerging as a major driving force in the development of smart drug delivery [132]. Just like many important functions in the human body are achieved in a site-specific and time-controlled manner, the responses to intrinsic endogenous and external stimuli provide more possibilities for the development of new drug delivery strategies [29, 39]. To this end, it can be realized to significantly improve the selectivity and targeting of drugs, deliver appropriate drug concentrations to the target site at a specific time, effectively reduce side effects, and meet the requirements of tissue regeneration and cancer treatment. Herein, typical endogenous and external stimuli are summarized, and their potential to deliver precise amounts of drugs in a spatiotemporally controllable manner is also described.

Endogenous Stimuli-Responsive Drug Delivery Systems

Differences in pH, enzyme expression, ROS levels, and glucose content in pathological environments compared to normal physiology can provide some ideas for the development of smart drug delivery platforms. Indeed, various types of nanofiber delivery systems responsive to endogenous stimuli have been developed based on microenvironmental changes in cells or tissues [68, 133].

By selecting the appropriate type of polymer and post-processing method, electrospun fibers can be endowed with pH-responsive drug release characteristics [134, 135]. pH-sensitive polymeric nanofibers change their own volume in response to external pH changes, enabling intelligent and responsive drug delivery [136]. Some nanofiber membranes contain chemical groups that are sensitive to hydrogen and hydroxide ions, enabling the controlled release of drugs by changing intermolecular forces of the polymers when external pH changes. For instance, under acidic conditions, the amino and acetyl amino groups of chitosan undergo a protonation reaction to form an amine cation [137]. Swelling of the nanofiber membrane is increased due to mutual repulsion between ammonia cations and hydrogen ions. Thus, the interaction forces between allicin and chitosan or polyvinyl alcohol (PVA) are weakened, accelerating the release of allicin from the fibrous membrane into the surrounding environment (Fig. 4a). However, in alkaline environments, interactions between hydroxide ions, chitosan and PVA are not obvious, reducing the degree of fiber membrane swelling.

Fig. 4 Endogenous stimuli-responsive drug delivery fiber systems. **a** Schematic illustration and SEM image showing the microstructure of CS/PVA/GO/Alli fiber mat, and the release of Alli from the fiber mat at different pH values. Reproduced with permission from Ref. [137]; Copyright 2020, Elsevier Limited. **b** Schematic illustration showing the pH-responsive release of liposomes from the surface of a nanofiber, and the release curves of liposomes from the electrospun fiber mat at different pH values. Reproduced with permission from Ref. [138]; Copyright 2020, Springer Nature Limited. **c** Schematic illustration showing the degradation-triggered release of esterase-sensitive prodrug from electrospun fiber mat followed by the enzyme-triggered release of IBU from the prodrug, and the release curve of IBU from the different types of scaffolds in the presence or absence of enzyme. Reproduced with permission from Ref. [143]; Copyright 2015, Elsevier Limited. **d** Schematic illustration showing that the thioketal linkers in polyurethane containing thioketal (PUTK) can be cleaved in response to ROS, and the cumulatively released percentage of MP in vitro from the electrospun fiber patch in PBS solution (pH = 7.4) and 1 mM H_2O_2 solution at 37 °C, respectively. Reproduced with permission from Ref. [31]; Copyright 2020, Elsevier Limited

In addition to fiber swelling, pH-responsive drug release can be triggered by external pH change through chemical bond breakage. For example, IL-4-loaded liposomes containing aldehyde groups were grafted onto the surface of fibers containing amino groups via Schiff base reactions (Fig. 4b) [138]. In acidic environments, these chemical bonds were broken due to hydrolysis reactions, and the liposomes were released from the nanofibers. The in vitro release profile showed that the release rate of liposomes was significantly faster at pH = 5.8 than at either pH = 7.4 or pH = 6.6.

In addition to the above methods for preparing pH-responsive nanofibers, a number of pH-responsive nanomaterials, such as liposomes, micelles and others, can also be encapsulated into nanofibers to realize controllable and responsive drug release. For example, electrospun PVA nanofibers were loaded with a reduction-responsive Pt (IV) prodrug micelle and dichloroacetate [139]. Simulation of the cancer cell state with s acetate buffer solution and sodium ascorbate better triggered the release of Pt (II), and levels of cleaved Pt rapidly accumulated to 50% within 24 h.

Enzymes play important roles in different biological processes and usually have high specificity, with various species of enzymes distributed across different tissues at specific concentrations. Therefore, in response to abnormal concentrations of enzymes, enzyme-responsive DDSs provide a way to increase selectivity and sensitivity [140]. In inflammatory locations and tumor tissues, some specific enzymes are significantly different from those in normal tissues,

so it is feasible to exploit this feature to enable enzyme-responsive controlled drug release [141, 142]. For example, an esterase-sensitive prodrug was loaded in electrospun nanofibers to realize enzyme-triggered release of ibuprofen, an anti-inflammatory drug [143]. As shown in Fig. 4c, in the presence of lipase, nanofibers loaded with prodrug-of-ibuprofen exhibited enzyme-triggered drug release, and the cumulative release of ibuprofen reached 100% within 14 weeks; in contrast, only a small amount of drug was released in the absence of the lipase enzyme.

ROS can regulate intracellular biological behaviors as signaling molecules [144, 145]. However, excessive ROS production usually causes severe oxidative damage to cells and tissues. At present, due to the high concentrations of ROS in pathological environments, a variety of ROS-responsive DDSs have been developed [146, 147]. As shown in Fig. 4d, ROS-responsive nanofibers can be prepared by electrospinning a biodegradable elastomer containing thioketone [31]. Nanofibers loaded with glucocorticoid methylprednisolone (MP) were incubated in 1 mM H_2O_2 solution for 2 weeks, and the release of MP was significantly higher than that of any other groups.

Since hyperglycemia patients have excess blood glucose in their plasma, a glucose-responsive DDS can be established based on a gradient in blood glucose levels [148]. At present, many researchers have realized the release of insulin triggered by hyperglycemia and have applied glucose oxidase to reduce the pH or oxygen content in hyperglycemic regions through an enzymatic reaction, thereby promoting insulin release [149, 150]. These glucose-responsive nanofibers are mostly used for monitoring blood glucose. By encapsulating glucose oxidase or glucose dehydrogenase into nanofiber scaffolds, blood glucose levels can be quickly and sensitively monitored [28]. Obviously, a system responsive only to an individual type of endogenous stimulus is unable to meet current needs. Therefore, to deliver therapeutic agents to the right place at the right time in physiologically relevant doses, it is particularly critical to develop endogenous stimuli-responsive nanofiber scaffolds that can respond synergistically to multiple signals.
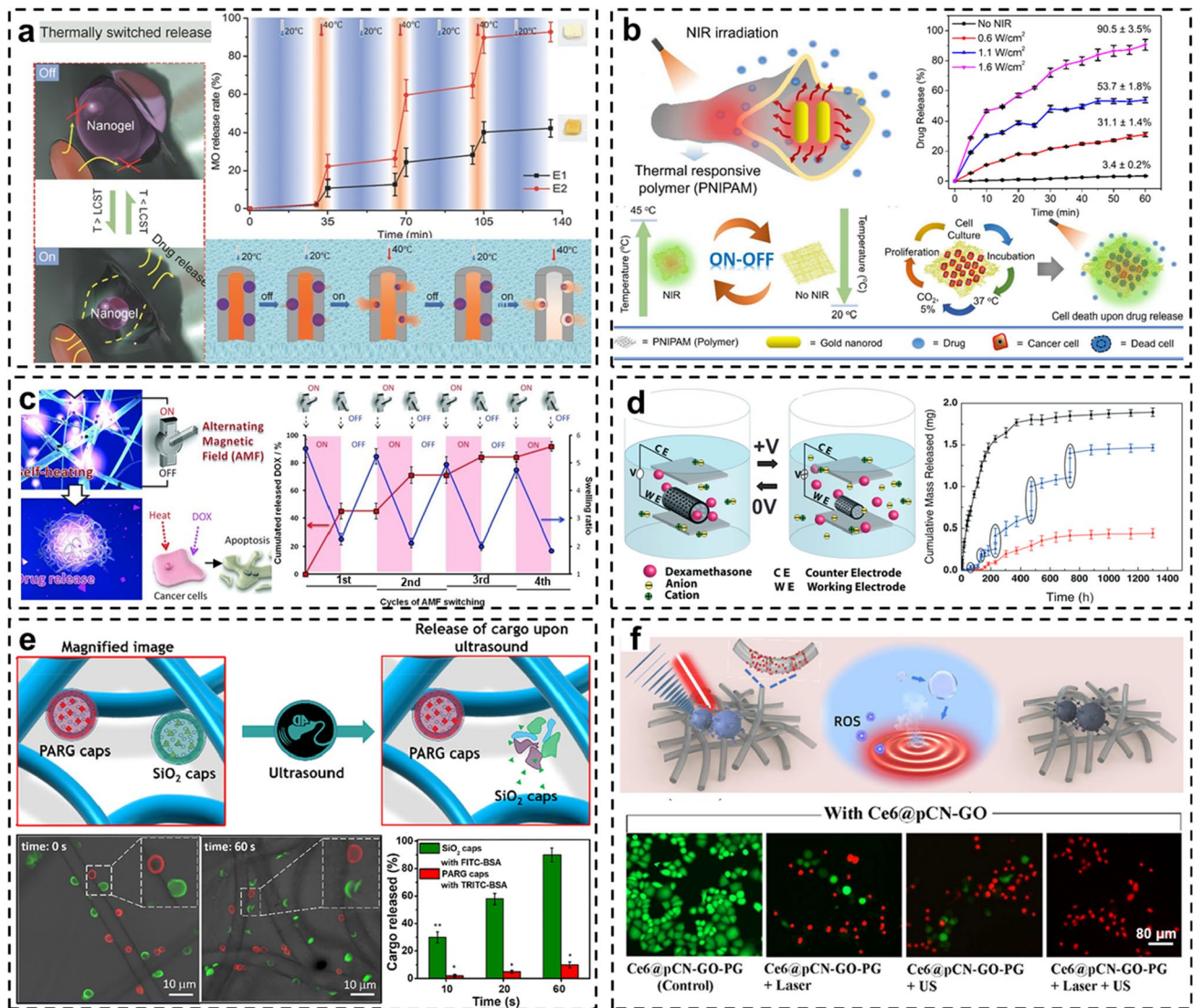
External Stimuli-Responsive Drug Delivery Systems

External stimuli, such as heat, light, electricity, magnetic fields, and ultrasound, have attracted much attention due to their non-invasive nature, high tissue penetration depth, and spatiotemporal controllability [38]. All these strategies can be combined with electrospun drug-loaded scaffolds to enable stimuli response and synchronize drug release profiles under real physiological conditions by manipulating the external environment, providing new avenues for tissue regeneration and cancer therapy.

Temperature controls almost all physical, chemical, and biological reactions, in addition to being critical regulatory parameter for the human body. Temperature-responsive materials can enable the controlled release of drugs by modulating the critical solution temperature (LCST) of thermosensitive polymers through volumetric phase transitions. As shown in Fig. 5a, a mixture of PCL and temperature stimuli-responsive nanogel was used to form the outer shell [151]. The nanogel was composed of temperature-responsive poly(N-isopropylacrylamide) copolymerized with acrylic acid, which could shrink or expand with ambient temperature changes. Therefore, the existence or disappearance of nanochannels between the nanogel and PCL could be controlled by varying the temperature. In this case, the drug-encapsulating shell acted as a valve to control ordered drug release. Three-cycle low-to-high temperature transition images of drug release demonstrated better temperature-responsive drug release properties when nanogels were encapsulated in the shell compared to when nanogels were omitted.

Considering the advantages of long-range and stronger penetration, near-infrared (NIR) light has been increasingly adopted as a light source in drug release-assisted tissue regeneration [152]. By introducing photothermal agents, electrospun fibers can be endowed with excellent photothermal properties, enabling the effecting delivery of nutrients and drugs [52]. Gold-based nanorods (GNRs) can also generate heat through the plasmonic resonance effect under NIR irradiation. As shown in Fig. 5b, GNRs-loaded poly(N-isopropylacrylamide) (PNIPAM) composite nanofibers were used to allow the controlled release of drugs by NIR irradiation [153]. The heat generated by the GNRs ensured the shrinkage of thermally responsive PNIPAM nanofibers to allow for the drug release, and this on-demand DDS could be regulated by the NIR power density. This convenient, remote-controllable, non-invasive approach provides new ideas for the on-demand delivery of required doses of drugs.

Magnetic fields, electric fields, and ultrasound are also research foci due to their relevance to corresponding stimuli and ease of operation. For magnetic fields, superparamagnetic iron oxide nanoparticles (IONPs) have been applied for osteogenic differentiation and axon extension [154, 155]. The hyperthermia caused by IONPs under magnetic field is also beneficial for reducing drug transmission loss and enhancing targeted delivery [37]. In one study, a nanofiber scaffold composed of temperature-responsive polymers, magnetic nanoparticles (MNPs), and an anticancer drug (DOX) was designed (Fig. 5c) [156]. The MNPs generated heat under an alternating magnetic field (AMF), which dissociated the polymer network in the nanofibers and allowed the release of DOX. By switching the "on–off" properties of the magnetic field, the drug could be delivered on demand.

Fig. 5 External stimuli-responsive drug delivery fiber systems. **a** Schematic illustration showing the mechanism of thermal switch-controlled drug release system, and the release rate of drug upon multiple cycles of low-to-high temperature transitions. Reproduced with permission from Ref. [151]; Copyright 2015, Wiley–VCH Limited. **b** Schematic illustration showing the thermal-responsive release of fluorescein from nanofibers containing gold nanorods upon NIR irradiation, and the release curves with NIR irradiation at different power densities. Reproduced with permission from Ref. [153]; Copyright 2021, Multidisciplinary Digital Publishing Institute Limited. **c** Schematic illustration showing the temperature-responsive release of DOX, and the cumulatively released percentages of DOX with alternating cycles of "ON–OFF" switching of AMF. Reproduced with permission from Ref. [156]; Copyright 2013, Wiley–VCH Limited.

d Schematic illustration showing the electrical-responsive release of DEX from PLGA nanofibers, and the cumulative mass release of DEX under the control of electrical stimulation. Reproduced with permission from Ref. [162]; Copyright 2006, Wiley–VCH Limited. **e** Schematic illustration showing the multimodal-responsive release of DEX from piezoelectric nanofibers by breaking the silica (SiO_2) capsules under the action of ultrasound, the images showing the situation after 60 s of sonication. Reproduced with permission from Ref. [32]; Copyright 2018, American Chemical Society Limited. **f** Schematic illustration of synergistic sono-photodynamic therapy for breast cancer via 808 nm laser and 1 MHz ultrasound, as well as the live/dead staining images. Reproduced with permission from Ref. [166]; Copyright 2020, American Chemical Society Limited

The generated heat and chemotherapeutic effects of the released DOX rapidly induced cancer cell apoptosis.

External electrical stimulation has also been used for bone repair [157], nerve regeneration [158], and drug delivery [159]. For example, electrical stimulation can modulate curcumin (CUR) delivery through volume changes

induced by the voltammetric response of PEDOT nanoparticles [160]. A PPy-PVDF electrospun system was used as a carrier to load growth factor complexed with streptavidin, and the release curve of the growth factor showed an obvious electro-sensitive release behavior [161]. As shown in Fig. 5d, dexamethasone (DEX) was released from the

PEDOT nanotubes by controlling the contraction or expansion of PEDOT by electrical stimulation [162]. The blue curve represents the cumulative mass release of DEX from PEDOT-encapsulated poly (lactic-co-glycolic acid) (PLGA) nanofibers when 1 V electrical stimulation was applied at five specific times.

As for ultrasound, it usually provides a sustained thermal effect from continuous oscillation of microbubbles and a mechanical effect upon rupture [163]. Ultrasound has been shown to trigger the release of drugs, as well as promote deep drug penetration with minimal thermal damage to surrounding tissues [164]. By encapsulating drugs into ultrasound-sensitive microcapsules, scaffolds can be effectively combined for multimodal triggered release [32]. Figure 5e shows that silica microcapsules in the fibers were destroyed, and TRITC-BSA was effectively released under the stimulation of ultrasonic waves. This approach can be extended to both exogenous (NIR irradiation, electrical stimulation) and endogenous (enzymatic treatment) stimuli to improve the precise delivery of multiple drugs.

Recently, attention has been drawn to the idea of applying multiple stimuli synergistically to deliver drugs. For example, a smart hyperthermic nanofiber has been developed with the ability to simultaneously switch two-stage drug release in response to AMF and heat [34]. In addition to their own effects on cell behavior and tissue regeneration, some related therapies, such as photothermal therapy, magnetothermal therapy, electromagnetic thermotherapy, and sonodynamic therapy, have also been derived from these strategies and show to have synergistic effects with drugs [165]. As shown in Fig. 5f, the synergistic sono-photodynamic therapy significantly promoted the generation of ROS and achieved a 95.8% inactivation rate of breast cancer cells under 808 nm NIR irradiation and 1 MHz ultrasound treatment [166]. These potential integrative mechanisms should be incorporated into drug-loaded electrospun fiber scaffolds to facilitate the development of future nanomedicines and promote tissue regeneration and cancer therapy.

Applications for Tissue Regeneration and Cancer Therapy

Electrospun fibers for DDSs have been developed and explored based on the diversity and simplicity of the preparation methods for drug-loaded electrospun fiber scaffolds, as well as the design of fiber structures, the selection of electrospinning parameters, post-treatment methods, and the combination of various stimuli. These products have been widely applied to tissue regeneration, including soft tissues (such as skin, nerve, cardiac, and blood vessels) and hard tissues (such as bone, cartilage, and musculoskeletal and dental systems), as well as cancer therapy.

Skin Tissue Engineering

Skin regeneration and wound healing are dynamic and complex processes that usually include four overlapping and different periods: hemostasis, inflammation, proliferation, and remodeling [167]. To promote wound repair, functional drug-loaded fibrous scaffolds can be prepared through electrospinning technology, which can effectively avoid wound infection, shorten the inflammatory stage, promote tissue proliferation and remodeling, and prevent granulation tissue proliferation and scar formation.

Bacterial infection is an inevitable and urgent problem during wound healing [168, 169]. Therefore, many researchers have loaded antimicrobial agents or nanoparticles into nanofibers by blending electrospinning technology to improve antibacterial function [170, 171]. For example, tetracycline hydrochloride has been loaded into poly (ω-pentadecalactone-co-ε-caprolactone)/gelatin/chitosan nanofibers to achieve excellent antibacterial effects against gram-positive and gram-negative bacteria [172]. However, given the increasing bacterial resistance and the burst release of drugs, it remains a great challenge to achieve sustained and efficient antibacterial activity at the wound site using the aforementioned methods [173]. In addition to exploring and synthesizing new types of alternative antimicrobial agents, antimicrobial peptides have also been incorporated in fibers to achieve deep bactericidal effects [174]. For instance, a Janus-type antibacterial dressing loaded with antimicrobial peptides was prepared by combining electrospinning nanofiber membranes with dissolvable microneedle arrays [175]. This antibacterial dressing could penetrate bacterial biofilms to effectively kill bacteria. To further enhance the antibacterial effect of these materials, as well as to achieve the controlled release of drugs, some drug-loaded fiber platforms have been explored with respect to external stimuli [176]. The obtained nanocomposite fiber scaffolds exhibited excellent NIR light-triggered controlled drug release behavior. As shown in Fig. 6a, the dressing caused irreversible damage to bacterial biofilms under NIR irradiation, thus effectively inhibiting infection by drug-resistant bacteria.

Hemostasis is a critical period in the wound healing process. Although the body has an inherent hemostatic system, it cannot stop bleeding quickly [43]. Therefore, many hemostatic agents have been incorporated into hemostatic dressings by electrospinning technology, and this approach has attracted wide attention. For example, an ultralight 3D gelatin sponge prepared by conjugate electrospinning technology was able to aggregate a large number of activated platelets and accelerate the formation of platelet clots [177]. An in vivo study showed that this gelatin nanofiber sponge could rapidly induce stable blood clots in a rabbit ear model of artery injury and was associated with reduced bleeding compared to gelatin nanofiber membrane (Fig. 6b).

Sustained inflammation also seriously postpones wound healing [178–180]. Especially in chronic wounds, high ROS levels often result in a failure of wound healing. Therefore, removing excessive ROS can reduce oxidative stress to effectively promote collagen deposition and ECM remodeling [181]. For example, poly (L-lactide-*co*-caprolactone)/gelatin core-sheath nanofibers loaded with epigallocatechin-3-O-gallate (EGCG) exhibited excellent ROS-scavenging ability, promoting skin regeneration and inhibiting subsequent wound infection [180].

In addition to excessive ROS, high expression of various pro-inflammatory chemokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which are secreted by neutrophils and macrophages, can also severely delay wound healing [182]. It has been shown that anti-inflammatory drugs released at a wound can effectively down-regulate expression of IL-6 and TNF-α [183]. At the same time, this approach can reduce inflammatory response at the wound, promote fibroblast proliferation, and accelerate the reconstruction of granulation tissue. For example, PCL nanofibers loaded with dimethyloxalylglycine can significantly promote angiogenesis and improve the re-epithelialization ratio [184]. Meanwhile, at the molecular level, this approach promoted wound healing by enhancing the expression of anti-inflammatory factors (IL-4) and reducing the expression of pro-inflammatory factors (IL-6) (Fig. 6c).
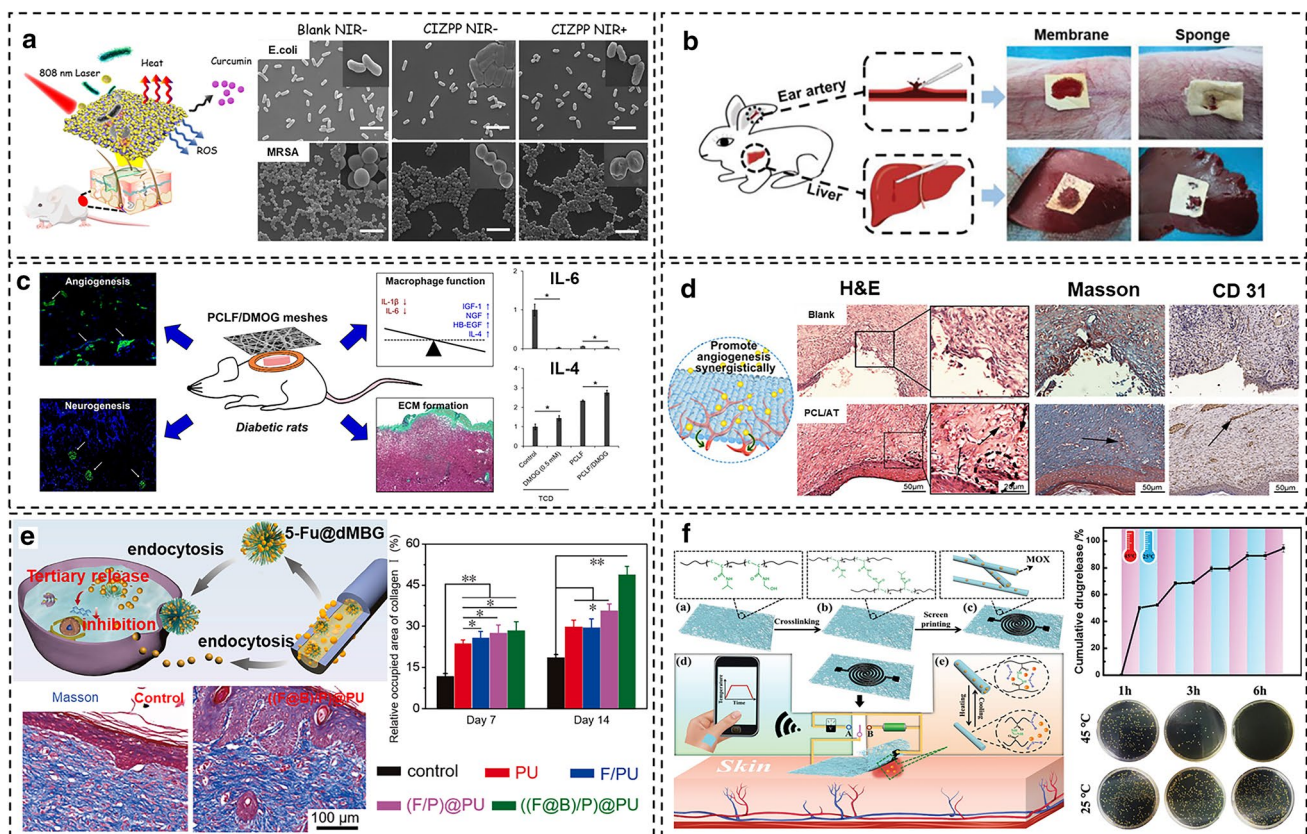
Fig. 6 Drug delivery systems based on electrospun fiber scaffolds for skin tissue engineering. **a** Illustration of dual stimuli-responsive fibrous membranes for drug-resistant bacterial infection, and SEM images of *E. coli* and MRSA incubated with or without NIR irradiation. Scale bar = 5 μm. Reproduced with permission from Ref. [176]; Copyright 2022, Elsevier Limited. **b** Illustration and macroscopic images of the different samples after in vivo hemostasis in an ear artery injury model and a liver trauma model of rabbits. Reproduced with permission from Ref. [177]; Copyright 2021, Wiley–VCH Limited. **c** Schematic illustration of PCL nanofibers loaded with dimethyloxalylglycine can significantly promote angiogenesis and re-epithelialization, and expression levels of IL-6 and IL-4 were detected in macrophages cultured for 2 days. Reproduced with permission from Ref. [184]; Copyright 2017, American Chemical Society Limited. **d** Schematic illustration of H&E, Masson's and CD31 immunohistochemical staining images of different groups of wound areas at 14 days. The black arrow indicates the blood vessel, the semi-black arrow indicates the keratinous basal cells, and the dotted circle shows the epithelial spike. Reproduced with permission from Ref. [185]; Copyright 2019, American Chemical Society Limited. **e** Schematic diagram of the synthesis of careob-like 5-Fu@dMBG/PEO@PEEUU nanofibers (((F@B)/P)@PU) and the quantitative analysis of relative occupied area of collagen I at post-surgery. Reproduced with permission from Ref. [189]; Copyright 2022, Elsevier Limited. **f** Schematic of the fabrication of on-skin electronic devices and temperature-sensitive on-demand drug release, the release profiles of MOX, and photographs of agar plates onto which *S. aureus* suspensions. Reproduced with permission from Ref. [196]; Copyright 2019, Wiley–VCH Limited

Tissue regeneration and remodeling involve angiogenesis, granulation tissue formation and re-epithelialization [167]. During the process of wound healing, angiogenesis is beneficial for the continuous delivery of oxygen and nutrients to the wound. As shown in Fig. 6d, an oriented, aligned PCL nanofiber membrane loaded with tazarotene promoted angiogenesis and significantly accelerated wound healing and re-epithelialization ratio [185]. In addition, various types of growth factors, peptides, and RNA can be delivered from electrospun nanofibers to promote angiogenesis [71, 74]. During the tissue regeneration stage, loading growth factors into nanofibers is an effective way to improve the wound healing rate. For example, PCL/PEG core–shell nanofibers loaded with EGF and basic fibroblast growth factor can significantly promote fibroblast proliferation and enhance collagen deposition and keratin synthesis [186].

If a wound is not treated properly, scar formation is very likely. Scar formation is primarily due to excessive inflammation, myofibroblast proliferation, and over-deposition of collagen [187]. Loading of nanofibers with scar inhibitors can effectively inhibit the formation of scars. At present, common scar inhibitors include TGF-β inhibitor [188], 5-fluorouracil [189], α-lactalbumin [190], 20(R)-ginsenoside Rg3 [191], palmatine, and triamcinolone acetonide [192, 193]. Typically, 5-fluorouracil (5-Fu)-loaded dendritic mesoporous bioglass nanoparticles (dMBG) are loaded in electrospun nanofibers by coaxial electrospinning, and the obtained scaffolds can significantly promote wound healing and inhibit scar formation (Fig. 6e) [189].

Currently, another challenge for wound dressings is that it is difficult to monitor the real-time state of wound repair while simultaneously meeting the needs of wound healing treatment [194]. With the emerging development of bioelectronics, many integrated electronic dressings have been developed to integrate diagnosis, monitoring, and treatment [195]. These techniques also allow the monitoring of wound status and on-demand controlled drug delivery based on changes in the wound microenvironment. As shown in Fig. 6f, a flexible and breathable thermal-responsive nanofiber membrane can monitor the temperature of wound tissue in real time and trigger the on-demand release of antibiotics from the fibers according to temperature changes [196].

Nerve Tissue Engineering

Injuries to the nervous system, including both the peripheral nervous system and the central nervous system, often lead to nerve cell death and tissue destruction, resulting in permanent loss of nerve function [197]. Although recent developments are promising, it nevertheless remains a great challenge to treat nerve injuries using tissue engineering scaffolds.

For peripheral nerve repair, nerve guidance conduits (NGCs) constructed from electrospun fibers are considered to be optimal nerve graft substitutes because of their excellent biocompatibility, tunable mechanical properties, porosity, and capacity to provide guidance cues [64]. Unmodified fiber-based NGCs often fail to overcome the barriers of limited regenerative capacity and disordered axonal growth, especially when used to repair thick nerves with large gaps [198]. To this end, integrating NGCs with topographic cues [48, 197] and biological signals [123, 124, 199, 200] is often done to overcome these barriers. One current potential strategy is to create nerve conduits based on topographical cues in combination with drugs, with different drug loading modes controlling drug release [3, 16]. For example, drugs physically attached to a scaffold usually have faster release rates, while drugs embedded in microspheres or fibers are hindered by complex cross-linking networks [201, 202].

Typically, gradient structures can provide chemotactic or haptotactic cues for accelerating cell migration and neurite extension. As shown in Fig. 7a, a concentration gradient of active functional groups was first generated on nanofiber surface, after which an NGF density gradient was successfully constructed based on the amphiphilic nature of heparin, ultimately promoting the directional outgrowth of neurites from DRG along the direction of increasing NGF concentration [200]. In addition to the adsorption or immobilization of growth factor on the fiber surface, bioactive particles have also been deposited on fibers. Figure 7b shows the application of a masked electrospray method to construct a density gradient of biomacromolecular nanoparticles on the surface of uniaxially aligned fibers by manipulating the deposition period with a movable physical mask [124]. The aligned fibers could guide neurite extension along the fiber alignment, while the density gradient of biological macromolecules further promoted directional extension of neurites along the direction of increasing particle density.

Another therapeutic approach is to combine external stimuli, such as light [203], electricity [204, 205], or magnetic field [206], to regulate cell behavior and induce tissue regeneration. Under the action of AMF, superparamagnetic iron oxide nanoparticles could be uniformly distributed in fibers, and the fabricated hybrid fibers could respond to a magnetic field and promote neurite extension (Fig. 7c) [206]. In addition, as electrically active tissues, neurite extension can be promoted by applying electrical stimulation at an appropriate intensity. For example, electrically conductive electrospun fibers can be loaded with NGF and combined with electrical stimulation to further accelerate the extension of neurites from PC12 cells along the direction of the electrical field (Fig. 7d) [158].

For peripheral nerve repair, some researchers rely on different drug release rates to design NGCs. As shown in Fig. 7e, core-sheath fibers loaded with two growth factors

were prepared by coaxial electrospinning [207]. The fast release of VEGF from the sheath layer promotes the migration, proliferation, and differentiation of endothelial cells, while the slow release of NGF promotes long-term axonal elongation. With the release of VEGF, intraneural vascularization, an important prerequisite for nerve regeneration [208], could be achieved. More importantly, the generated blood vessels could provide guidance for cell migration and transport oxygen and nutrients to axons and Schwann cells [60, 209], which is particularly significant for the repair of thick nerve defects. Polymer microspheres [210] and inorganic nanoparticles [211] can also serve as carriers of neurotrophic factors and be incorporated with electrospun fibers to regulate conduit delivery behavior.

Furthermore, hydrogels can encapsulate a variety of bioactive substances, and their degradability can be varied by regulating the degree of cross-linking [2, 212]. In addition, hydrogels can simulate the ECM of natural tissues and generate a 3D microenvironment conducive to nerve tissue regeneration [213]. Therefore, the development of electrospun fiber-hydrogel drug loading systems has significant potential. Multiple small conduits can be sequentially embedded within a larger conduit to simulate the multibundle structure of human nerves, effectively reducing side effects associated with disordered axon growth [61]; furthermore, this type of NGC can be combined with drug loaded-hydrogels to additionally promote nerve repair. Distinct properties can be introduced into each lumen to optimize conduit performance, so this highly bionic structure will be ideal for nerve tissue regeneration.

Distinct from peripheral nerves, neurons of the central nervous system (CNS) can hardly regenerate axons due to the harsh microenvironment after CNS injury [138, 214]; therefore, remodeling the microenvironment can support CNS regeneration [215]. Furthermore, more endogenous cells should be promoted to migrate, infiltrate into the damaged area and differentiate into neurons to rebuild the damaged neural circuit network [216]. The main approach is to release anti-inflammatory drugs to reduce inflammation and regulate the acidic microenvironment. MP, a strong anti-inflammatory drug, can be loaded on the electrospun fiber scaffold with polysialic acid to promote axonal regeneration [217]. As shown in Fig. 7f, MP can effectively inhibit inflammatory reactions and glial cell proliferation while ensuring axon growth. In contrast to direct release, anti-inflammatory drugs can be loaded in liposomes and grafted onto scaffolds by chemical bonds that can be broken in response to the acidic pH of the inflammatory environment [138], thereby reducing the risk to benign areas. In addition, proteoglycans in the ECM of neurons condense around neurons to prevent the influence of harmful substances. However, proteoglycan condensation becomes a physical barrier to nerve recovery after spinal cord injury, so the addition of proteases could

decompose these proteoglycans and break down this barrier [214]. Thus, protease- and neurotrophic factor-based fiber scaffolds can build renewable bridges in spinal cord defects. In summary, electrospun fiber scaffolds for the repair of spinal cord injury require a combination of multiple optimization factors to regulate the microenvironment and promote nerve regeneration [218].

Brain tissue is a complex nerve tissue, and common brain diseases include traumatic brain injury [219, 220], stroke [221] and others. In the repair of brain injury, it is also important to promote endogenous cells to migrate toward the damaged area and differentiate into neurons to rebuild the damaged nervous system [216]. Neurotrophic factors play an important role in the protection and migration of nerve cells. However, they cannot be delivered to injured sites because of their lack of permeability through the blood–brain barrier (BBB) [222, 223]. Engineering bioactive electrospun fiber scaffolds can enable the treatment and repair of brain diseases. Monosialotetrahexosylganglioside (LysoGM1) is one kind of drug that can protect neurons and promote nerve regeneration [224]. By chemically grafting LysoGM1 onto fiber scaffolds, its biological activity can be maintained, and the diffusion effect could be weakened to some extent [220]. As shown in Fig. 7g, the scaffold could continuously deliver drugs to the injured area in a traumatic brain injury model, contributing to a reduction in the number of astrocytes and good regeneration of nerve tissue. Meanwhile, neurodegenerative diseases, including Alzheimer's disease [225] and Parkinson's disease [226], are common mental disorders caused mainly by the decreased ability of neurons and glial cells to secrete nutritional factors. Therefore, the ability of electrospun fibers to deliver nutritional factors to brain tissue is highlighted again, and the release profile of factors is more suitable than that associated with current clinical drug administration methods; thus, the frequency of drug administration could be reduced [227]. Of note, electrospun fibers also play an important role in detecting diseases, including potential diagnosis of neurodegenerative diseases through a variety of physiological indicators [228, 229]. For instance, coupling dopamine receptors to electrospun fibers can enable the detection of neurodegenerative disorders with high sensitivity and rapid responsiveness [229].

Great progress has been achieved in applying drug-loaded electrospun fiber scaffolds to promote nerve regeneration, but some side effects remain due to fast drug diffusion, resulting in high local drug concentrations. In addition, short drug half-lives also present a major challenge for nerve repair [209]. Therefore, the long-term maintenance of drug activity in vivo and precise response to microenvironmental changes at various stages remain the key foci of follow-up research. Moreover, axonal myelin formation is another key factor in functional recovery, and ways to regulate the phenotype of Schwann cells should be included
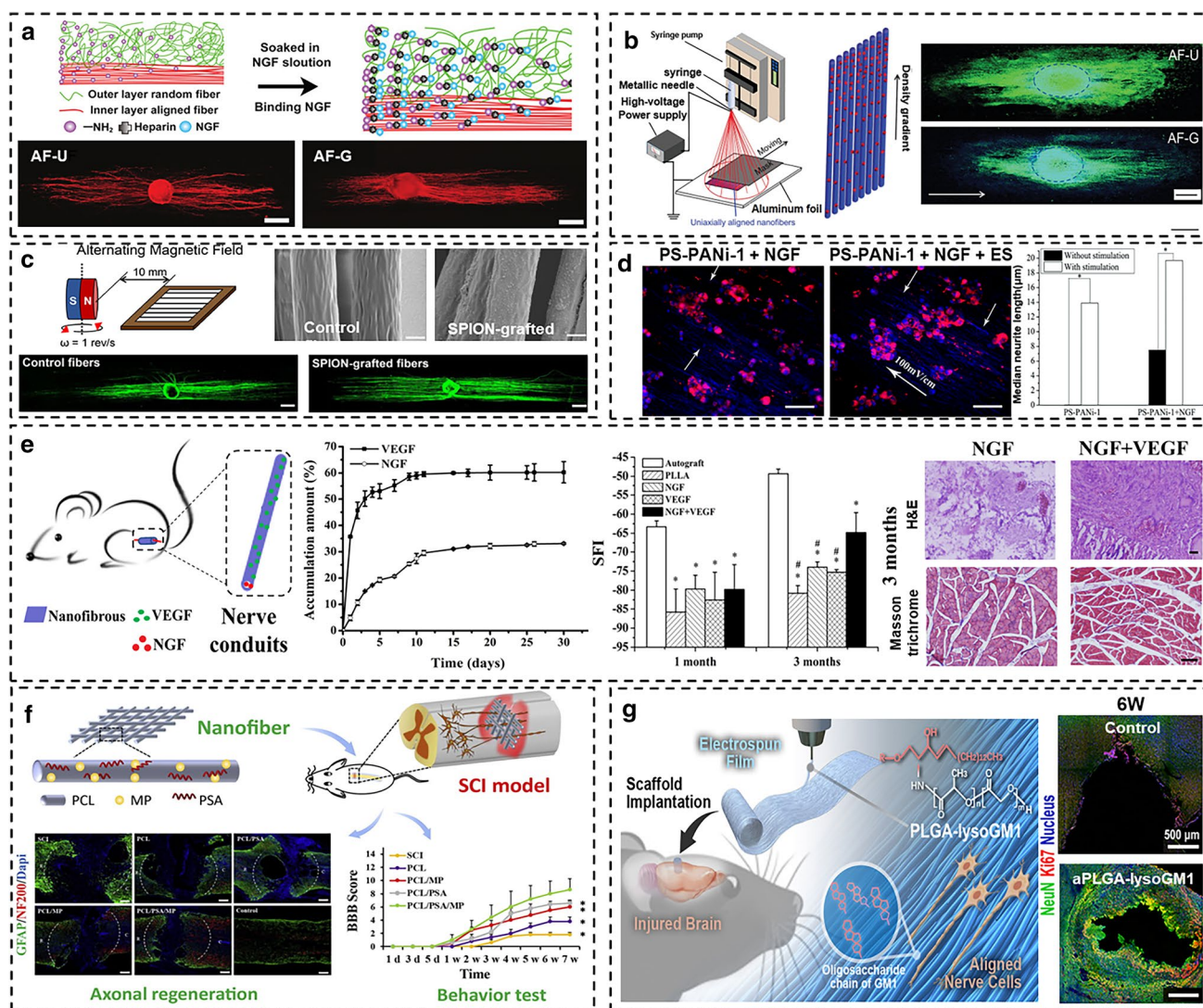
Fig. 7 Drug delivery systems based on electrospun fiber scaffolds for nerve tissue regeneration. **a** Schematic illustration showing the construction of concentration gradient of NGF on aligned fibers by amino and heparin functionalization, and fluorescence micrographs showing the extension of neurites from DRGs on the uniform and gradient scaffolds. Scale bar = 500 μm. Reproduced with permission from Ref. [200]; Copyright 2020, Wiley–VCH Limited. **b** Schematic illustration showing the generation of density gradient of biomolecular nanoparticles on the surface of uniaxially aligned electrospun fibers using masked electrospray method, and fluorescence micrographs showing the extension of neurites from DRGs on the uniform and gradient scaffolds. The neurites were stained with Tuj1 (green). Scale bar = 500 μm. Reproduced with permission from Ref. [124]; Copyright 2020, Wiley–VCH Limited. **c** Schematic of external stimulation device, SEM images showing the morphology of pristine fibers and SPION-grafted fibers, and fluorescence micrographs showing the extension of neurites from DRGs on the blank and SPION-grafted scaffolds. The neurites were stained with neurofilament (green). Scale bar = 500 μm. Reproduced with permission from Ref. [206]; Copyright 2021, Elsevier Limited. **d** Fluorescence micrographs showing the extension of neurites from PC12 cells on the scaffolds without/

with electrical stimulation, and the chart showing the promoting effect of electrical stimulation on neurite growth. Scale bar = 50 μm. Reproduced with permission from Ref. [158]; Copyright 2014, The Royal Society of Chemistry Limited. **e** Schematic illustration of simultaneous loading of NGF and VEGF in the scaffold, the chart showing the different diffusion rate of different growth factors, and both of SFI value and Tissue section staining images showing the scaffold with NGF and VEGF has a good ability to promote repair. Scale bar = 25 μm. Reproduced with permission from Ref. [207]; Copyright 2018, Elsevier Limited. **f** Schematic illustration of scaffold loaded with MP and polysialic acid (PSA) implanted in the model of spinal cord injury in mice, and both of BBB score and Tissue section staining images showing the scaffold has the abilities to inhibit inflammation and promote spinal regeneration. Scale bar = 100 μm. Reproduced with permission from Ref. [217]; Copyright 2018, Elsevier Limited. **g** Schematic illustration of scaffold containing LysoGM1 implanted in traumatic brain injury model, and the scaffold have abilities to promote cell migration and differentiation. Tissue section staining image also present the enhancement of nerve regeneration. Scale bar = 500 μm. Reproduced with permission from Ref. [220]; Copyright 2020, American Chemical Society Limited

in future scaffold design [230]. In addition, scaffold neuro-imaging will have great potential in future applications, as it is indisputable that non-invasive imaging helps monitor nerve regeneration and enables real-time adjustments based on individual regeneration differences.

Cardiac Tissue Engineering

Due to the limited regenerative capacity of cardiac tissue, it is difficult for ischemic myocardial tissue to repair itself after myocardial infarction (MI) [231]. Although heart transplantation is the most effective way to restore cardiac function, the shortage of donor organs and side effects after transplantation seriously limit its application [232]. Electrospun nanofibers can mimic the natural ECM structure, provide temporary physical support for damaged heart tissue, and limit ventricular dilatation and remodeling [233]. Therefore, it is possible to use nanofibers for cardiac tissue engineering because of their controllable fiber structure and capacity to improve the retention rate of bioactive substances.

During the necrotic phase after MI, a large number of cardiomyocytes necrotize while releasing excessive ROS and other cellular contents into the surrounding microenvironment [234, 235]. As a result, many immune cells are recruited to the damaged cardiac tissue. After MI, this inflammatory environment disrupts cell homeostasis, leading to more severe oxidative damage. Therefore, to avoid the occurrence of inflammation, scavenging of excessive ROS can effectively inhibit pathological remodeling of the left ventricle. For example, MP-loaded polyurethane fiber patches can release anti-inflammatory drugs to remove excess ROS [147]. As shown in Fig. 8a, fiber patches containing MP could significantly promote cardiac functional repair and angiogenesis while reducing fibrosis and cardiac remodeling. In addition to the local delivery of anti-inflammatory drugs by nanofibers to reduce inflammation, many anti-inflammatory nanoparticles can be loaded into nanofibers to effectively remove excessive ROS and relieve inflammation. For example, a cerium oxide nanoparticles-loaded PCL/gelatin nanofiber scaffold can significantly reduce ROS levels in the MI area and inhibit cardiomyocyte hypertrophy [236].

After MI, the hypoxic state is highly susceptible to oxidative stress and irreversible cardiomyocyte death, so the restoration of oxygen supply is extremely important [237–239]. Therefore, a bilayer cardiac patch loaded with calcium peroxide and adipose stem cell exosomes was fabricated to enable continuous oxygen supply, alleviate oxidative stress, and promote angiogenesis [240]. In addition to reducing inflammation, an ideal cardiac patch also needs to provide adequate blood supply to the left ventricle. To this end, a cardiac patch was prepared by covalently combining nitrate

pharmacological functional groups with biodegradable PCL [241]. To further reduce cardiac fibrosis, an alternative strategy induces fibrotic cardiomyocytes into new cardiomyocytes. In particular, functionalized nanofibers can effectively support the proliferation and adhesion of cardiomyocytes to promote the self-repair of cardiac tissue. For example, PLGA nanofibers covalently coupled with two adhesion peptides, YIGSR and RGD, could promote the adhesion and proliferation of cardiomyocytes [242].

Functionalized nanofibers also support the adhesion and proliferation of other cells that can differentiate into cardiomyocytes. For example, a VEGF-coated nanofiber scaffold can significantly promote the differentiation of human mesenchymal stem cells into cardiomyocytes [243]. In addition, as shown in Fig. 8b, a chitosan/serin protein-modified cellulose nanofiber patch not only improved the survival rate of adipose tissue-derived mesenchymal stem cells but also reduced myocardial fibrosis and inhibited ventricular remodeling after MI [244]. Beyond exogenous cell therapy, two muscle-specific microRNAs can be delivered using nanofibers with different topologies, after which they reprogram cardiac fibroblasts into cardiomyocyte-like cells and reduce myocardial fibrosis [245].

After MI, the electrical microenvironment usually undergoes pathological changes, such as abnormal contraction, disruption of the conductive network, and irregular propagation of electrical signals, which severely limit repair of the damaged myocardium [246]. Usually, various conductive agents can be added to improve the electrical microenvironment in the MI area [247]. However, it is difficult to achieve real electrical anisotropy matching the natural myocardium by simply loading conductive materials or adjusting the orientation of the fiber structure. In one study, a reduced graphene oxide functional silk fibroin nanofiber patch was developed with a similar anisotropic conductivity to natural myocardium to improve the electrical microenvironment of infarcted myocardium (Fig. 8c) [248]. In addition to improving the electrical microenvironment of the myocardium, it is particularly important for the myocardium to beat synchronously and rhythmically [249]. Although it has been verified that spontaneous cardiomyocyte contraction can be observed when cardiomyocytes are cultured on fibers, it is also essential that they beat synchronously with the natural myocardium. The mechanical properties, arrangement structure, chemical composition and electrical conductivity of fibers significantly affect the beating of cardiomyocytes on fibers [250]. When cultured on parallelly aligned conductive polyaniline/PLGA nanofibers, all cardiomyocytes within a single cluster were found to beat synchronously [251].

Congenital heart disease is a congenital disease distinct from MI [252], and autologous cardiomyocyte therapy is the main treatment method. Due to the low retention rate of injected cells, one promising solution for the treatment of
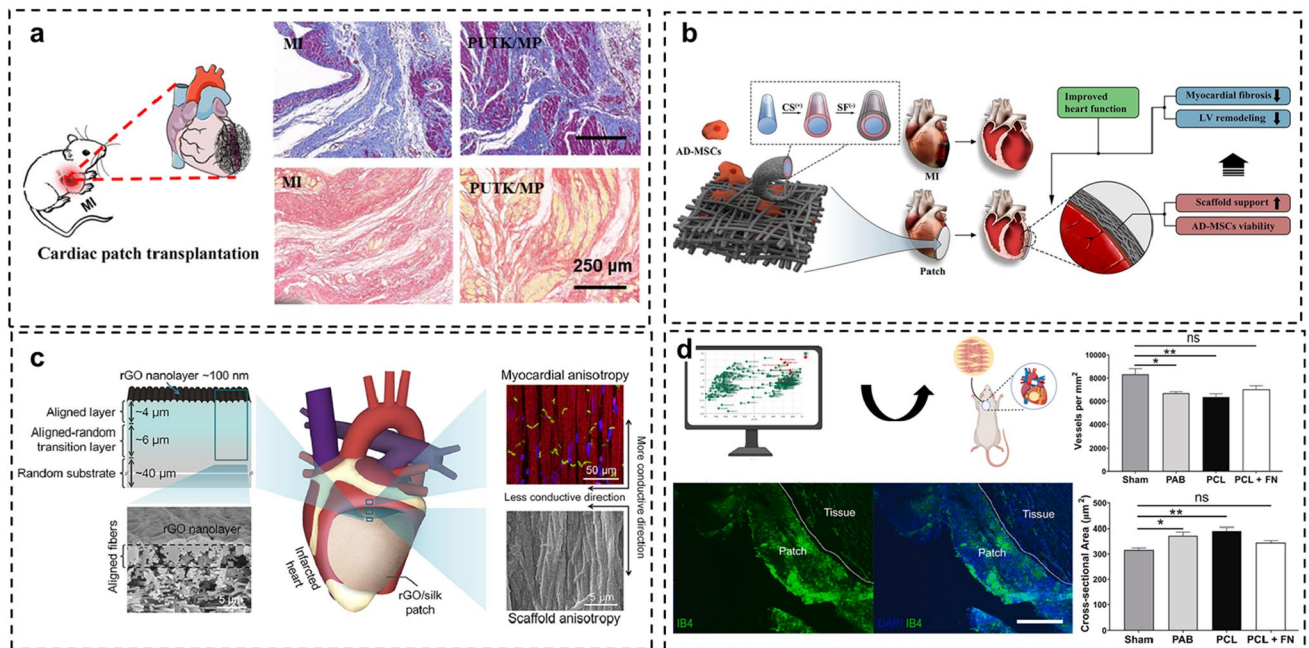
Fig. 8 Drug delivery systems based on electrospun fiber scaffolds for cardiac tissue engineering. **a** Schematic illustration showing the application of a methylprednisolone (MP)-loaded PUTK fiber patch to suppress inflammation, and Masson and Sirius red staining shows the pathological examination of the hearts. Reproduced with permission from Ref. [31]; Copyright 2020, Elsevier Limited. **b** Schematic illustration showing the application of chitosan/silk fibroin-modified nanofiber patch seeded with mesenchymal stem cells for preventing heart remodeling post-MI in rats. Reproduced with permission from Ref. [244]; Copyright 2018, Elsevier Limited. **c** Schematic and cross-sectional SEM images illustrating the structure of the rGO/silk fibroin scaffolds, from the bottom to the top, consisting of a ran-

domly arranged layer, randomly oriented layer and oriented layer, the thickness between different layers, and the conductive anisotropy that can be transmitted through the patch through implantation were used to reconstruct the anisotropic electrical microenvironment of the infarcted myocardium. Reproduced with permission from Ref. [248]; Copyright 2022, Elsevier Limited. **d** Schematic illustration of using computational methods to design patient-specific electrospun fiber-based cardiac patches for pediatric heart failure, representative images of patches attached to the RV in tissue sections collected after 4 weeks following implantation, and quantification of vessel density and myocyte hypertrophy. Scar bar = 200 μm. Reproduced with permission from Ref. [256]; Copyright 2022, Elsevier Limited

congenital heart disease is the delivery of c-Kit cardiac progenitor cells via nanofiber scaffolds [253, 254]. For example, nanofibers coated with gelatin and/or fibronectin effectively enhance the metabolism of c-Kit + cardiac progenitor cells [255]. However, the quality of c-Kit+ progenitor cells differs significantly across patients. To solve these problems, a computational modeling approach has been used to determine the repair mechanisms of cardiac-derived c-Kit cells and understand how these mechanisms can be used to design biomaterials to improve cardiac patch performance [256]. As shown in Fig. 8d, a nanofiber patch for pediatric heart failure patients was designed and prepared by computational methods and was confirmed to effectively achieve antifibrosis and angiogenesis.

DDSs based on electrospun nanofiber scaffolds can be engineered with anti-inflammatory capabilities to promote myocardial cell adhesion and proliferation and achieve cardiac phenotype and function for cardiac tissue engineering. To enable versatility and achieve these functions simultaneously and comprehensively, multiple regulatory signals need to be integrated on a single platform. Moreover,

achieving synchronized contraction and electrical anisotropy that matches the natural myocardium remain major challenges. Electrically active biomaterials can combine electrical stimulation with scaffolds to promote cardiac tissue regeneration and maintain synchronized beating contractions of heart tissue. Continuous delivery of different bioactive factors at typical time points is also important to improve repair efficacy. In situ measurement of delivered drug concentrations during the delivery period remains difficult. In addition, real-time monitoring of the regeneration process is important. The integration of imaging techniques can further address both issues and has important implications for the exploration of physiological processes in cardiac tissue regeneration, as well as the study of the regulatory behaviors of materials in vivo.

Bone Tissue Engineering

As a typical hard tissue, bone tissue exhibits a complex and highly stratified structure with high density and involves various growth factors and endogenous signals [257]. Bone

tissue engineering also involves many aspects, including osteogenic differentiation, angiogenesis, bone healing, and the treatment of bone-related diseases [258]. Electrospun fiber scaffolds provide a structure that simulates the bone environment and have drug-delivery advantages (for small molecule drugs and growth factors, etc.), which are expected to solve problems related to limited donor sites for autologous transplantation and to provide a promising avenue for bone tissue engineering.

To promote bone tissue regeneration, the primary task is to enhance osteogenic activity. To this end, researchers have investigated a series of electrospun fibers combined with the delivery of bioactive substances that promote osteogenesis [259–261]. For example, a layered micro/nanofiber biomimetic periosteum with sustainable release of VEGF has been developed (Fig. 9a) [117]. VEGF was encapsulated in hyaluronan (HA)-poly(L-lactide) acid (PLLA) core-sheath fibers and released in a sustained manner to promote angiogenesis, and collagen self-assembly on the fibers greatly mimicked the microenvironment necessary for intramembranous osteogenesis. The 3D reconstruction images of the defect at 4 and 8 weeks post-surgery showed that the repair effect of the mat was the most satisfactory, suggesting a synergistic effect of hierarchical structure and VEGF in promoting osteogenesis. In view of the complexity of the bone repair process, co-delivery or sequential delivery of multiple drugs is generally required, so it is particularly important to design electrospun fiber scaffolds that can carry multiple drugs and allow their release in a controlled manner [262]. Coaxial electrospinning and LBL provide good methods for this. For example, a nanofiber mat made of core-sheath fibers with PVA as the core and SF/PCL as the shell was prepared, BMP-2 introduced into the core, and connective tissue growth factor (CTGF) was bound to the surface of the nanofibers through LBL technology (Fig. 9b) [263]. Fluorescent labeling in vivo showed the sustained release of BMP-2 over 30 days, while CTGF rapidly dropped to minimum levels within 6 days, indicative of an early, transient release. In vivo studies showed that areas of alkaline phosphatase (ALP) positive tissues and angiogenesis were both significantly increased compared with a single BMP-2 release system. Similarly, the combination of DEX and BMP-2 also had a synergistic effect on ALP expression and osteogenesis [264].

The regulation of the activity balance between osteoblasts and osteoclasts is another important factor to be considered in bone repair [265]. As shown in Fig. 9c, the scaffold could achieve the simultaneous dual delivery of alendronate (ALN) and silicate to further adjust the balance between bone resorption and bone formation, thus accelerating bone repair. ALN encapsulated in MSN was released from nanofibers and inhibited the bone resorption process by preventing the expression of GTP-related proteins, while silicate released upon MSN hydrolysis accelerated the bone formation process by promoting angiogenesis and bone calcification [106]. Coaxial electrospinning can also provide a similar dual-delivery system to modulate the osteogenesis–osteoclastogenesis balance. In particular, the rapid release of substance P enhanced the migration and osteogenic differentiation of BMSCs, while the sustained release of ALN reduced bone resorption [266]. Of note, delivery systems programmed to match the spatiotemporal specificity of bone healing are increasingly being developed.

The ability of exogenous stimuli to regulate cells is gradually being appreciated. Most commonly, bioelectrical signals in native bone serve as key factors in regulating bone growth, structural reconstruction, and healing [36]. Some studies have confirmed that electrical stimulation treatment promotes the adhesion, growth, and proliferation of osteoblasts, as well as significantly enhancing calcium and phosphorus deposition [267, 268]. Similarly, the heat generated by NIR not only penetrates the tissue but also regulates the expression of heat shock proteins (HSPs) and enhances the expression of osteogenesis-related proteins [269]. By incorporating MoS_2, an osteogenesis promoter and photothermal agent, into electrospun fibers, the obtained scaffold exhibits stronger cell growth and osteogenic ability in combination with photothermal therapy [270]. Under NIR-triggered mild photothermal treatment for 30 or 60 s, the expression levels of OPN and OCN, osteogenesis-related genes, were upregulated in BMSCs after 7 and 14 days of culture, and the ability to accelerate osteogenesis and bone healing was also demonstrated in vivo in a rat tibial defect model (Fig. 9d). In addition to the introduction of stimulatory components, the design of 3D-structured fiber scaffolds can also better simulate the bone environment. For example, a radial 3D scaffold obtained by $NaBH_4$ foaming not only provides topographical clues and a good bone repair environment but also allows the loading of various growth factors to promote the bone healing process [63]. In the future, it remains a key challenge to incorporate stimulation into 3D electrospun fiber scaffolds to develop 4D bone tissue scaffolds.

One of the main causes of bone defects is bone tumors, so the design of bone tissue scaffolds requires the consideration of bone repair and prevention of bone tumor recurrence. For example, DOX was intercalated into lamellar hydroxyapatite and dissolved in PLGA for electrospinning, after which the surface of the electrospun fibers was further coated with PDA to obtain a PDA@DH/PLGA scaffold. The PDA coating prolonged the drug release (Fig. 9e) [271]. More importantly, the PDA@DH/PLGA scaffold significantly inhibited tumor cells growth initially, then subsequently improved osteoblast proliferation and promoted the repair of bone defects caused by tumor resection in vivo. The development of electrospun drug-loaded fiber scaffolds for bone tumor treatment is still worthy of further investigation, while the extensive ability to incorporate drugs into electrospun fibers
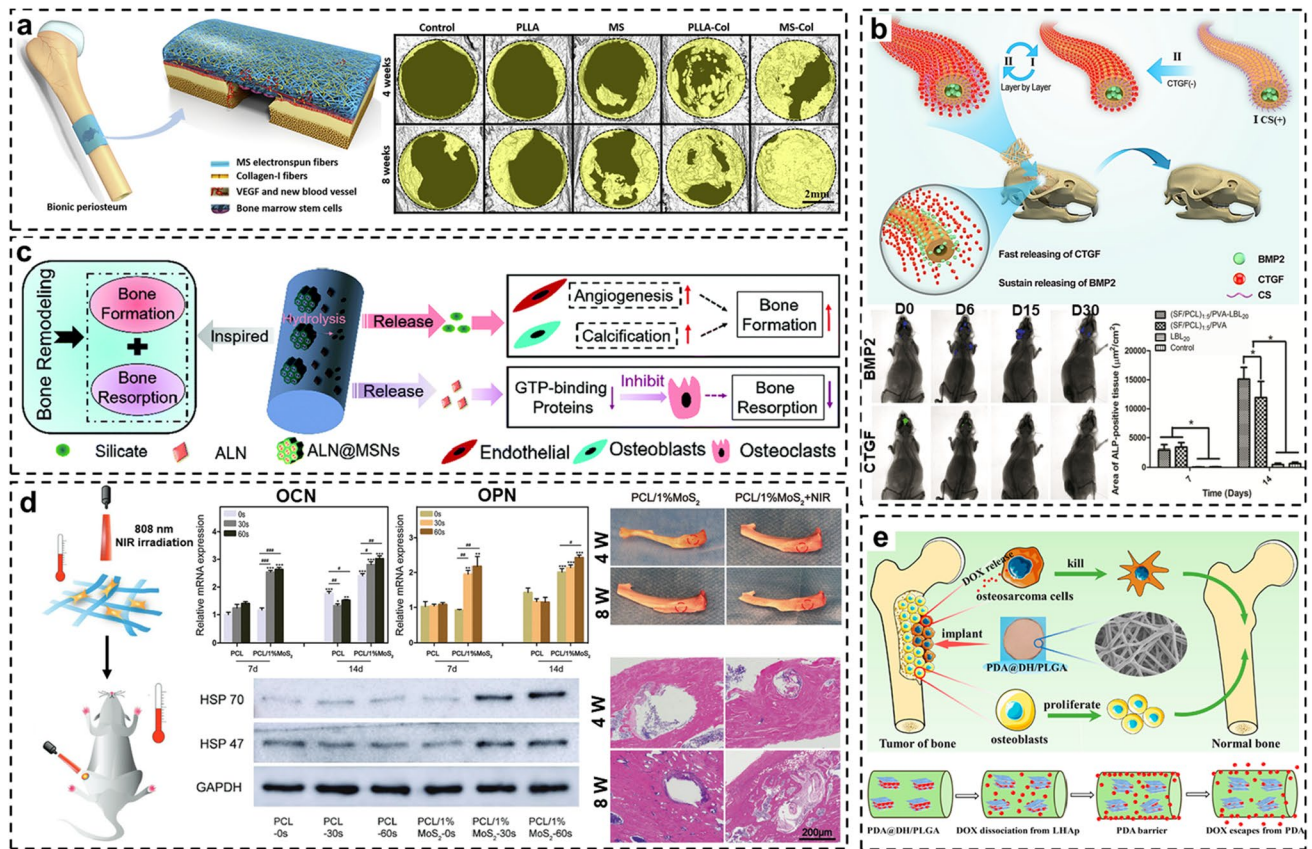
Fig. 9 Drug delivery systems based on electrospun fiber scaffolds for bone tissue engineering. **a** Schematic illustration showing the construction of a nanofiber-based biomimetic periosteum for periosteum and bone regeneration and 3D reconstructed images of the regenerated bone after implantation for 4 and 8 weeks, respectively, in a rat calvarial critical size defect model. Reproduced with permission from Ref. [117]; Copyright 2020, Elsevier Limited. **b** Spatiotemporally controlled release of BMP-2 and CTGF for bone repair by combining coaxial electrospinning and LBL technology, and in vivo tracing of fluorescent dye-labeled BMP-2 and CTGF, as well as ALP-positive tissue areas in a model of ectopic osteogenesis. Reproduced with permission from Ref. [263]; Copyright 2019, American Chemical Society Limited. **c** Schematic illustration showing design of nanofiber for simultaneously dual delivery of ALN and silicate, as well as tuning the balance between bone resorption and bone formation. Reproduced with permission from Ref. [106]; Copyright 2019, The Royal Society of Chemistry Limited. **d** Schematic illustration showing PCL/MoS$_2$ nanofibrous mat with photothermal property, the relative expressions of OCN, OPN, and HSPs genes with or without NIR irradiation, as well as photos of the rat tibias with implants and H&E staining of the tissues after implanting with PCL/1%MoS$_2$ electrospun mat for 4 and 8 weeks with or without NIR irradiation, respectively. Reproduced with permission from Ref. [270]; Copyright 2021, Wiley–VCH Limited. **e** Schematic illustrations showing a dual function nanofibrous scaffold for tumor suppression and bone repair by loading DOX and modifying PDA, as well as the release route of DOX from the scaffold. Reproduced with permission from Ref. [271]; Copyright 2021, American Chemical Society Limited

provides a good alternative for bone tumor treatment and postoperative repair.

Cartilage Tissue Engineering

Articular cartilage, which is primarily composed of chondrocytes and ECM, is responsible for reducing interface friction and assisting in bearing loads. Due to its low level of regeneration and limited self-healing capacity [272], the clinical pressures of cartilage-related diseases have been increased with population aging. Thus, there is an urgent need to develop new biomaterial scaffolds to treat cartilage damage, and various drugs and growth factors have been explored for application to cartilage regeneration. To avoid rapid drug clearance and ensure controlled release [273], electrospun fibers are widely applied due to their customizable structures and selectable properties with regards to drug binding, enabling these scaffolds to mimic the different morphologies of cartilage ECM and control drug delivery [274].

In general, PLLA [275–277] and PLGA [278, 279] are rarely used due to their potential to cause inflammation during degradation, while PCL [280–282] and polyhydroxybutyrate [283] can be applied after modification or blending. Methylsulfonylmethane, a typical drug to inhibit inflammation and promote chondrocytes differentiation [284, 285], was loaded on PLGA fiber mats to accelerate cartilage
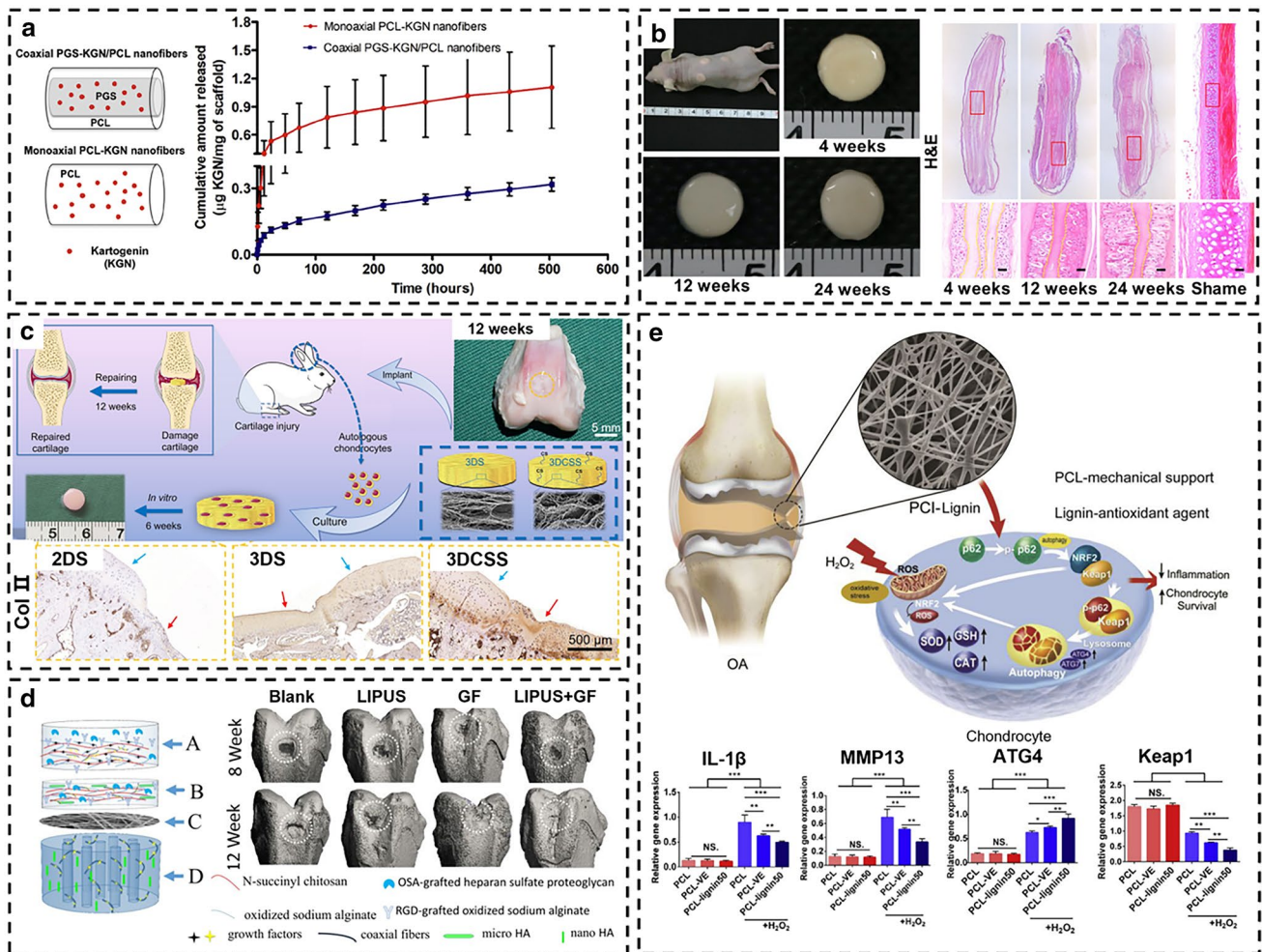
Fig. 10 Drug delivery systems based on electrospun fiber scaffolds for cartilage tissue engineering. **a** Schematic of kartogenin-loaded monoaxial and coaxial nanofibers, and comparison of their release profile. Reproduced with permission from Ref. [289]; Copyright 2020, Elsevier Limited. **b** The gross view and H&E staining images of regenerated cartilage after implanting the cECM-loaded PCL membrane into mice. Reproduced with permission from Ref. [292]; Copyright 2020, Elsevier Limited. **c** Gas-foamed chondroitin sulfate crosslinked PLCL/SF-based three-dimensional scaffold enhances cartilage regeneration, with gross view at 12 weeks and stain results of COL-II revealing its effects. Reproduced with permission from Ref. [295]; Copyright 2021, Elsevier Limited. **d** Schematic illustration of the structure of the biomimicking multilayer scaffold loaded with FGF-2, BMP-2, as well as some other components promotes deep cartilage defect from regenerating, and results of micro-CT examination at different time points. Reproduced with permission from Ref. [296]; Copyright 2018, Elsevier Limited. **e** PCL nanomembranes realized sustained release of lignin, thus suppress inflammation factors, scavenge ROS, restrain osteoarthritis from deteriorating by suppressing expression of IL-1β, MMP13 and Keap1, at the same time upregulate the expression of ATG4 to adjust autophagy. Reproduced with permission from Ref. [301]; Copyright 2020, Elsevier Limited

regeneration [279]. However, the release curve reached stability within 24 h after the initial burst release, indicating a deficiency in sustained release. Candidate drugs [278] and effective natural plant components [286] have faced similar problems. To this end, the design of fiber structures and in-depth exploration of drug combinations remain under way. For example, Kartogenin [287, 288], has been shown to promote cartilage defect repair, was loaded into coaxial fibers [289]. As shown in Fig. 10a, the existence of the PCL sheath successfully alleviated burst release and lengthened the drug release process to more than 20 days. At 14 days, levels

of glycosaminoglycan deposited on the coaxial fibers were lower than those found on monoaxial ones, but they were modestly higher at 21 days, implying the advantages of long-lasting sustained release. For the same purpose, nanoparticles loaded with small molecular drugs [290] and growth factors [277] have been combined with electrospun fiber scaffolds to maintain bioactivity and enable long-term controllable delivery. Multidrug delivery systems have also been developed to recruit endogenous cells and promote cartilage regeneration [291]. Cartilage-derived extracellular matrix (cECM), which contains various growth factors and natural

components, possesses an imaginably unique potential. In one study, cECM was mixed with PCL for electrospinning, and the as-obtained scaffold was seeded with chondrocytes and implanted into nude mice [292]. Figure 10b shows the repair effects, as well as H&E staining at different times, indicating that cECM has a positive effect on regenerated cartilage after 24 weeks, and more interestingly, the Young's modulus of the regenerated cartilage reached approximately native auricular levels.

It is well known that larger pores are favorable to cell infiltration and proliferation [293]. Nevertheless, 2D membranes are relatively dense and unsuitable for deep defects. As a result, studies aiming at developing 2D membranes to 3D scaffolds have arisen. For instance, 3D structures fabricated using NaBH$_4$ exhibit large pores that facilitate cell attachment and proliferation [294]. Chondroitin sulfate (CS), a common component extracted from cartilage, can be grafted to the matrix by chemical modification to further enhance the effects of 3D scaffolds [295]. The lowest levels of inflammatory cytokines and the highest glycosaminoglycan content were detected in 3D scaffolds crosslinked with CS in vitro, and the optimal repair effects were confirmed by the results of morphological analysis and immunohistochemical staining, as shown in Fig. 10c. With respect to deep osteochondral defects, multilayer scaffolds can be developed to meet variable needs. A four-layer hydrogel-fiber composite was fabricated in which a fibrous membrane was used as a barrier to limit cell migration [296], and BMP-2 loaded coaxial fibers were incorporated to promote subchondral bone formation. Micro-CT images in Fig. 10d reveals that the boundaries between the defect and surrounding tissues almost disappeared at 12 weeks, with the exception of the blank group. In addition, electrospun fibers can be combined with freeze-drying [284, 297, 298] and 3D printing [299, 300] approaches to develop multi-dimensional scaffolds that promote cartilage regeneration.

Injured cartilage gradually leads to osteoarthritis, with inflammation serving as the main culprit. As a durable antioxidant, lignin can efficiently alleviate excessive oxidative stress. In one study, modified lignin was mixed with PCL for electrospinning to prevent the development of osteoarthritis. As shown in Fig. 10e, non-significant differences were found among the groups without H$_2$O$_2$ stimulation, while PCL-lignin50 increased the expression of inflammatory factors (MMP13 and IL-1β) after H$_2$O$_2$ treatment, thereby effectively preventing hydrogen peroxide-induced chondrocyte inflammation. Moreover, lignin can upregulate the relative expression of allied enzyme under the influence of H$_2$O$_2$, and higher expression of ATG4 indicated that lignin can also prevent chondrocytes from experiencing excessive oxidative stress by activating autophagy. Their work also demonstrated that low intensity pulsed ultrasound (LIPUS) may further

enhance regeneration capacity [301]. With the deepening of research on injectable hydrogels, it is becoming possible to disperse electrospun fibers in hydrogels to form injectable DDSs, which is an excellent potential approach.
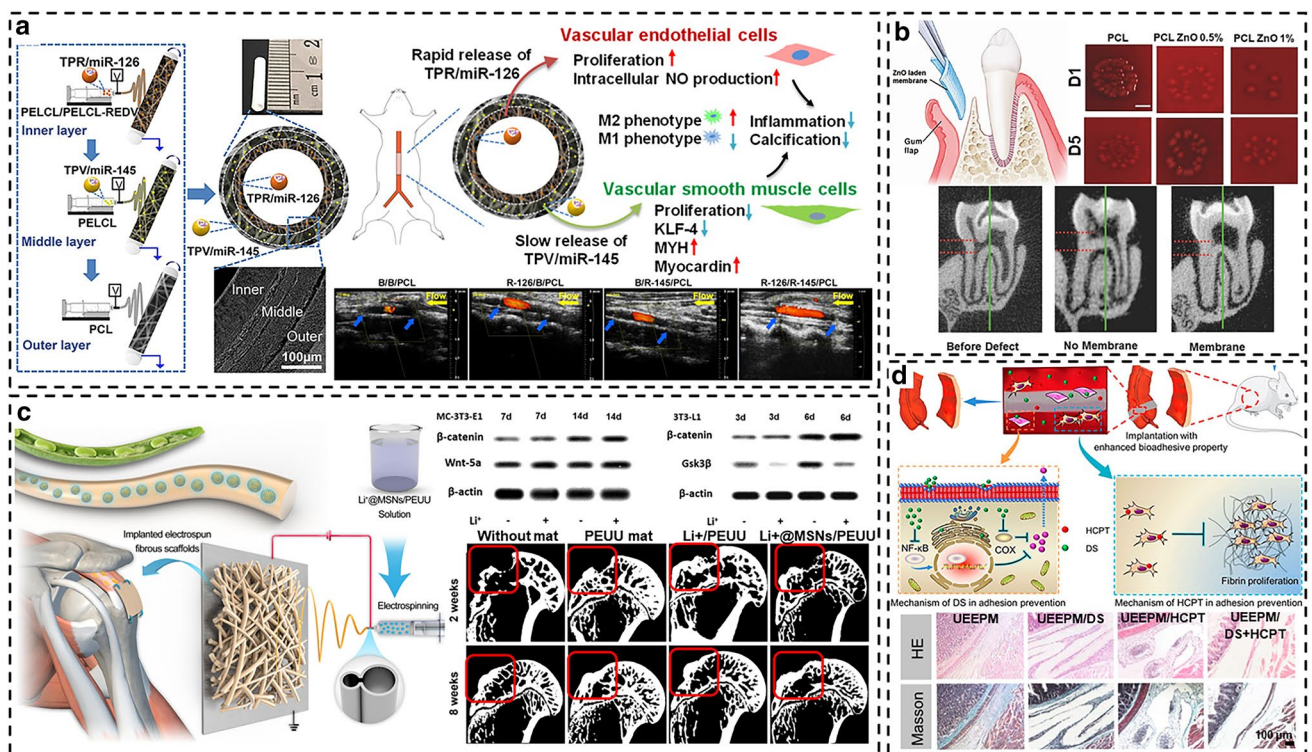
Other Tissue Engineering

In addition to the above-mentioned applications, drug-loaded electrospun fiber scaffolds have also been developed for the engineering of vascular, dental and musculoskeletal tissues, among others. The high specific surface area and porosity of electrospun fiber scaffold ensure excellent gas exchange and nutrient transport properties, making it to become a good choice for artificial vascular grafts [302]. Considering the structure of natural blood vessels, tubular morphologies with multilayered vessel walls have attracted much attention due to their mimicry. As shown in Fig. 11a, a conduit composed of a tri-layer electrospun fiber (R-126/R-145/PCL) was prepared by encapsulating microRNA-126 and microRNA-145 in the inner and middle layers of poly(ethylene glycol)-*b*-poly(ʟ-lactide-*co*-ε-caprolactone) fibers, respectively, in combination with an outer layer of PCL fibers [131]. The fiber mat enables the fast release of microRNA-126 and slow release of microRNA-145. Tri-layered electrospun grafts can promote the growth and intracellular nitric oxide production of vascular endothelial cells, modulate the phenotype of vascular smooth muscle cells, and suppress calcification. More importantly, color doppler ultrasound imaging demonstrated prominent vascular patency in the fiber graft. Although the functions of electrospun fiber-based vascular scaffold are continuously optimized, thrombosis and intimal hyperplasia still inevitably occurred [303]. The addition of a variety of bioactive substances can be beneficial to accelerating the replacement of autologous blood vessels and improving the treatment of cardiovascular diseases [304].

As described above for bone tissue, a combination of electrospun fibers and osteogenic factors can also be used to guide dental bone regeneration [305–307]. In this case, it is necessary to consider the impact of the oral environment [308]. Guided bone regeneration membranes with dual functions of anti-infection and osteogenesis have been extensively studied [309–312]. In particular, in addition to the good antibacterial properties of metronidazole, some inorganic particles can exhibit good anti-infective effects [313]. For example, ZnO can endow PCL fiber membrane with good osteo-conductivity and antibacterial properties (Fig. 11b) [314]. The number of Colony forming units of *Pseudomonas gingivalis* on the membrane surface was reduced, and micro-CT analysis of the rat maxilla confirmed the effectiveness of ZnO-loaded PCL fibers in periodontitis-related bone regeneration. This drug-loaded electrospun fiber membrane can also be applied as an oral drug delivery patch for the treatment of oral diseases

[315], this approach not only maintains good oral adhesion but also provides continuous and controllable drug delivery capabilities to kill bacteria and eliminate inflammation [316–318].

Tendon is an important part of musculoskeletal tissues, and tendon grafts and tendon sutures used in surgical treatment cannot satisfy requirements relating to flexibility, anti-adhesion, and permanent remodeling [319]. To address these problems, electrospun drug-loaded scaffolds can serve as a potential alternative for the treatment and regeneration of injured tendon tissue. In one study, thymosin β4 (Tβ4)-loaded oriented fibers not only mimicked the ultrastructure of natural tendon tissue but also showed 28-day sustained release that promoted the migration and proliferation of human adipose-derived mesenchymal stem cells and supported tendon differentiation [320]. In addition to direct drug delivery, nanoparticles can also be doped in electrospun fibers to deliver therapeutic ions for tendon repair. For example, inspired by the structure of cowpea, lithium was loaded in MSNs and doped in electrospun poly(ester urethane) urea (PEUU) nanofibers (Li$^+$@MSNS/PEUU), allowing the slow release of Li$^+$ to inhibit rotator cuff fat penetration and promote tendon and bone healing (Fig. 11c) [321]. Western blotting results showed that Gsk3β was inhibited, while Wnt5a and β-catenin were up-regulated under the influence of Li$^+$ ions. At the proximal tendon-bone junction, the osteogenic effects of the Li$^+$-containing fiber patch were significantly higher than those of the fiber patch without Li$^+$ ions. Micro-CT analysis showed that the bone mineral density (BMD) and bone volume fraction (bone volume/total volume, BV/TV) of the group using Li$^+$@MSNS/PEUU nanofiber patch were significantly higher than those in other groups after implanted for 2 and 8 weeks, respectively.

Fig. 11 Drug delivery systems based on electrospun fiber scaffolds for other tissue engineering. **a** Illustration of three-layered vascular grafts prepared by successive three-step electrospinning to encapsulate miR-126 and miR-145 in the inner and middle layers of fibers, respectively, as well as its multiple efficacies, including of patency testing after in vivo implantation for 4 weeks. Arrows indicate blood flow (yellow) and suture sites (blue). Reproduced with permission from Ref. [131]; Copyright 2020, American Chemical Society Limited. **b** Depiction of periodontal defect in rats with fibrous membrane implantation, *P. gingivalis* colony forming units (CFUs) on membrane surface and micro-CT analysis of rat maxilla after implantation for 6 weeks. Reproduced with permission from Ref. [314]; Copyright 2018, Wiley–VCH Limited. **c** Schematic illustration of pea-like bi-stranded nanofibers prepared by electrospinning in the repair of chronic rotator cuff tears, the effect of lithium ion on the expression of osteogenesis and adipogenic-related proteins in vitro was indicated by western blotting, and the repair effect of each group was shown by micro-CT image after implantation for 2 weeks and 8 weeks. Reproduced with permission from Ref. [321]; Copyright 2020, Elsevier Limited. **d** Schematic diagram of the preparation of HCPT and diclofenac sodium (DS) composite membrane and the synergistic anti-adhesion combined with physical isolation and drug treatment, as well as H&E and Masson's trichome staining of repair sites after 14 days. Reproduced with permission from Ref. [324]; Copyright 2018, American Chemical Society Limited

Tissue anti-adhesion is another research hotspot, especially with respect to tendon tissues. By loading engineered growth factors and related small molecular drugs into electrospun fibers, not only can the purpose of controlled release be achieved, but also the formation of adhesion can also be inhibited [322, 323]. As shown in Fig. 11d, the synergistic prevention of peritoneal adhesions can be enabled by loading HCPT and diclofenac sodium (DS) into the sheath and core of nanofibers, respectively, to exert anti-fibrin proliferative and anti-inflammatory effects [324]. Histological staining confirmed that collagenous tissue was compartmentalized in the group loaded with HCPT and DS, with little adhesion formation. Although electrospun drug-loaded scaffolds have widespread applications in tissue engineering, it is worthwhile to continue to develop new DDSs based on electrospun fiber scaffolds to broaden tissue regeneration strategies.

Cancer Therapy

Surgical resection of the tumor in combination with systemic chemotherapy is one of the most common strategies for cancer treatment [325–327]. However, as a result of its systemic administration and poorly targeted delivery, conventional chemotherapy often causes serious side effects to other normal tissues [328, 329]. Therefore, it is urgent to develop a new anticancer drug delivery platform to solve the above problems. Electrospun fibers can allow the local delivery of anticancer drugs, so they have been widely applied in tumor therapy [12]. In a recent study, CUR was incorporated into MSNs and embedded into PLGA nanofibers by blending electrospinning [76]. The nanofibers had an excellent ability to scavenge tumor cells. In addition to the passive release of anti-cancer drugs from drug-loaded nanofibers, many researchers have designed pH-responsive fibers to deliver anti-cancer drugs based on the acidic tumor microenvironment [12]. For instance, DOX-loaded MSNs were doped into nanofibers, and $CaCO_3$ was used as an "inorganic cap" to control the opening of the MSN hole inlet [330]. In the acidic tumor microenvironment, $CaCO_3$ reacted with hydrogen ions to generate carbon dioxide, promoting the release of DOX from MSNs. This type of intelligent-response drug delivery can be further endowed with targeting capacities to enhance the utilization efficacy of chemotherapeutic drugs. Hydrophobic DOX was first encapsulated in folic acid-coupled PCL self-assembled micelles, after which core–shell nanofibers loaded with the micelles were prepared by coaxial electrospinning (Fig. 12a) [331]. Compared with repeated intravenous injection, the delivery of targeted micelles can greatly reduce the dose, administration frequency, and side effects of chemotherapy drugs.

Compared to chemotherapy with a single type of drug, multi-drug combination chemotherapy has obvious advantages [332]. Combination chemotherapy allows the use of multiple chemotherapeutic drugs to improve the therapeutic effects of chemotherapy. Meanwhile, combination chemotherapy can induce apoptosis of tumor cells through different signaling pathways, exerting a synergistic effect in killing tumor cells [333]. For example, pluronic F127-modified nanofibers loaded with camptothecin and CUR could achieve the simultaneous and sustained release of the two drugs [334]. Camptothecin can convert topoisomerase I into a cytotoxic agent by inhibiting the movement of replication forks, leading to tumor death, while CUR inhibits tumor cell growth by inhibiting the kB and Wnt signaling pathways [335, 336]. The use of combination chemotherapy can effectively inhibit the growth of colon cancer cells by inhibiting different signal pathways in tumor cells. Drug delivery platforms loaded with multiple drugs can facilitate different therapeutic effects and avoid drug toxicity and side effects associated with prolonged overuse of a single drug. For instance, hierarchical nanofibers loaded with DOX and matrix metalloproteinases-2 were fabricated through coaxial electrospinning [120]. With this approach, the rapid release of DOX from the fibrous nuclear layer could kill remaining tumor cells, while the loading of matrix metalloproteinase-2 inhibitor disulfiram in the fibrous shell could effectively inhibit tumor erosion and prevent metastasis. In addition, the time-programmed release of multiple drugs is the most critical factor in combination chemotherapy. For example, as shown in Fig. 12b, DOX formed periodic chambers inside the fibers, while the double walls of the fibers were made of polylactic acid and PCL containing the angiogenesis inhibitor apatinib. In vivo experiments showed that a good synergistic effect was obtained by transplanting the fiber into subcutaneous tissue near the tumor site in mice [337].

Although chemotherapy has great advantages in cancer treatment, the tolerance of tumors to chemotherapy drugs highlights the urgency of integrating these approaches with other types of technologies. The delivery of photothermal agents or photosensitizers by nanofibers can effectively kill tumor cells [338–340]. As illustrated in Fig. 12c, the efficacy of nanofiber scaffolds loaded with albumin-chloro-6-manganese dioxide nanoparticles (ACM) for tumor treatment was evaluated using an in situ rabbit model of esophageal cancer [341]. In the presence of endogenous hydrogen peroxide, a nanofiber scaffold implanted into the area of tissue damage could produce oxygen and alleviate tumor hypoxia. At the same time, ACM nanoparticles gradually diffused out from the scaffold to the tumor, resulting in effective photodynamic therapy for cancer treatment.

For tumors in the skin, bone and breast, surgical resection causes serious tissue defects. Therefore, the removal of remaining tumor cells needs to be accompanied by the promotion of tissue regeneration [342]. Therefore, it is
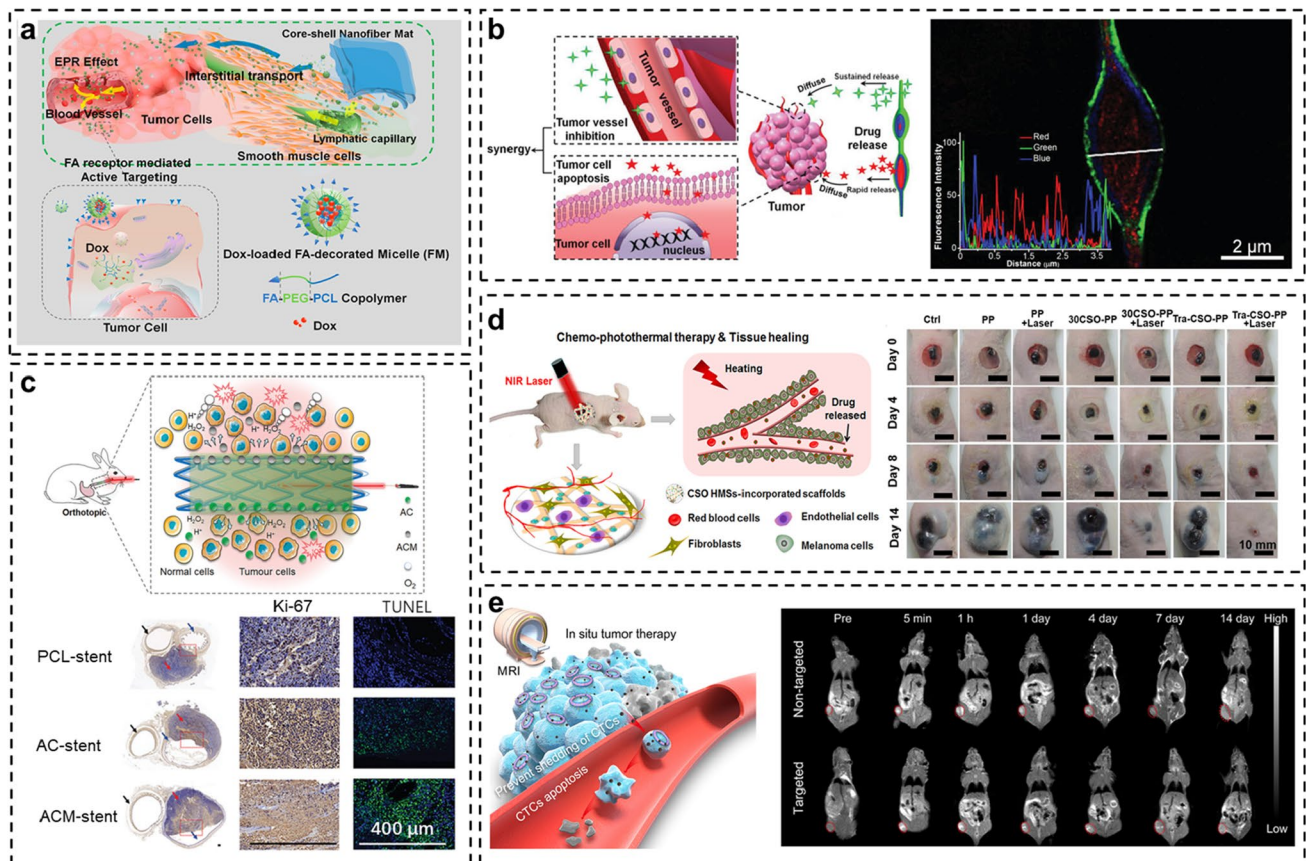
Fig. 12 Drug delivery systems based on electrospun fiber scaffolds for cancer therapy. **a** Mechanism diagram of tumor clearance by the implantable DOX loaded active-targeting micelle-nanofiber platform and the micelles transfer from nanofiber matrix to tumor tissue, and finally to tumor cells. Reproduced with permission from Ref. [331]; Copyright 2015, American Chemical Society Limited. **b** The release of dual drugs from fibers and their synergistic treatment of tumor, and CLSM image of cavity and fluorescence colocalization analysis. Reproduced with permission from Ref. [337]; Copyright 2020, Wiley–VCH Limited. **c** Schematic illustration of chemical relief of the hypoxia environment with in situ release of ACM nanoparticles for oesophageal cancer photodynamic therapy as well as Ki-67 and TUNEL-stained slices of oesophageal cancer of each group. Black arrows indicate tracheas. Reproduced with permission from Ref. [341]; Copyright 2019, Wiley–VCH Limited. **d** Schematic illustration of the application of Tra-CSO-PP scaffolds and representative photographs of tumors and skin wounds on days 0, 4, 8, and 14. Reproduced with permission from Ref. [343]; Copyright 2018, American Chemical Society Limited. **e** Schematic illustration of DOX@PLGA fibrous rings for simultaneous tumor therapy and metastasis inhibition, and T1-weighted MR images at different time points. Reproduced with permission from Ref. [346]; Copyright 2022, Elsevier Limited

particularly important to functionalize nanofiber scaffolds to enable them to scavenge tumor cells and promote tissue regeneration. In the study shown in Fig. 12d, drug-loaded copper silicate hollow microspheres were loaded into nanofiber scaffolds, which exhibited excellent photothermal effects and the capability to trigger drug release under NIR irradiation [343]. Upon NIR irradiation, the scaffold could both eliminate tumors and promote skin tissue healing.

Circulating tumor cells are cancer cells that are shed from the tumor and enter the circulatory system; therefore, capturing circulating tumor cells is critical to delaying cancer metastasis [344]. However, it is quite difficult to capture tumor cells from circulating blood in vivo. Due to the advantages of high specific surface area and flexible surface

modification of nanofibers, the targeted aptamer-modified nanofiber surface can be used to capture circulating tumor cells. For example, coating anti-CD146 antibodies-to-melanoma on the surface of PLGA nanofibers can enable the capture of circulating melanoma cells [345]. As shown in Fig. 12e, to achieve cancer treatment, tumor metastasis inhibition, and magnetic resonance imaging, DOX-loaded PLGA fiber mats were immersed in a salt solution to form fibrous rings [346]. The fibrous rings were functionalized with the chelating agent gadolinium and DNA aptamers via the ethylenediamine-mediated coupling reaction. Analysis showed that the multifunctional fibrous rings could simultaneously deliver tumor chemotherapy, enable magnetic

Table 1 Representative types of drug-loaded electrospun fiber scaffolds for tissue engineering and cancer therapy

Polymers	Drugs	Techniques	Applications	References
PCL	Tazarotene (TA)	Blend electrospinning	Skin tissue engineering	[185]
PLCL/gelatin	Epigallocatechin-3-O-gallate (EGCG)	Coaxial electrospinning	Skin tissue engineering	[180]
PLA	Curcumin (Cur)	Physical adsorption	Skin tissue engineering	[176]
PCL/PEG	Epidermal growth factor (EGF); basic Fibroblast growth factor (bFGF)	Coaxial electrospinning	Skin tissue engineering	[186]
PEO/ PEEUU	5-Fluorouracil (5-Fu); dendritic Mesoporous bioglass nanoparticles (dMBG)	Coaxial electrospinning	Skin tissue engineering	[189]
PCL	Collagen; Fibronectin	Electrospray	Nerve tissue engineering	[124]
PCL	Methylprednisolone (MP); Polysialic acid	Blend electrospinning	Nerve tissue engineering	[217]
PLLA	Nerve growth factor (NGF); Vascular endothelial growth factor (VEGF)	Emulsion electrospinning; Physical adsorption	Nerve tissue engineering	[207]
PVP/RLPO	Levodopa (LD); Carbidopa (CD)	Coaxial electrospinning	Nerve tissue engineering	[227]
PUTK	Methylprednisolone (MP)	Blend electrospinning	Cardiac tissue engineering	[31]
PCL/gelatin	Cerium oxide nanoparticles (nCe)	Blend electrospinning	Cardiac tissue engineering	[236]
PCL/gelatin	Vascular endothelial growth factor (VEGF)	Blend electrospinning or Coaxial electrospinning	Cardiac tissue engineering	[243]
PCE	Bone morphogenetic protein-2 (BMP-2); Dexamethasone (DEX)	Blend electrospinning	Bone tissue engineering	[53]
PLGA/gelatin	Substance P (SP); Alendronate (ALN)	Coaxial electrospinning	Bone tissue engineering	[266]
SF/PCL/PVA	Bone morphogenetic protein 2 (BMP-2); Connective tissue growth factor (CTGF)	Coaxial electrospinning; Physical adsorption	Bone tissue engineering	[263]
PLGA	Doxorubicin (DOX)	Blend electrospinning	Bone tissue engineering	[271]
PCL/gelatin	Metronidazole (MNA)	Blend electrospinning	Bone tissue engineering	[309]
PLGA	Methylsulfonylmethane (MSM)	Blend electrospinning	Cartilage tissue engineering	[279]
PGS/PCL	Kartogenin (KGN)	Coaxial electrospinning	Cartilage tissue engineering	[289]
PCL/gelatin	Chondrocyte	Electrospray	Cartilage tissue engineering	[282]
PLCL/SF	Chondroitin sulfate (CS)	Covalent immobilization	Cartilage tissue engineering	[295]
PCL	Kaempferol/Dexamethasone (KAE/DEX)	Second carrier electrospinning	Cartilage tissue engineering	[290]
PCL	MicroRNA-126; MicroRNA-145	Blend electrospinning	Vascular tissue engineering	[131]
PCL	Epigallocatechin gallate (EGCG); Dexamethasone (DEX)	Covalent immobilization; Physical adsorption	Vascular tissue engineering	[303]
PCL	Zinc oxide (ZnO) nanoparticles	Blend electrospinning	Dental tissue engineering	[314]
PVP	Lysozyme	Blend electrospinning	Oral tissue engineering	[317]
PLGA	Thymosin beta-4 (Tβ4)	Blend electrospinning	Tendon tissue engineering	[320]
PCL	Mechano-growth factor (MGF)	Covalent immobilization	Tendon tissue engineering	[322]
PEUU	Lithium-containing mesoporous silica (Li$^+$@MSNs)	Blend electrospinning	Musculoskeletal tissue engineering	[321]
PLLA	Mitomycin-C (MMC)	Blend electrospinning	Anti-adhesion	[323]
mPEG-b-PLGA	10-Hydroxycamptothecin (HCPT); Diclofenac sodium (DS)	Blend electrospinning	Anti-adhesion	[324]
mPEG-b-PLGA	10-Hydroxycamptothecin (HCPT); Hydrophilic tea polyphenols (TP)	Emulsion electrospinning	Cancer therapy	[334]
PCL	Epigallocatechin-3-O-gallate (EGCG)	Blend electrospinning	Cancer therapy	[327]

Table 1 (continued)

Polymers	Drugs	Techniques	Applications	References
PLA; PGA	Matrix metalloproteinases-2 (MMP-2); Doxorubicin hydrochloride (DOX·HCl)	Coaxial electrospinning	Cancer therapy	[120]
PLGA	Curcumin (CUR); Mesoporous silica nanoparticles (MSNs)	Second carrier electrospinning	Cancer therapy	[76]
PLGA	Anti-CD146 antibodies	Covalent immobilization	Cancer therapy	[345]

resonance imaging, and anchor circulating tumor cells, ultimately inhibiting the migration and erosion of tumor cells.

Conclusions and Perspectives

Over the past decades, electrospun fibers have been increasingly applied for controlled drug delivery in the fields of tissue regeneration and cancer therapy. To meet the needs of target tissues, electrospinning provides customizable process parameters, collection devices, and post-processing procedures. Correspondingly, electrospun fiber scaffolds with multiple structures, architectures, and dimensions, including aligned, core-sheath, porous, grooved, and gradient features, have been fabricated to regulate cellular states and match the anatomical structures of regenerating tissues. By combining various therapeutic drugs, electrospun fiber-controlled drug delivery platforms with customizable characteristics have gradually broadened the potential applications of soft tissue engineering, hard tissue engineering and cancer treatment. Thanks to the unremitting efforts of scientific researchers and developments in nanoscience, advances have been made to the design of electrospun fiber structures, the in-depth exploration of combinations of electrospun fibers and drugs, and the combination of stimuli with controlled properties. Herein, some representative examples of electrospun fibers loaded with functional therapeutic agents and their applications are listed in Table 1. It is believed that the electrospun fiber drug-loading platform can provide continued possibilities for the development of new drug delivery strategies, characterized by the valuable capacity to deliver precise amounts of drugs at specific locations and times in tissue regeneration and cancer therapy.

For smart drug-loading platforms, electrospun fiber scaffolds are offering predictable potential. The emergence of technologies such as special collectors and gas foaming has enabled 3D electrospun fiber scaffolds to maintain their original nano-morphology with larger porosity and pore size, broadening the applications of electrospun drug-loaded scaffolds in tissue engineering [347, 348]. In addition, by introducing stimuli-responsive components, drugs can be precisely programmed for release in vivo. The combination of drugs with photothermal therapy, photodynamic therapy,

magnetothermal therapy, sonodynamic therapy and multiple therapies trigger by exogenous stimuli can achieve better therapeutic effects. Similarly, the introduction of unique imaging properties enables drug delivery to simultaneously support long-term stable tracking and real-time monitoring, thereby greatly advancing the process of drug visualization therapy [346, 349–351]. Furthermore, artificial intelligence (AI) has also expanded the future of intelligent DDSs. Some strategies integrating electronic components into scaffolds have been recently proposed, and these techniques allow remote monitoring of tissue function and intervention through stimulation and controlled drug release [352, 353]. We foresee that the integration of microelectronic devices into electrospun drug-loaded scaffolds will provide a better way to monitor patient health [354–356]. These additional advantages are likely to further optimize electrospun fibers-controlled DDSs as ideal disease treatment platforms and individually customizable therapeutic regimens.

Although the design of DDSs based on electrospun fiber scaffolds has reached a new stage, there is still a long way to go to translate into clinical and commercial applications. The first consideration is the biosafety of drug-loaded electrospun fiber scaffolds. All components should be stable and nontoxic, and the long-term immune and host responses after in vivo implantation should be well understood. It is also a great challenge to match the degradation properties of electrospun fiber scaffolds with tissue repair rates in practical applications, which is expected to be solved by optimizing combinations of substrate materials, adding other components or modifying the scaffolds. During these processes, the implanted scaffold material can be adjusted by monitoring tissue repair through real-time imaging. In addition, the fate and pharmaceutic kinetics of drugs after entering the body remain unclear. More detailed studies of fiber- and drug-induced inflammatory responses and healing mechanisms are also required. Furthermore, the design of drug-loaded systems is currently based mostly on experimental trials and experience, so great advances could be made by applying in-depth machine learning and AI to predict interactions between drugs and fibers and optimize drug selection, release behavior, and simulation of tissue degradation, among other factors, to direct system construction. Finally, there is still a gap in the industrialization of

drug-loaded electrospun fiber scaffolds. It is important to realize the high-throughput preparation of electrospun fibers and maintain quality control during the scale-up process, as this also determines the effectiveness and repeatability of drug release behavior. In the chain of manufacturing-experimental validation-clinical trial-commercialization, it encourages more dialogue and in-depth cooperation among scientists working in the areas of materials science, nano-technology, pharmacy, biomedicine, and clinical medicine to solve these challenges.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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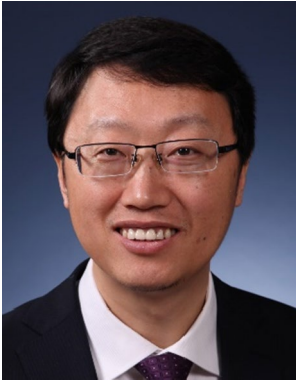
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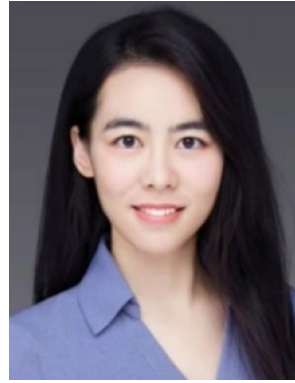
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