Bioactive Materials 40 (2024) 597–623

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Review article

Developing fibrin-based biomaterials/scaffolds in tissue engineering

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ARTICLE INFO

Keywords:
Fibrin
Scaffold
Tissue engineering
Tissue repair

ABSTRACT

Tissue engineering technology has advanced rapidly in recent years, offering opportunities to construct biologically active tissues or organ substitutes to repair or even enhance the functions of diseased tissues and organs. Tissue-engineered scaffolds rebuild the extracellular microenvironment by mimicking the extracellular matrix. Fibrin-based scaffolds possess numerous advantages, including hemostasis, high biocompatibility, and good degradability. Fibrin scaffolds provide an initial matrix that facilitates cell migration, differentiation, proliferation, and adhesion, and also play a critical role in cell-matrix interactions. Fibrin scaffolds are now widely recognized as a key component in tissue engineering, where they can facilitate tissue and organ defect repair. This review introduces the properties of fibrin, including its composition, structure, and biology. In addition, the modification and cross-linking modes of fibrin are discussed, along with various forms commonly used in tissue engineering. We also describe the biofunctionalization of fibrin. This review provides a detailed overview of the use and applications of fibrin in skin, bone, and nervous tissues, and provides novel insights into future research directions for clinical treatment.

1. Introduction

The regeneration of organs and tissues after tissue injury or disease poses significant clinical challenges. Tissue and organ defects or partial loss of function not only influence the quality of life of the patient but can also be life threatening [1–3]. While human tissues and organs possess inherent healing capabilities, they cannot cope with severe damage. The preferred treatment option for traditional tissue damage is organ transplantation, which is currently hindered by a shortage of donor organs, susceptibility to rejection, and cross-infection. Tissue engineering techniques have developed rapidly in recent years as alternative therapies to address organ and tissue defects. Tissue engineering integrates the knowledge of mechanical materials with cellular molecular biology to construct biologically active tissues or organ substitutes to replace, repair, or even enhance the functions of diseased tissues and organs [4,5]. With advancements in the field, tissue engineering technology has now been applied to repair damage to multiple organs and tissues, such as muscle, bone, skin, etc., as well as playing an important role in multiple fields, such as drug transport systems and artificial organ development.

Tissue engineering comprises three basic elements to support cell-based tissue regeneration: suitable cell sources, bioactive components, and appropriate scaffolding materials [6–9]. The cells are mostly derived from the body of the specific patient and are cultured *in vitro*, introduced into the scaffolding material, and implanted into the body [10]. During such processes, growth factors and other active ingredients are used as auxiliary materials to promote angiogenesis and cell proliferation, and to guide the coordination of cellular activities in tissues [11]. For example, the introduction of transforming growth factor-β (TGF-β) significantly enhances type II collagen production through

Peer review under responsibility of KeAi Communications Co., Ltd.
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https://doi.org/10.1016/j.bioactmat.2024.08.006
Received 7 June 2024; Received in revised form 8 August 2024; Accepted 9 August 2024

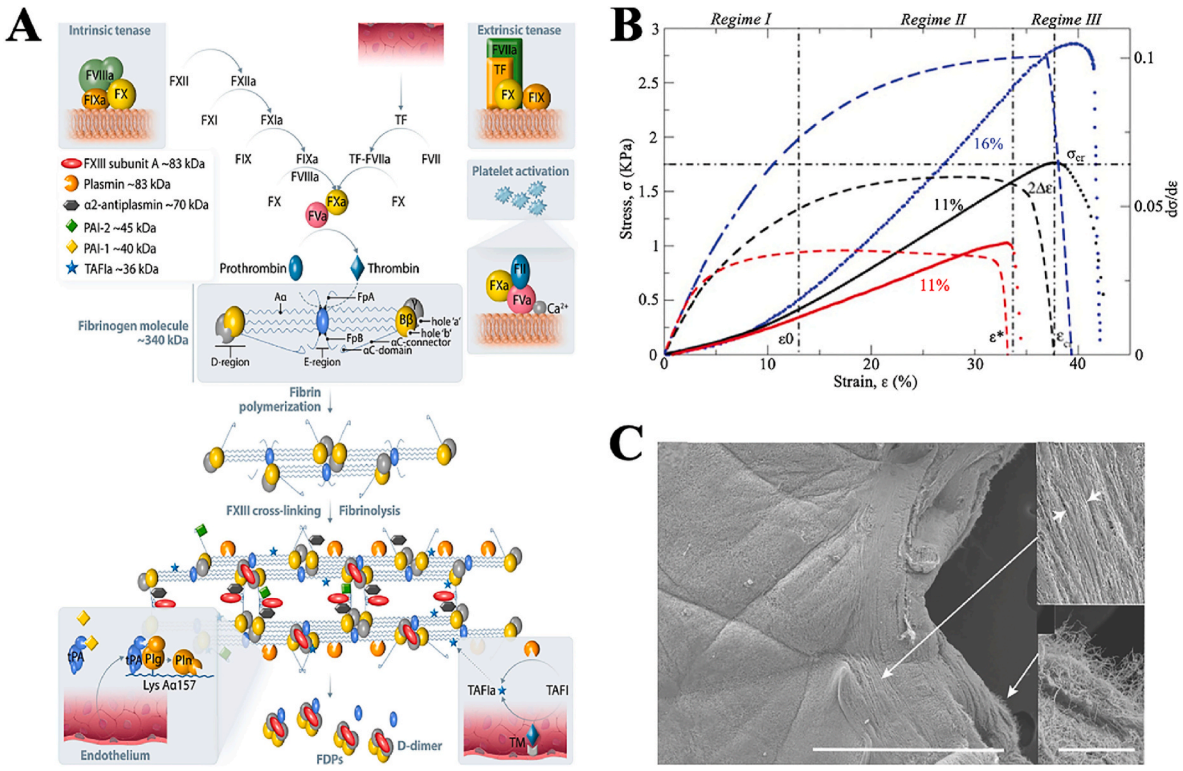

Fig. 1. Composition, structure, and properties of fibrin. **(A)** Formation and dissolution of fibrin networks. The Figure is reproduced with minor adaptations from Ref. [45] with permission, based on Creative Commons Attribution License (CC BY), *Copyright © 2023 The Author(s). Published by Oxford University Press on behalf of the European Society of Cardiology.* **(B)** Experimental stress-strain curve analysis of fibrin clot samples with unilateral cracks. The Figure is reproduced with minor adaptations from Ref. [52] with permission, *Copyright © 2023 The Authors. Advanced Healthcare Materials published by Wiley-VCH GmbH.* (License number: 5,824,030,012,134). **(C)** Scanning electron microscope (SEM) images of stretched and ruptured fibrin gel. The Figure is reproduced with minor adaptations from Ref. [60] with permission, *Copyright © 2021 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.* (License number: 5,824,030,257,607).

mobilization of the Smad pathway, and promotes cartilage repair to a greater extent than that of gels that do not contain TGF-β [12]. As framework materials that support cell growth into complete tissues, scaffolding materials play a vital role in maintaining tissue volume, providing mechanical support, and releasing biologically active substances; consequently, they are the foundation of tissue engineering technologies [13–15]. To date, several natural polymers (i.e., fibrin and collagen) and synthetic polymers (i.e., polylactic acid and polyurethanes) have been engineered into three-dimensional (3D) porous structures for the construction of tissue engineering scaffolds [16–20].

Compared with most synthetic materials, fibrin has markedly high biocompatibility, non-toxicity, and low immunogenicity; compared with natural materials, in addition to the properties of cell adhesion and degradability, fibrin's effects in hemostasis, anti-inflammation, and promotion of wound healing make it unique in the field of tissue engineering [21]. As a plasma protein, fibrin naturally forms a scaffold after tissue injury, and its excellent hemostatic efficacy has led to its clinical application as a hemostatic material in cardiac, gastrointestinal, and other surgeries [22,23]. Fibrin is naturally derived and exhibits the good biocompatibility and degradability, greatly reducing the risk of infection, inflammation, foreign body reactions, and tissue necrosis. Its composition and structure closely resemble those of the natural extracellular matrix (ECM), making it an ideal initial matrix that contributes to cell differentiation, migration, adhesion, and proliferation, thereby facilitating cell-matrix interactions and wound healing [24,25]. Moreover, fibrin-based biomaterials have been reported to promote the stable and sustained release of growth factors, enhancing tissue repair. They also demonstrate high inoculation efficiency and excellent adhesion capacity [26,27]. Furthermore, due to several interaction sites with cells and proteins, fibrin can serve as a biologically active matrix in cellular as well as biomolecular transport systems [28]. Several studies have demonstrated the significant potential of fibrin scaffolds in tissue regeneration across various types of tissue injuries, including bone, skin, nerve, heart, and cartilage tissues. This review provides a brief introduction to fibrin, focusing on its composition, structure, and biological and other properties, while also outlining its modification and cross-linking modalities. Additionally, it summarizes the diverse application forms of fibrin and it's biofunctionalization, as well as detailing its specific applications in tissues such as skin, bone, and cardiac tissues. Finally, it offers insights into future research directions in this field.

2. Fibrin

2.1. Composition and structure of fibrin

Fibrin, a linear protein formed by the aggregation of fibrinogen in the presence of thrombin [29,30], is a glycoprotein that is pivotal in blood coagulation and is mainly synthesized by hepatocytes. It weighs approximately 340 kDa and consists of three interweaved polypeptide chains—Aα, Bβ, and γ—linked by disulfide bonds [31]. In addition, it contains expanded globular structural domains at both ends (D-domains) and a central structural domain (E-domain), which are connected by three α-helical peptide chains [32]. Stimulation by exogenous or endogenous factors leads to the activation of coagulation factors, after which thromboplastin is converted to thrombin under calcium ion catalysis. Thrombin binds to the substrate site of the fibrinogen E-domain and cleaves fibrinopeptide A (FPA), a 16-peptide-long peptide, from the N-terminus of the Aα chain. It also cleaves fibrinopeptide B (FPB), a 14-peptide-long peptide, from the N-terminus of the Bβ chain, leaving only the fibrin monomer. Fibrin monomers spontaneously form insoluble fibrin through non-covalent binding between the D and E structural domains, while interactions between the α-α and α-γ chains

promote side aggregation [33]. However, this fibrin structure is unstable and susceptible to lysis, and coagulation factor XIII is known to further strengthen the fibrin network [34]. Coagulation factor XIII is a transglutaminase that promotes linkage of the ε-amino group of a lysine residue to the γ-amino group of a glutamine residue to form a peptide bond [35]. Under calcium ion catalysis, thrombin not only degrades fibrinogen to release peptides A and B, but also activates coagulation factor XIII to produce coagulation factor XIIIa. This activation leads to the formation of covalent cross-links through assembly of the antiparallel C-terminal ends of the γ-chains between the polymerized fibrin molecules, ultimately leading to the generation of a stable and insoluble fibrin multimer (Fig. 1A) [36,37].

2.2. Extraction of fibrinogen

Several methods have been reported for the extraction of fibrinogen from whole blood, including cryoprecipitation and chemical precipitation [38]. Cryoprecipitation is the preferred method for fibrinogen extraction. In this approach, anticoagulated blood is centrifuged at 600 *g* for 10–20 min to separate plasma from the blood cells, and this plasma is then subjected to repeated freeze–thaw cycles to precipitate the fibrinogen, which is collected by centrifugation at 1000–6500 *g* for 5–15 min after thawing at 4 °C overnight. Cryoprecipitation is time-consuming and entraps other plasma components (e.g., albumin and antibodies), but there are no additional chemical reagents required, limiting the adverse effects on the body. In addition, this method has a high extraction rate and high purity of fibrinogen, which makes it suitable for large-scale industrial production [39]. Chemical precipitation methods include ammonium sulphate, ethanol, polyethylene glycol (PEG) precipitation and so on. The ammonium sulphate precipitation method involves mixing the isolated plasma with an appropriate dose of ammonium sulphate and centrifuging at 3000 rpm for 3–15 min to obtain fibrinogen. The ethanol precipitation method is performed by adding 10 % v/v ethanol to the plasma obtained from isolation and centrifuging for 15 min to collect fibrinogen. PEG precipitation is performed by adding 30 % w/v PEG to the isolated plasma to achieve a final concentration of 10 % w/v and centrifuging the plasma at 8000 rpm for 10 min to obtain fibrinogen. Chemical precipitation is less time-consuming, with simple operations and easily controlled conditions, but studies have shown that extracted fibrinogen is not as pure as that obtained by cryoprecipitation [40,41]. As an alternative approach, the fibrinogen used in commercial fibrin sealants can be prepared using Cohn fraction I in addition to cryoprecipitation. This approach, which is also known as the equivalent fraction method, involves precipitating human whole blood plasma in 8–10 % ethanol at a low temperature and a neutral pH, resulting in higher levels of factor XIII in the obtained fibrinogen [42].

2.3. Biological properties of fibrin

Fibrin and fibrinogen interact with various cells and molecules, including platelets, red blood cells, and endothelial cells, exhibiting unique roles in anticoagulation, thrombosis, wound healing, inflammation, infection, cancer, and other diseases [43]. For example, there are ligands at the carboxyl terminus of fibrin γ chains that bind to the platelet cell membrane surface glycoprotein IIb-IIIa (GPIIb-IIIa) receptor, which belongs to the integrin family of adhesion receptors and is expressed in megakaryocyte-profiled cells and platelets. Actin turnover occurs on the platelet surface under certain stimuli and GPIIb-IIIa is activated to bind to fibrin, which promotes platelet aggregation and achieves hemostasis [44–46]. The function of fibrin in promoting leukocyte adhesion is also achieved by binding to its surface integrin receptor. Meanwhile, there are several strong and weak binding sites for calcium ions in fibrinogen, among which the strong binding sites are located in four coordinating amino acid residues on the γ-chain, namely γAsp318, γAsp320, γGly324, and γPhe322. These high affinity sites protect the fibrin structure from degradation when combined with calcium ions [47]. In addition, it is also possible to cross-link the signaling molecule to fibrin using the transglutaminase substrate sequence (NQEQVSP), enabling the functionalization of the signaling molecule in fibrin. This mode of action will be described in detail later. Fibrin is one of the major components of the ECM but is not stably present in the ECM [48]. When tissue damage occurs, fibrinogen cross-links into fibrin in the presence of thrombin and other enzymes. The fibrin network exerts hemostatic effects and participates in the formation of ECM in the wound bed to promote wound healing. When an inflammatory response occurs, fibrin is also deposited at the inflammation site, working in concert with immune cells to alleviate inflammation. After completing its hemostatic and anti-inflammatory effects, fibrin is degraded by the fibrinolytic system to prevent excessive deposition. Fibrin promotes the synthesis and release of various growth factors and confers a high cell proliferation and migration activity. It also has vasculogenic activity, interacting with angiogenic factors to enhance angiogenesis and repair damaged epithelium. Fibrin provides a stable external environment for cells, playing a crucial role in tissue regeneration and wound healing. Consequently, it is commonly used to treat burns, wounds, and ulcers [49,50]. In addition, the application of fibrin at injury sites effectively alleviates the degree of fibrosis, while promoting the recovery of other ECM components, such as hyaluronic acid. Furthermore, fibrin promotes collagen deposition and helps reduce scar thickness at the wound healing site [51]. Fibrin is biocompatible, non-toxic, and well-tolerated by living tissues. These properties allow it to be accepted by organisms without causing adverse reactions; therefore, the potential risks of infection and inflammation are significantly reduced in clinical applications. Fibrin occurs naturally in the human body and has a low immunogenicity, generally not causing any immune response. However, when fibrin undergoes further treatment, such as modification, its immunogenicity may be altered due to the introduction of chemical reagents, the generation of new functional groups, etc.; thus, extra care should be taken when applying treated fibrin. Moreover, fibrin is readily modifiable and can be subjected to various targeted modifications or alterations in its organizational structure to enable its application under a range of conditions. For example, the methacryloyl reaction can alter the structure of fibrin, while the introduction of cross-linking agents can increase the cross-linking density and strength of fibrin, thereby enhancing its stability and slowing its degradation rate.

2.4. Mechanical properties of fibrin

Fibrin is a viscoelastic material with unique characteristics, endowing it with superior properties compared to other protein polymers [52,53] (Fig. 1B). Hooke's law states that for elastic solids, the strain is proportional to the stress or force applied to each region; however, the stress is independent of the strain rate, implying that for viscous materials, the stress is proportional to the strain rate, not to the strain itself [54,55]. Thus, fibrin exhibits both elastic and viscous characteristics, wherein the former imparts solid-like properties (i.e., strength, elasticity, and stability), while the latter imparts liquid-like properties (i.e., flow characteristics that vary with temperature, time, and loading) [56]. Fibrin is essential for promoting thrombus formation, and its viscoelastic characteristics determine how the thrombus responds to the deformations and stresses generated by flowing blood. For example, the thrombus can be affected by pulsatile hydrodynamic stresses caused by an oscillating blood flow or fluctuations in the vessel wall. Additionally, reversible or irreversible deformations and ruptures can be generated by an impact force, often leading to the generation of a larger embolus [57]. During hemostasis, a certain stiffness of fibrin network is required to rapidly stop bleeding; but at the same time, its mechanical strength should not be too high, which may lead to vascular obstruction. However, in the field of tissue engineering, fibrin is mainly used as a scaffold for loading cells to provide physical support for these cells; therefore, a greater mechanical strength is required to maintain the stability of the

scaffold and to avoid the deformation of the scaffold structure, which may affect tissue regeneration. Yang et al. [58] used electrospinning to construct polyurethane (PU)/fibrin vascular networks, and the introduction of PU promoted intermolecular interactions, rendering the scaffolds more mechanically robust. After implantation of the hybrid scaffold into rats, it was found that the maximum stress, strain at break, and elastic modulus of the scaffold were similar to those of native blood vessels after 3 months, which demonstrated the feasibility of the hybrid scaffold as an artificial vascular scaffold. Fibrin is known to exhibit a strain-hardening phenomenon where the fibrin network exhibits a nonlinear mechanical response under shear or tensile stress. More specifically, at low strains, the stress is proportional to the strain, but when applying large strains, the stiffness of fibrin increases by up to 20-fold [52]. Cell differentiation and migration, as well as interactions with fibrin, are related to mechanical properties, such as fibrin stiffness and cell growth, and interactions can be artificially regulated accordingly. Tomasch et al. [59] investigated the effect of fibrin hydrogels with different moduli of elasticity on the proliferative capacity of the mouse myoblast cell line C2C12. As the modulus of elasticity of the hydrogel increased, the cell proliferation rate was slower. Additionally, the high scalability of fibrin has been confirmed by tensile testing, as it can be stretched more than four times its natural length without breaking. Stretching fibrin gels with unilateral cracks reveals that fiber densification and fiber alignment occur before fiber rupture (Fig. 1C) [60]. Investigating and modifying fibrin's mechanical properties can lead to the development of fibrin materials that can adapt to various clinical applications, making it particularly suitable for tissue engineering.

2.5. Degradation properties of fibrin

The fibrin network is degraded *in vivo* by activated fibrinolytic enzymes through a process known as fibrinolysis (Fig. 1A). Catalytically active fibrinolytic enzymes are formed by the cleavage of plasminogen in the presence of fibrinogen activators, such as tissue-type fibrinogen activator (t-PA) and urokinase-type fibrinogen activator (u-PA). The former is a protein cleaving enzyme, which can be positively regulated by fibrin, while the latter is a specific membrane protein receptor [61]. Fibrinolytic enzymes exhibit poor substrate specificities and can break the lysine–arginine linkages in peptide chains. Under the action of fibrinolytic enzymes, fibrin is gradually broken down into fibrinogen and eventually into soluble protein fragments, collectively known as fibrin degradation products, which typically no longer aggregate or clot, but are removed from the blood. The presence of large amounts of anti-fibrinolytic substances in the blood and the adsorption of fibrin to fibrinolytic activators ensure the localization of fibrinolysis without spreading to other parts of the organism. Moreover, plasminogen activator inhibitors (PAI)-1 and −2 along with α2-antiplasmin (α2-AP) are important regulators of fibrinolysis and can inhibit fibrinolytic activity [62,63]. The degradation properties of tissue-engineered scaffolds significantly impact cell proliferation and tissue regeneration. Matching the rate of scaffold degradation and regenerated tissue formation is key to the successful regeneration of tissues and organs [64]. A good scaffold should maintain its structural integrity and provide the necessary mechanical support until the cells have fully adapted to the environment and secrete sufficient amounts of ECM to meet the needs of survival. After a period of proliferation, when the cells no longer require support from the scaffold, the scaffold can be completely removed by the organism and replaced with new tissue. Fibrin is a natural polymer that is able to be degraded and fully absorbed by the body without toxic side effects, eliminating the need for secondary surgery to remove the implant, thereby rendering it an ideal scaffolding material. The degradation rate of natural fibrin *in vivo* is tightly physiologically regulated to prevent pathological changes caused by its excessive deposition. However, when applied as a scaffold for tissue engineering, the degradation rate of fibrin was significantly faster than the rate of tissue regeneration [65]. To address this aspect, modifications such as sulfonate or physical and chemical cross-linking can be implemented to render the fibrin structure more solid and compact. Hybrid scaffolds can also be prepared by combining fibrin with other stable biopolymers to compensate for the rapid degradation rate. In this context, Jung et al. [66] modified dextran using glycidyl methacrylate to obtain dextran-MA, and combined dextran-MA with fibrin to create an interpenetrating polymer network (IPN) that retained the biological functions of fibrin while incorporating the excellent mechanical strength of dextran. IPN has been reported to exhibit tunable physical properties that are related to the raw material concentrations and the degree of cross-linking. The results showed that the pure fibrin hydrogels were completely degraded after 8 days, and the time required for the degradation of fibrin and dextran-MA-based hydrogels increased with an increasing dextran-MA concentration. At a fibrin concentration of 40 mg mL^{-1} and a $CaCl_2$ concentration of 50 mM, the final mass after 6 days was 30–40 % and 40–50 % at dextran-MA concentrations of 200 and 300 mg mL^{-1}, respectively; a dextran-MA concentration of 400 mg mL^{-1} exhibited the slowest degradation, with a final mass of 65–75 % after 8 days.

2.6. Changes in fibrin during tissue damage

Fibrin formation and dissolution are influenced by changing conditions within the body, such as the occurrence of bacterial infections, liver injuries, and fractures [67]. Bacterial infections often lead to fibrin deposits in infected tissues and organs. Inhibition of fibrin deposition promotes the spread of pathogens and increases patient mortality. Studies have been conducted on mice with low plasma fibrinogen levels, where it was found that bacterial clearance was significantly reduced following infection with *Staphylococcus aureus* [68]. It has also been reported that some chemicals, such as chloroform and carbon tetrachloride, can cause varying degrees of acute or chronic liver injury, which is often accompanied by fibrin deposition. In such systems, the site of fibrin deposition usually coincides with the area of liver damage [69]. Furthermore, central hepatic necrosis has been reproduced in dogs through prolonged anesthesia with chloroform, and it was reported that the plasma fibrinogen levels decreased or even disappeared completely as the degree of liver damage increased; however, the fibrinogen levels gradually returned to normal as the liver recovered. Moreover, fractures also cause fibrin deposition, which on the one hand exerts a hemostatic effect, but on the other hand, affects fracture vascularization, prevents bone healing, and even leads to dystrophic calcification of adjacent soft tissues, which ultimately develops into heterotopic ossification (HO). After fibrin removal from plasminogen-deficient mice, fracture healing returned to normal and HO was significantly reduced [70].

Fibrin is a naturally occurring biomolecule in the human body, formed by cross-linking fibrinogen in the presence of substances such as thrombin. Fibrin networks are highly biocompatible, degradable, and have excellent mechanical properties such as viscoelastic characteristics and strain-hardening phenomenon. In addition, it promotes cell adhesion and proliferation, migration, and plays a role in hemostasis, anti-inflammation, and wound healing. The above properties are the basis for the application of fibrin scaffolds in tissue engineering.

3. Modification and cross-linking of fibrin

3.1. Modification of fibrin

Fibrin has gradually become the ideal biomaterial for cell encapsulation and tissue regeneration, and several fibrin products have been developed for biomedical applications, such as fibrin hydrogels and fibrin glue (FG) [71–73]. However, fibrin still has some drawbacks, including an excessive degradation rate, poor mechanical properties, and uncontrolled shrinkage behavior. To produce fibrin scaffolds that meet various specific regenerative medicine requirements without any loss in their biological properties, modifications such as methacryloyl reaction, sulfonation, and silylation are performed. Altering the fibrin

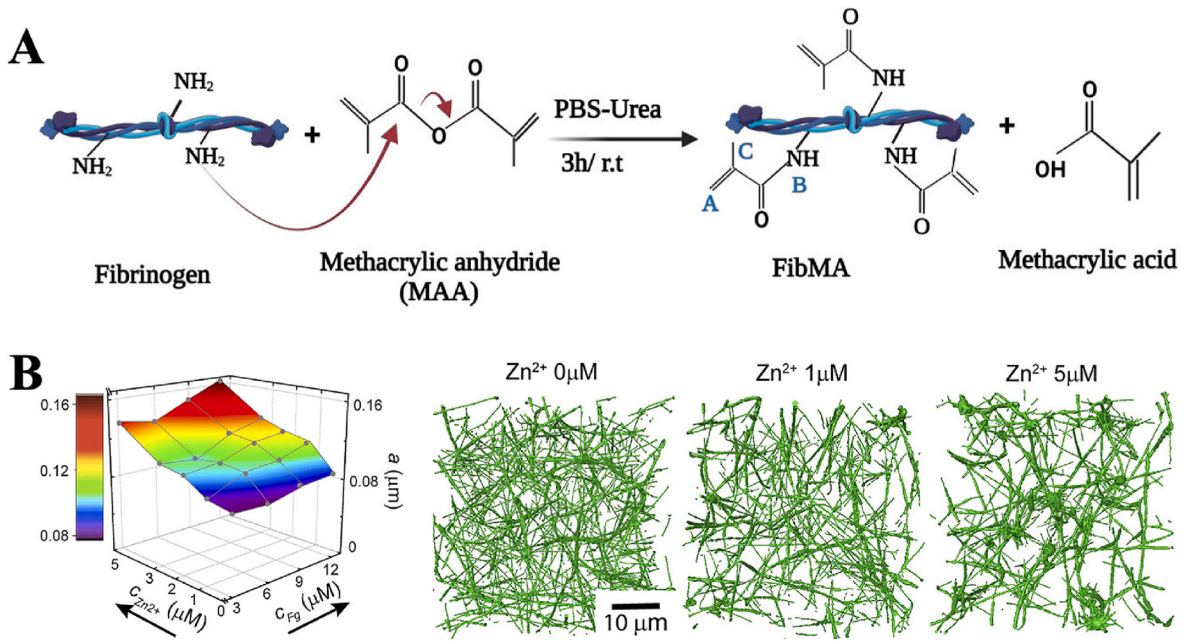

Fig. 2. Modification and cross-linking of fibrin. **(A)** Methacrylic anhydride and fibrinogen chemically react to form covalent bonds. The Figure is reproduced with minor adaptations from Ref. [75] with permission, *Copyright © 2023 Published by Elsevier Ltd on behalf of Acta Materialia Inc.* (License number: 5,824,030,669,961). **(B)** Based on ionic interactions, the fibrin diameter increases with an increasing Zn^{2+} concentration. The Figure is reproduced with minor adaptations from Ref. [80] with permission, *Copyright © 2024 The Proceedings of the National Academy of Sciences.*

function and structure, either alone or in combination with the aforementioned methods, enables the precise regulation of the scaffold characteristics, such as the physicochemical properties, porosity, stability, mechanical strength, and degradation rate, providing new possibilities for their application in tissue engineering [74]. The methacryloyl reaction is a reaction that occurs between fibrin and methacrylic anhydride (MAA), where the amino group in fibrin reacts with the anhydride of MAA to form an amide bond to obtain fibrin derivatives. The fibrin obtained by this technique has photocross-linking ability and can be solidified to form stable scaffolds under specific light, which greatly extends the application range of fibrin. Simaan-Yameen et al. [75] dissolved fibrinogen in phosphate-buffered saline (PBS) and urea at room temperature to obtain a fibrinogen solution. After adjusting the solution pH using NaOH, excess MAA was added, and the methacrylic acid moieties reacted with the free amine groups on the fibrinogen lysine residues to obtain methacrylated fibrinogen (FibMA) (Fig. 2A). In the presence of PEG, a highly cross-lined FibMA hydrogel was obtained, which exhibited significantly delayed degradation and improved mechanical properties. After subcutaneous implantation of the FibMA hydrogel in mice, there was no degradation of the hydrogel at 1 week, and only a partial inflammatory response at the periphery was observed; a significant reduction in the volume of the hydrogel and a holistic inflammatory response within it could be observed at 3 weeks; the volume of the hydrogel was reduced to half of the initial volume after 8 weeks. Sulfonation refers to the introduction of sulfonic acid groups through a reaction between electrophilic sulfonation reagents and the amino or hydroxyl groups present in fibrin. This enhances fibrin stability and provides an improved hydrophilicity and ion-exchange capacity, often leading to its application in drug carriers. Silylation modification refers to the reaction of organosilane reagents (R'-Si $(OR)_3$) with fibrin macromolecules. The organic group R' interacts with the fibrin chains, and the alkoxysilane groups are involved in the formation of a siloxane Si–O–Si network. Silanes bearing hydrophobic groups exhibit surfactant-like properties, which can influence the mechanical and chemical properties of the modified fibrin. Wang et al. [76] selected several common silanes to develop and characterize hybrid silica-fibrin hydrogels wherein fibrin interacted closely with the silanol moiety. They planted and cultured muscle C2C12 cells in mixed hydrogels and found that the mixed hydrogels exhibited a similar cell proliferation profile to that of the pure fibrin hydrogels for the first 6–8 days, whereas the hydrogels with 3-aminopropyl-triethoxysilane exhibited a significantly higher cell proliferation rate than the pure fibrin hydrogels after 8 days.

3.2. Cross-linking of fibrin

The use of fibrin in long-term 3D cell cultures is restricted by its low stability, poor mechanical strength, and excessive degradation rate. The chemical and physical cross-linking of fibrin to develop strong 3D network structures has been reported to enhance its structural stability and mechanical strength, while also prolonging its degradation time [72,77]. Several studies have been conducted to prepare carefully designed fibrin network structures that satisfy the needs of various applications. Physical cross-linking involves the formation of connections through non-covalent interactions, including hydrogen bonding, electrostatic interactions, and van der Waals forces. As these reactions are reversible, fibrin can be restored to its original state by controlling the reaction environment [78]. Commonly employed physical cross-linking methods include the freeze-thaw, self-assembly, and ionic cross-linking approaches. Compared with chemical cross-linking, physical cross-linking is more biocompatible and does not require the addition of large amounts of chemical reagents, thereby reducing or completely avoiding toxic side effects. However, the fibrin derivatives generated by physical cross-linking have poor mechanical properties and limited stability. In a study by Wachendörfer et al. [79], cross-linking was accomplished in fibrin-collagen hydrogels through physical interactions, such as the physical entanglement of fibers and molecules, with pH levels significantly impacting the hydrolytic stability and mechanical strength of the synthesized hydrogels. The ion cross-linking method is also important for the cross-linking of fibrin. It was demonstrated that the stiffness of fibrin gels is positively correlated with the Ca^{2+} cross-linker concentration, and that Ca^{2+} promotes a change in the fibril structure from filaments to networks. In another report, Jing et al. [80] studied the 3D structures of fibrin hydrogels in the presence of Zn^{2+}

Table 1
Modification and cross-linking approaches used for fibrin development.

Scaffold	Type of modification	Mechanism	Cross-linking agent or influencing factor	Changes in scaffold degradation rates	Improvement	Reference
FibMA Hydrogel	Methacryloyl reaction	Methacryloyl introduction	Methacrylic anhydride	After 8 weeks of *in vivo* implantation, the hydrogel shrinks to approximately 50 % of its original size.	A highly crosslinked structure is generated, significantly delaying degradation.	[75]
Fibrin hydrogel	Silicon modification	Siloxane Si–O–Si network formation	Organosilane reagents	/	Fibrin interacts closely with the silanol groups to significantly promote muscle cell proliferation.	[76]
Fibrin-silica hydrogels	Silicon modification	Siloxane Si–O–Si network formation	Tetraethoxysilane, aminopropyltriethoxysilane	/	Silicification of fibrin networks improves their mechanical properties while retaining their ability to promote cell proliferation.	[86]
Fibrin-Collagen hydrogels	Physical cross-linking	Physical entanglement	pH	/	It enhances stability and mechanical strength.	[79]
Fibrin hydrogel	Physical cross-linking	Ionic cross-linking	Zn^{2+}	/	Fibrin length decreases, and diameter increases.	[80]
PRF Gel	Chemical cross-linking	Enzymatic cross-linking	TA	The degradation rate was 63 % without the addition of TA and the degradation rate decreased to 8 % with the addition of 10 % TA.	It increases tensile strength and reduces swelling.	[82]
Fibrin/PVA scaffold	Chemical cross-linking	Enzymatic cross-linking	Glutaraldehyde	Glutaraldehyde-crosslinked pure fibrin scaffolds were completely degraded after 1 day, in contrast to glutaraldehyde-crosslinked fibrin/PVA scaffolds, which were completely degraded after 5 days.	It increases mechanical strength and stability against protein hydrolysis.	[83]
Alginate-fibrin scaffold	Chemical cross-linking	Double cross-linking	$CaCl_2$	Reduction in 7-day mass of 39.36 ± 6.14 % for fibrin-free hydrogels and 35.20 ± 3.6 % for fibrin-containing hydrogels.	Hybrid inks with improved mechanical properties and higher viscosities are generated.	[85]

Abbreviations: FibMA: methacrylate-based fibrinogen; PRF: platelet-rich fibrin; TA: tannic acid; PVA: polyvinyl alcohol; $CaCl_2$: calcium chloride.

and found that an increased concentration of Zn^{2+} promoted a decrease in fiber length and an increase in diameter (Fig. 2B). Additionally, the bundled protofibrils were loosely coupled to one another with increased concentrations of Zn^{2+}, leading to a concomitant decrease in the modulus of elasticity.

Chemical cross-linking utilizes chemical reactions to generate covalent bonds. This process is irreversible and results in fibrin networks that are more stable, mechanically strong, and resistant to degradation [81]. However, this process requires the use of additional reagents, and has the potential to produce toxic substances. Chemical cross-linking approaches include enzyme cross-linking, chemical interactions between complementary groups, the use of high-energy radiation, and free radical polymerization. Haghparast-Kenarsari et al. [82] improved the mechanical and physical properties of platelet-rich fibrin (PRF) gel scaffolds using different concentrations of tannic acid (TA) as a cross-linking agent and found that the tensile strengths of the PRF gel scaffolds increased, the amount of swelling was reduced, the cytotoxicity and antimicrobial capacity were enhanced at higher TA concentrations, and the incorporation of TA effectively reduced the rate of scaffold degradation. Furthermore, Zhou et al. [83] prepared fibrin/poly (vinyl alcohol) (PVA) scaffolds by covalently cross-linking with glutaraldehyde by means of an emulsion stenciling method. Consequently, the mechanical strength and hydrolytic stability were enhanced compared to those of the pure fibrin scaffolds. Application of fibrin/PVA scaffolds in a full-thickness dermal excision model can be found to significantly promote vascular network generation and wound healing at the defect site and accelerate epithelial regeneration. Moreover, horseradish peroxidase (HRP) has been used as a catalyst for the enzymatic cross-linking of tissue-engineered hydrogels, wherein H_2O_2 is employed as a substrate to generate phenol radicals that produce dipyrimidine moieties within the polymer-phenol conjugate. The application of HRP-catalyzed dityrosine cross-linking to fibrin scaffolds has been reported to enhance the tensile strength and stiffness, mechanical properties, and degradation resistance without affecting the biocompatibility of the scaffold; such materials are applicable in the area of regenerative medicine. Recently, 3D bioprinting has gained popularity in regenerative medicine because of its capability to accurately model complex multicellular tissue architectures. Introduction of cross-linking technology can effectively adjust the printability characteristics of bioinks and optimize the mechanical properties and degradation rates. For instance, gelatin methacryloyl (GelMA) is widely used in 3D bioprinting. Upon combining fibrinogen with GelMA and exposing the mixture to ultraviolet (UV) light, chemical cross-linking takes place to generate a more stable structure with an enhanced mechanical strength [84]. The stabilities of gelatin/fibrin polymers can be further improved by introducing alginate, which prevents early scaffold degradation. For example, Budharaju et al. [85] employed a dual cross-linking strategy to bioprint alginate-fibrinogen structures. This involved the initial pre-cross-linking of alginate with $CaCl_2$ to increase the number of printable rows of the alginate bioinks. Subsequently, the alginate bioinks were mixed with fibrinogen at the appropriate concentrations, and cross-linking was performed in the presence of $CaCl_2$ and thrombin. Using such approaches, hybrid bioinks with superior mechanical properties, higher viscosities, and improved printability characteristics have been successfully prepared, and have great potential for the regenerative engineering of myocardial tissues.

The modification and cross-linking methods of fibrin are diverse and have different characteristics. For example, the methacryloyl reaction gives fibrin the ability to be cured using light; sulfonation modification improves the hydrophilicity and ion-exchange ability of fibrin derivatives; chemical cross-linking results in derivatives that are more structurally stable but may be chemically toxic; physical cross-linking is safer and more reliable, but the derivatives have a slight deficiency in mechanical strength. The cross-linking method can be flexibly selected according to different applications, so that fibrin scaffolds can better match the needs of injured tissues. Table 1 summarizes a selection of modification and cross-linking approaches used for fibrin scaffold development.

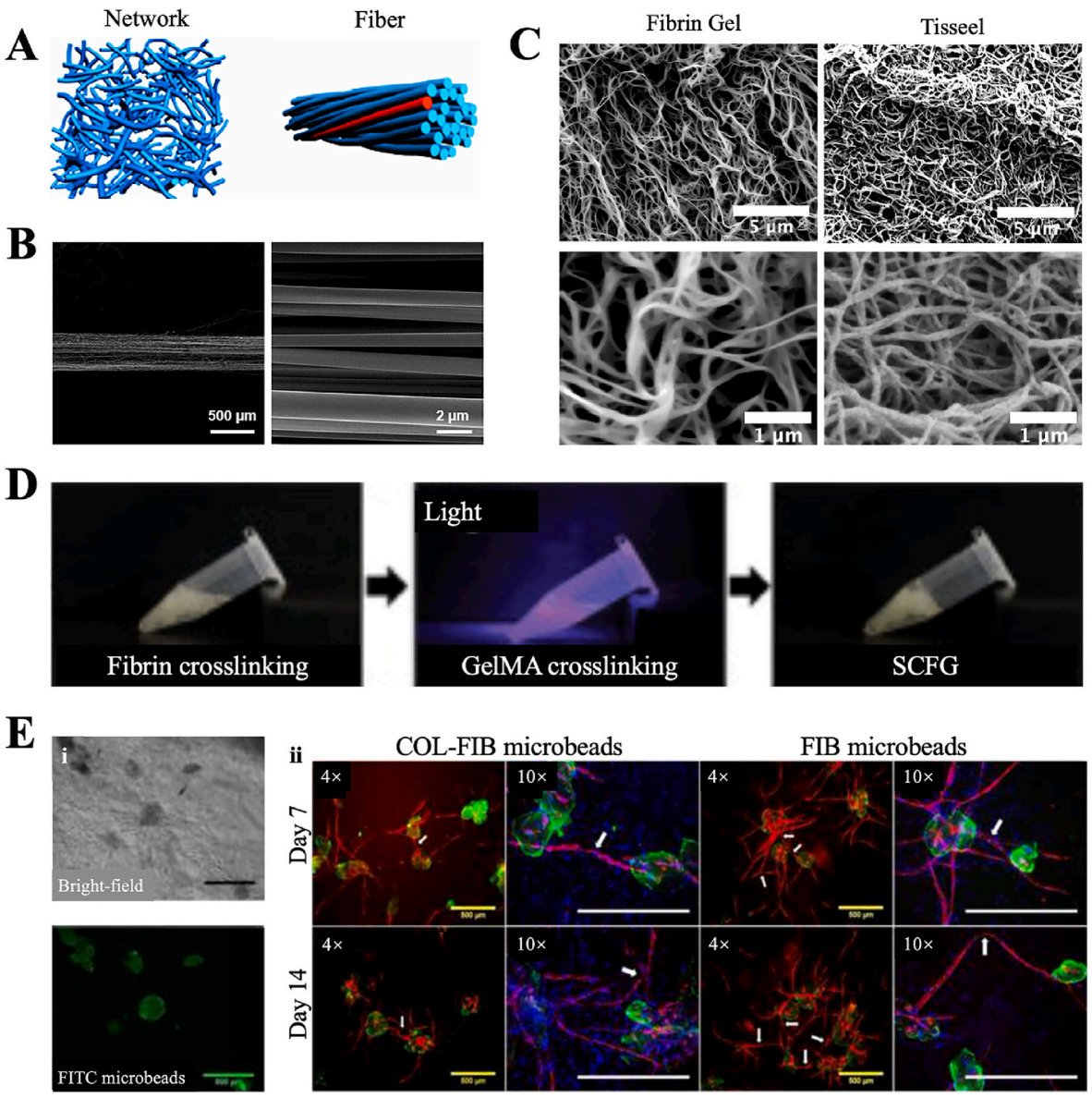

Fig. 3. Application forms of fibrin. **(A)** Schematic diagram of the fibrin network. The Figure is reproduced with minor adaptations from Ref. [119] with permission, *Copyright © 2017 International Society on Thrombosis and Haemostasis. Published by Elsevier Inc. All rights reserved.* (License number: 5,824,031,358,429). **(B)** SEM image of collagen-fibrin (Col-FB) fibrous hydrogel for spinal cord repair at high alignment. The Figure is reproduced with minor adaptations from Ref. [120] with permission, *Copyright © 2022, American Chemical Society.* **(C)** Differences in the microstructure of fibrin hydrogel and fibrin sealant, Tisseel. The Figure is reproduced with minor adaptations from Ref. [99] with permission, based on Creative Commons Attribution License (CC BY), *Copyright © 2023 Pereira, EzEldeen, Ugarte-Berzal, Martens, Malengier-Devlies, Vandooren, Vranckx, Matthys and Opdenakker.* **(D)** Digital photograph of sequential cross-linking fibrin glue (SCFG) formation process. The Figure is reproduced with minor adaptations from Ref. [106] with permission, based on Creative Commons Attribution 4.0 International Public License (CC BY 4.0), *Copyright © 2023 The Authors. Advanced Science published by Wiley-VCH GmbH.* **(E)** (i) Bright field and fluorescence images of fibrin (FIB) microbeads after embedding (day 0) and 7 days of incubation; (ii) Vascular network formation between microbeads. The Figure is reproduced with minor adaptations from Ref. [110] with permission, *Copyright © 2015 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.* (License number: 5,824,040,989,554).

4. Application forms of fibrin

Fibrinogen can be cross-linked to form fibrin networks with the help of substances such as thrombin, which can be used in tissue engineering (Fig. 3A). Fibrin can be used to prepare various materials, including fibrin hydrogels, FG, and fibrin microbeads (FMBs).

4.1. Fibrin hydrogels

Hydrogels are 3D polymer networks consisting of chemically or physically cross-linked hydrophilic polymers with a certain solubility in water and a certain degree of physical integrity [87,88]. Fibrin hydrogels have been prepared from a mixture of fibrinogen and thrombin, wherein coagulation factor XIIIa was also added to generate a stable and insoluble fibrin network (Fig. 3B). Optimization studies have demonstrated that the concentrations of these three components influence the mechanical properties of the final hydrogels, thereby resulting in varying effects on cell migration, differentiation, spreading, and proliferation through mechanotransduction. For instance, one study found that lower levels of fibrinogen and thrombin promoted cell proliferation. Thrombin is often solubilized in a $CaCl_2$ solution to provide sufficient calcium ions to promote the activation of coagulation factor XIIIa, which contributes to the stabilization of the fibrin network [89]. The NaCl concentration has also been found to affect the

physicochemical properties of fibrin hydrogels. More specifically, physiological salt (PS) fibrin gels and high salt (HS) fibrin gels were constructed at NaCl concentrations of 145 mM (physiological level) and 250 mM, respectively. The time required for *in vitro* degradation of the HS gel was reported to be approximately three times longer than that of the PS gel; the PS gel was completely degraded after 1 week of subcutaneous implantation, whereas the HS gel remained intact, demonstrating its potential for use as a delivery system [90]. Furthermore, the addition of tranexamic acid, an anti-fibrinolytic solvent that is non-toxic to cells, was found to prevent premature degradation of the fibrin scaffolds before cell proliferation reached a stable level [91–93]. Fibrin scaffolds with finer structures can be prepared via electrospinning, which implements an electrical field to deposit fibrin on a target substrate, generating porous fibers with a high surface area/volume ratio and a high spatial interconnectivity similar to that of the natural ECM [94,95]. Using electrospinning methods, it is possible to selectively engineer fiber orientation through a varying spinning rate and fibrin concentration [96]. In this context, Du et al. [97] used molecular self-assembly and electrospinning to construct a 3D hierarchical aligned fibrin hydrogel with a structure similar to that of native fibrin cables. Their system adequately mimicked the microenvironment at the beginning of nerve regeneration and promoted axon regeneration, proliferation, and migration of Schwann cells.

In addition to good biocompatibility and excellent cell adhesion properties, fibrin hydrogels possess uniform porous structures and high porosities [98]. This architecture increases the surface area, which is more conducive to cellular interactions and promotes angiogenesis, as well as the absorption and elimination of nutrients and waste [99,100]. The pore size of the network structure is also an important feature of a hydrogel and has a major influence on its controlled swelling properties and drug release [5,101]. Studies have shown that the pore size that is most conducive to fibroblast proliferation and migration, and which promotes wound healing to an optimal extent, is approximately ~20–124 μm. Additionally, fibrin hydrogels are extremely hydrophilic, with high water absorption capacities and good swelling rates [102]. Consequently, they can rapidly absorb the tissue exudates around wounds whilst maintaining a humid environment at the surface of the wound, thus promoting healing and protecting the wound [3,103]. Fibrins are known to exhibit anti-inflammatory and antioxidant properties that create a conducive environment for tissue regeneration and wound healing. In this context, Pereira et al. [99] applied a fibrin hydrogel to full-thickness skin wounds and demonstrated that it significantly improved inflammation at the wound site, with a decrease in pro-inflammatory cytokine levels and an increase in interleukin (IL)-10 levels. They also reported a marked increase in the multiplication of skin endothelial cells, fibroblasts, and keratinocytes, along with an increase in the migration of keratinocytes, which accelerated wound healing. Moreover, fibrin hydrogels have been demonstrated to exhibit both viscous and elastic behaviors as well as liquid and solid properties under different conditions, which facilitate their application as cellular scaffolds in tissue and organ regeneration [104]. Fibrin hydrogels, with their unique mechanical properties, also play a part in controlling neurite extension in immature neurons. More specifically, hydrogels prepared using low concentrations of fibrinogen promote the extension of dorsal root ganglion nerve synapses in mice to a greater extent than those prepared using higher concentrations [36]. In addition, as an injectable scaffold material, fibrin hydrogels can be used in close contact with the tissue, overcoming defects associated with solid scaffolds, which cannot be completely fitted to the tissue.

4.2. Fibrin glue

FG, also called fibrin tissue adhesive or fibrin sealant, is a biocompatible and biodegradable fibrin clot prepared from a mixture of thrombin with autologous or allogeneic fibrinogen (Fig. 3C). FG not only exhibits the hemostatic function of fibrin itself, but also possesses a high tensile strength and adhesive properties, leading to its clinical application in intraoperative hemostasis when traditional hemostatic methods are ineffective. Additionally, FG has been used as a sealant for closing tissue defects, owing to its ability to connect tissues without the requirement for excessive force, thereby avoiding tissue damage [105]. Yu et al. [106] combined the rapid cross-linking properties of fibrin with the strong bonding ability of GelMA to construct a sequentially cross-linked fibrin glue (SCFG) (Fig. 3D). Two consecutive network cross-links occur during SCFG formation, resulting in stronger adhesion and the effective promotion of tissue hemostasis and repair. With the development of tissue engineering, FG has also been employed as a delivery vehicle and scaffold matrix in tissue engineering applications, such as in the promotion of hemostasis and wound contraction, to induce anti-inflammatory effects, in chronic wound healing, and for the relief of skin ulcers and severe burns [107]. Owing to its excellent adhesive properties, FG is widely used for the fixation of tissue-engineered scaffolds at the respective sites. Compared with other scaffolds, as fibrinogen precipitated from plasma may contain higher concentrations of active substances (i.e., coagulation factors and various growth factors), the resulting FG can exhibit greater degrees of hemostasis, cell survival, matrix synthesis, wound healing, and tissue regeneration [72,108]. FG is available from both autologous and commercial sources. Commercial FG tends to contain a higher fibrinogen concentration and greater mechanical strength, thereby rendering it more effective as a sealant and an adhesive. However, because of the complexity of the ingredients and inadequate sterilization, commercial FG carries a greater risk of allergies and viral infections, such as blood-borne viruses (i.e., human immunodeficiency virus, hepatitis B, and hepatitis C). This limitation can be ameliorated by the rigorous screening of blood donors, plasma pairs, and related sterilization steps. Commercially available fibrin has been used in a variety of clinical applications, including as tissue adhesives. In addition, FG is used for hemostasis of wounds in pre- and post-operative surgical procedures. In contrast, autologous FG is extracted from the blood of patients and contains high concentrations of both clotting factors and cytokines, thereby eliminating the risk of infection from blood transfusion; nonetheless, the preparation process is relatively complex. Owing to the various growth factors and other biologically active substances present in autologous blood, autologous FG is more conducive to cell survival, hemostasis, the promotion of angiogenesis, wound healing, and tissue regeneration, ultimately providing a suitable matrix for cell growth and differentiation, whilst inhibiting bacterial reproduction to a certain extent. Recently, new production methods have been developed to generate autologous FG more rapidly and cost-effectively.

4.3. Fibrin microbeads

FMBs are spherical dense beads with diameters ranging from 50 to 250 μm and are typically composed of natural fibrin combined with other raw materials via a water-in-oil emulsification strategy (Fig. 3E). More specifically, after mixing a fibrin stock solution with thrombin to prepare a FMB precursor solution, this solution is added dropwise to polydimethylsiloxane oil to obtain the desired FMBs [109]. These FMBs are extensively used as scaffold materials in tissue engineering to provide an ECM-like environment for cell migration and proliferation, as well as to promote tissue regeneration. The denatured fibrinogen in FMBs is extremely sensitive to mesenchymal-type cells, e.g., fibroblasts and endothelial cells. Thus, for vascularization applications in tissue engineering, endothelial cells and fibroblasts are usually granulated and suspended in the FMB precursor solution for implantation into the FMB structure [110]. The cells present in tissues and organs rely on blood vessels to provide nutrients and oxygen, and consequently, insufficient vascularization can lead to tissue hypoxia, nutrient deficiency, reduced cellular activities, and tissue necrosis [111,112]. In tissue engineering, specifically for larger tissues, vascularization inside the implanted scaffolds determines the cell survival, proliferation, and migration rates,

which in turn affect tissue regeneration [113,114]. Although spontaneous vascularization of the implant occurs, it is slow; therefore, the requirements for tissue growth often cannot be met. Fibrin, which is a component of natural ECM, possesses multiple sites for the adhesion of cells and bioactive substances, and plays a significant role in promoting angiogenesis [115,116]. Under these circumstances, Rioja et al. [110] developed modular FMBs with embedded human endothelial cells and fibroblasts. They observed that the cells embedded in the FMBs maintained a high cell viability with active cell proliferation and migration. The endothelial cells proliferated and formed vascular networks under the influence of bioactive substances released by the fibroblasts, and vascular network anastomoses were observed between adjacent microbeads.

Fibrin has a number of distinctive application forms, including fibrin hydrogel, FG, and FMB. Fibrin hydrogels are highly porous and extremely hydrophilic but lack sufficient mechanical strength. Currently, they are widely used in a variety of tissue engineering applications, including those related to skin, adipose, and skeletal muscle tissues [117,118]. Additionally, FG, which is also known as fibrin sealant, exhibits a high tensile strength and high adhesion capacity, which has significant advantages in promoting the healing of burns and chronic wounds, as well as playing an adjunctive role in stabilizing other scaffolds in tissue engineering. Furthermore, the denatured fibrinogen in FMBs is highly sensitive to mesenchymal-type cells and is widely used for stem cell isolation and culture. Different applications require specific characteristics, and the appropriate application can be selected according to the clinical application.

5. Biofunctionalization of fibrin

5.1. Growth factor-loaded fibrin

The scope of application of fibrin in tissue engineering can be further extended through its combination with other active ingredients, including loading with growth factors under catalysis by transglutaminase factor XIIIa [121–123]. More specifically, the biologically active structural domain is pre-coupled to a transglutaminase substrate sequence (NQEQVSP) to generate a bifunctional or bistructural domain peptide, which is subsequently covalently cross-linking with fibrin in the presence of transglutaminase to introduce exogenous growth factors into the fibrin matrix [124,125]. The release of these growth factors can subsequently be determined by their mode of interaction with fibrin, the fibrin degradation rate, and the strength of cross-linking, wherein the release rate ultimately determines the therapeutic effect. In the ECM, heparin exhibits a strong binding affinity to various peptide growth factors and regulates their bioactivities, thereby facilitating the immobilization of growth factors and slowing their degradation; these compounds are collectively known as heparin-binding growth factors (HBGFs) [126,127]. Representative HBGFs, such as the basic fibroblast growth factor (bFGF) and the acidic fibroblast growth factor (aFGF), promote mitosis in various cells, including endothelial cells, fibroblasts, and chondrocytes, and are also known to stimulate angiogenesis, ECM synthesis, and ECM degradation [128–131]. During catalysis by transglutaminase, peptide chains bearing heparin-binding structural domains are covalently cross-linked to fibrin. Subsequently, the heparin-binding structural domains that have been cross-linked to fibrin bind to heparin, which in turn binds to various HBGFs to yield a heparin-binding delivery system. This equates to the immobilization of HBGFs onto fibrin, contributing to their slow and sustained release, which in turn enhances fibrin's ability to facilitate cell migration, proliferation, and tissue regeneration.

5.2. Exosome-loaded fibrin

Exosomes containing bioactive molecules, such as complex RNAs and proteins, can also be encapsulated in fibrin to facilitate tissue regeneration. This approach can compensate for the fact that exosomes do not readily accumulate at injury sites when traditional drug delivery methods are employed. Thus, He et al. [132] developed an exosome-containing fibrin hydrogel (Gel-Exo) and explored its role in the repair of spinal cord injuries. More specifically, they found that fibrin hydrogels implanted with exosomes derived from rat bone marrow mesenchymal stem cells (BMSCs) delivered and immobilized exosomes at spinal cord injury sites. After Gel-Exo treatment, the protein and mRNA expression levels of the nerve growth factor-inducible protein (VGF) were significantly upregulated at the lesion site in rats with spinal cord injuries. This enhanced expression of VGF promoted the proliferation and maturation of oligodendrocytes, leading to significantly improved rat motor functions. Cui et al. [133] deposited BMSC-derived exosomes and fibrin on the surface of a micro-nanostructured tantalum coating and found that BMSC-derived exosomes exhibited the strongest ability to adhere, proliferate, and differentiate osteoblasts at an exosome concentration of 1 μg μL^{-1}. By implanting this integrative coating into rabbit tibia, a large amount of bone matrix was deposited on the implant surface, with increased matrix secretion being observed by the osteoblasts, along with active osteogenic mineralization, and significant enhancements in osteogenesis and osseointegration. In addition to BMSC-derived exosomes, adipose stem cell-derived exosomes (ASC-Exos) have attracted attention as cell-free treatments for tendon healing in rotator cuff tears. In this context, Wang et al. [134] constructed a fibrin hydrogel containing ASC-Exos and applied it to a rabbit model of partial-thickness rotator cuff tears (PTRCTs). They found that ASC-Exos/fibrin was effective in preventing progression of the tear site and in promoting high-quality healing of the tendons. Furthermore, immunohistochemistry results revealed that ASC-Exos/fibrin reduced type III collagen deposition while promoting type I collagen production, thereby suggesting that this combination hydrogel is useful in reducing scar formation and promoting natural repair of the injured area.

5.3. Drug-loaded fibrin

Traditional drug delivery methods have numerous drawbacks, including the requirement for repeated administration, poor drug specificities, unpredictable drug release rates, and serious side effects [135]. Additionally, drugs administered via the skin tend to experience permeability issues and cannot easily reach the inside of tissues. Similarly, drugs administered via the digestive tract may be denatured by gastric acid, digestive enzymes, and other substances found in the digestive tract. Therefore, the development of simple, effective, and non-toxic drug delivery systems is essential. As previously mentioned, fibrin has been widely used in drug delivery systems for wound healing, tissue regeneration, and other applications [126,136]. Fibrin networks are highly stable and porous polymers with high drug-loading capacities and are also capable of releasing controlled doses of drugs in target tissues and organs according to the diffusion coefficients of natural biomolecules. Importantly, they can maintain high drug concentrations in the desired tissues while minimizing drug toxicity and preventing the body from developing a tolerance to the corresponding drugs [137,138]. Additionally, fibrin imparts drugs with enhanced stabilities and reduces the potential for their enzymatic degradation or denaturation. As previously discussed, to prepare hydrogels for specific applications, the fibrinogen, thrombin, and coagulation factor XIIIa concentrations can be adjusted, or the hydrogel can be modified or cross-linked to alter its pore size and modify its drug delivery capacity [139]. Fibrin-based drug delivery systems can be administered orally or through the buccal mucosa, skin, or eyes, among other routes. Oral use of drug-containing fibrin reduces the possibility of drug deformation and deactivation under the influence of digestive enzymes and gastric acid compared to the oral route of drug-only administration, leveraging the particle size of the fibrin network to achieve targeted delivery, thereby avoiding uncontrolled drug release and reducing toxic drug effects. Additionally, the

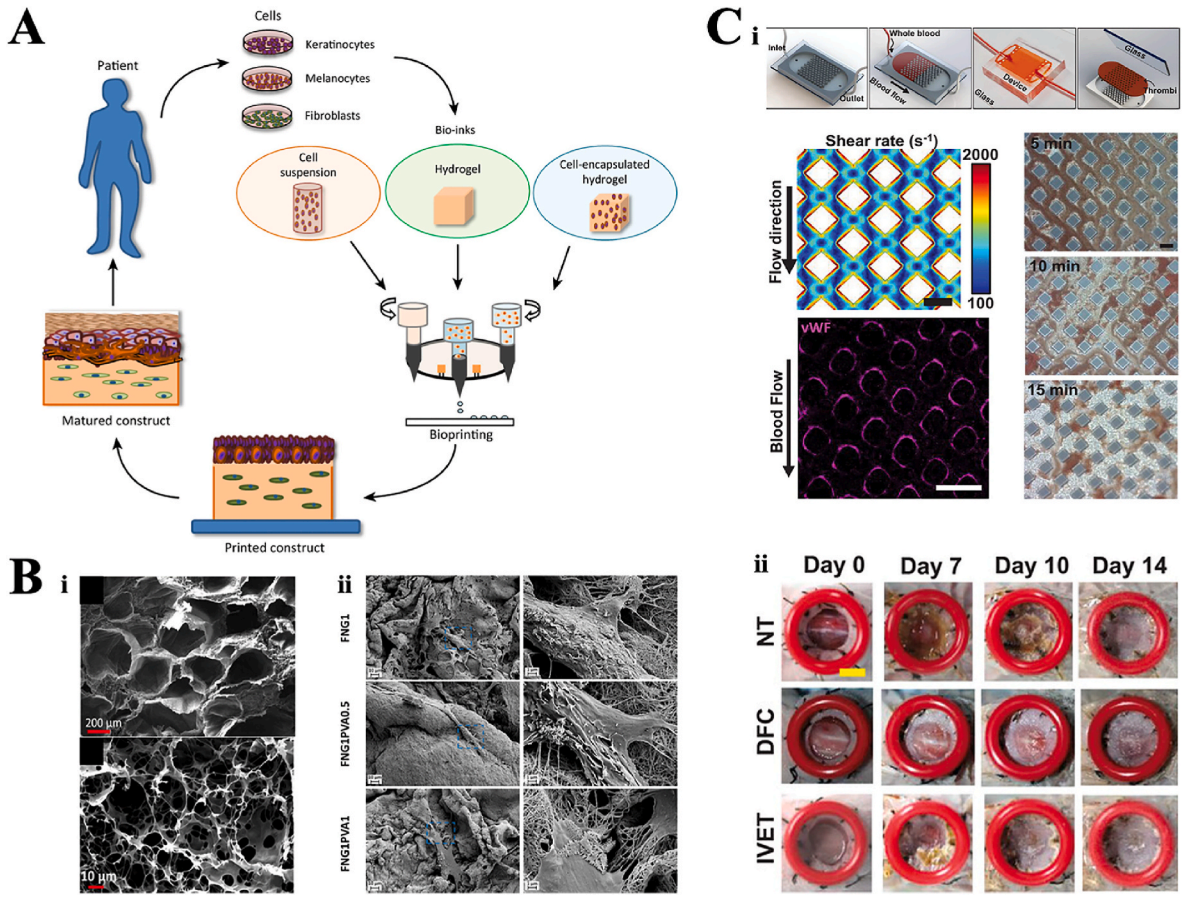

Fig. 4. Application of fibrin in skin/wound healing. **(A)** Schematic diagram of skin tissue engineering The Figure is reproduced with minor adaptations from Ref. [154] with permission, *Copyright © 2016 Elsevier Ltd. All rights reserved.* (License number: 5,824,041,197,079). **(B)** (i) Low- and high-power SEM displaying the porous structure of the fibrin (FNG)/polyvinyl alcohol (PVA) scaffold (FNG1PVA0.5 scaffold); (ii) SEM images of mesenchymal stem cells (MSCs) on pure FNG scaffold (FNG1), FNG/PVA scaffold with different ratios (FNG1PVA0.5, FNG1PVA1 scaffolds) after culturing for 14 days. The Figure is reproduced with minor adaptations from Ref. [83] with permission, based on Creative Commons Attribution License (CC BY). **(C)** (i) Microfluidic technology to generate autologous implantable engineered thrombi; (ii) Implantable vascularized engineered thrombi (IVET) promotes angiogenesis and skin healing in mouse skin wounds. The Figure is reproduced with minor adaptations from Ref. [153] with permission, *Copyright © 2023 Wiley-VCH GmbH.* (License number: 5,824,041,506,191).

combination of fibrin hydrogels with submicron particles to develop nanoscale hydrogel particles has also received research attention. These particles can transport drugs to tissues through transcellular pathways, and tend to exhibit superior control over drug release, whilst facilitating drug delivery to tissues via small capillaries. Consequently, these systems have been used extensively in the treatment of organ and tissue damage, including in the central nervous system [140]. Moreover, owing to FMBs' small diameters, they are also particularly advantageous in the context of drug release from small pericapillary tissues.

The biofunctionalization of fibrin with active molecules can help to expand its application scope in the field of tissue engineering, as well as to improve the shortcomings of active molecules that do not easily reach and accumulate at the site of injury. A variety of loaded species, including growth factors, exosomes, and drugs, have been developed, which hold great promise for clinical application.

6. Application of fibrin in tissue engineering

6.1. Skin/wound healing

The skin, which serves as an efficient shield between the environment and the human body, is susceptible to physical and chemical injuries that can lead to the formation of wounds, such as burns and diabetic ulcers [141,142]. If left untreated, such wounds may lead to infection, inflammation, and tissue necrosis, among other serious consequences [143,144]. Traditionally, autologous skin grafts have been used to treat severe cutaneous traumatic defects [145], an approach that can cause serious complications, such as infection and necrosis of the grafted skin, and may result in severe scarring due to the lack of a functional dermis. To address these problems, tissue engineering techniques have been increasingly applied to the skin tissue (Fig. 4A) [146]. By obtaining autologous keratinocytes and culturing these species in fibrin scaffolds to rebuild skin tissue, the barrier system is restored in the damaged area, wound healing is promoted, and both over-proliferation and scar formation are inhibited, whilst avoiding damage to the healthy skin [143,147–150]. Fibrin scaffolds are particularly advantageous in that they can closely adhere to the wound, are extremely hydrophilic, possess high water absorption capabilities and good swelling rates, and can rapidly absorb the tissue exudates around wounds while maintaining a humid environment at the surface of the wound. These characteristics help to protect the surface of the wound and facilitate healing. Fibrin is usually used in combination with other polymers for enhancing its mechanical properties and providing a suitable degradation rate in skin tissue engineering applications. In this context, Martin-Piedra et al. [151] constructed a human skin model using autologous dermal fibroblasts, epidermal keratinocytes, and fibrin-agarose biomaterials. This model was applied as an advanced therapeutic agent in patients with burns, wherein full-thickness biopsies of the grafted areas were performed after 30, 60, and 90 days. It was found that the epidermis differentiated and matured rapidly after

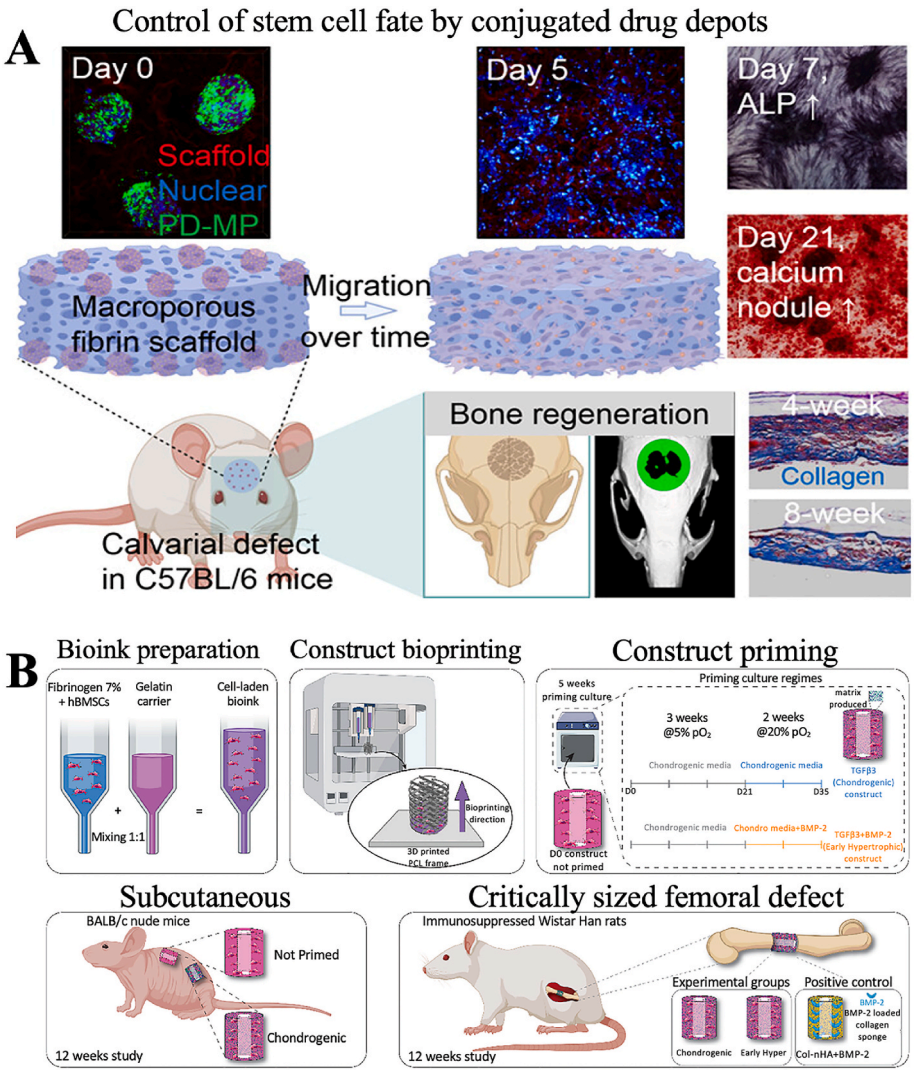

Fig. 5. Application of fibrin in bone. **(A)** Mesoporous fibrin scaffolds (MFS) supported mesenchymal stem cell (MSC) spheres to target bone regeneration. The Figure is reproduced with minor adaptations from Ref. [162] with permission, *Copyright © 2023, American Chemical Society.* **(B)** 3D printing of cartilage models based on fibrin and polycaprolactone (PCL) for the treatment of bone injury The Figure is reproduced with minor adaptations from Ref. [164] with permission, based on Creative Commons Attribution License (CC BY), *Copyright © 2022 The Authors. Published by Elsevier Ltd on behalf of Acta Materialia Inc.*

transplantation to reestablish the barrier system, whereas the dermis matured at a slightly slower rate but promoted collagen production, induced the growth of host blood vessels into the grafts, and enriched the blood supply. The introduction of polyvinyl alcohol (PVA) into fibrin has also been found to improve the fibrin scaffold mechanical strength, while also reducing the costs associated with scaffold production. In this context, Zhou's team [83] fabricated porous nano-scaffolds with high biocompatibilities, high tensile strengths, and high stabilities. This was achieved by mixing fibrin with PVA via the emulsion stencil method, and subsequent evaluation of the scaffold effectiveness on wound re-epithelialization was conducted in a mouse full-thickness skin excision defect model (Fig. 4B). Their results revealed that fibrin/PVA scaffolds with good cell adhesion properties and a high cytocompatibility significantly accelerated wound healing, promoted collagen fiber formation, and facilitated angiogenesis. Importantly, no inflammatory exudation was observed during scaffold integration or upon absorption by the body. The above-mentioned results demonstrate that fibrin/PVA scaffolds can effectively promote wound repair and re-epithelialization, suggesting their potential for applications in skin tissue engineering.

Bacterial infection is a primary factor in the healing of wounds, and fibrin scaffolds alone do not tend to exhibit effective antimicrobial properties. Metal nanoparticles have therefore attracted considerable attention in the area of tissue engineering due to their distinctive antibacterial and anti-inflammatory properties. For example, silver nanoparticles are known to possess a good electrical conductivity and electrochemical activity, along with extremely strong antimicrobial properties. Chitosan also exhibits a good antimicrobial ability; therefore, the combination of both silver nanoparticles and chitosan can further enhance the properties of fibrin scaffolds to promote wound healing. For instance, Sanmugam et al. [152] used electrospinning to prepare fibrin/chitosan-encapsulated silver nanoparticle (CH:F:SPG-CH:SNP) composite bandages and applied the obtained material to a full-thickness dermal excision defect model in Albino Wistar rats. They found that their developed bandage promoted fibroblast proliferation, wound healing, and re-epithelialization, in addition to preventing bacterial infection. Moreover, fresh skin regeneration occurred at the site of skin loss without scarring or inflammatory exudation. However, skin tissue engineering is hindered by its slow vascularization rates, wherein the artificial dermis takes longer to reestablish blood vessels, and ultimately, to achieve wound healing and skin regeneration. To address this shortcoming, Jung's team [153] constructed implantable vascularized engineered thrombi (IVET) by forming nematic 3D fibrin fibers using a microfluidic approach. These thrombi were applied to full-thickness skin wounds in mice and rats (Fig. 4C), and it was found that the IVET

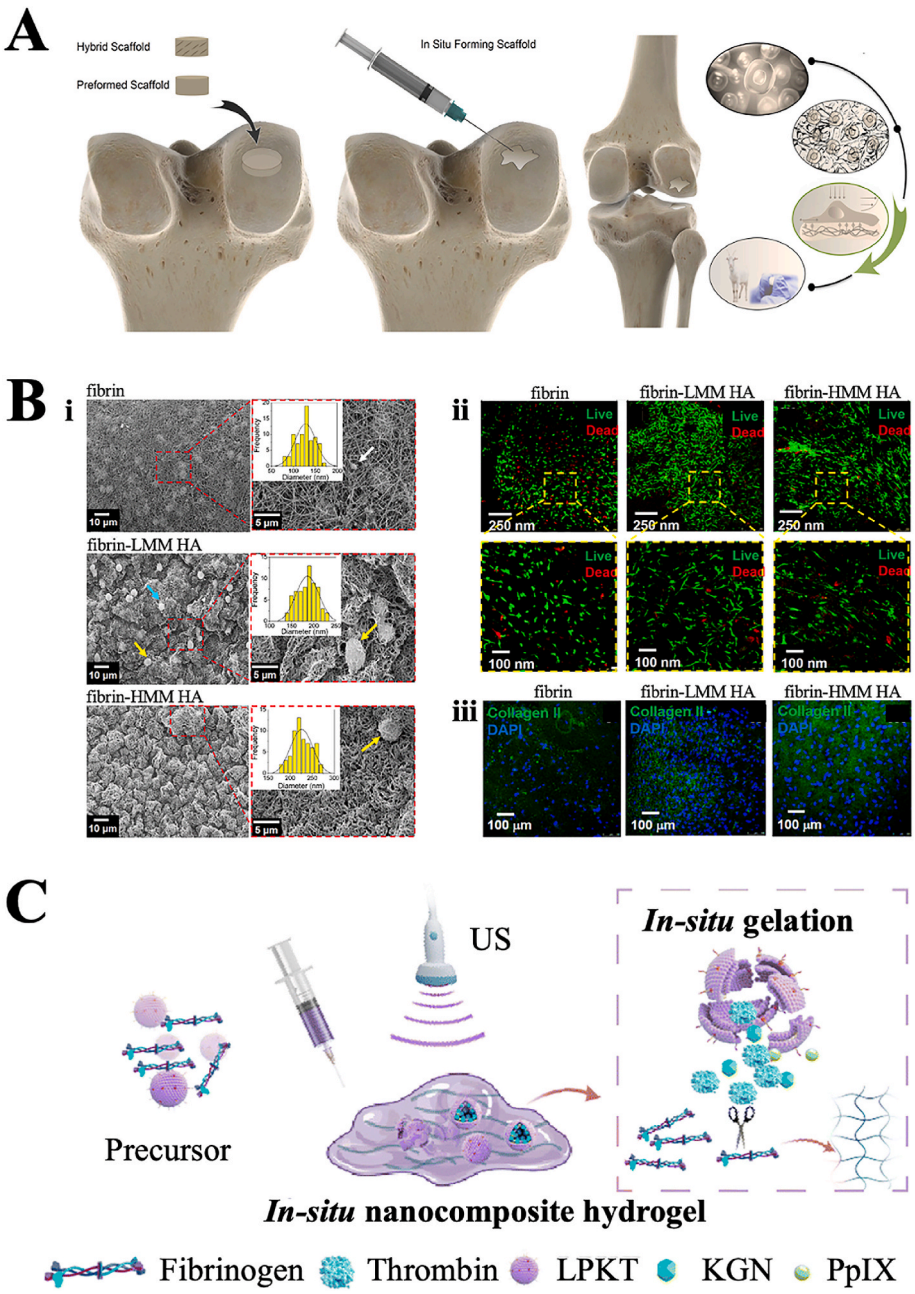

Fig. 6. Application of fibrin in cartilage. **(A)** The effective regeneration of hyaline cartilage tissue. The Figure is reproduced with minor adaptations from Ref. [177] with permission, based on Creative Commons Attribution 4.0 International Public License (CC BY 4.0), *Copyright © 2021 The Authors. Published by Elsevier Masson SAS.* **(B)** (i) SEM images of fibrin, fibrin-low molecular mass hyaluronic acid (LMM HA), and fibrin-high molecular mass (HMM) HA. (ii) LIVE/DEAD images of the cells with fibrin, fibrin-LMM HA, and fibrin-HMM HA taken on day 7. (iii) Collagen II production in different scaffolds. The Figure is reproduced with minor adaptations from Ref. [174] with permission, *Copyright © 2019 Elsevier B.V. All rights reserved.* (License number: 5,824,050,732,768). **(C)** Schematic diagram of the *in-situ* nanocomposite hydrogel preparation process. The Figure is reproduced with minor adaptations from Ref. [175] with permission, *Copyright ©2023 The Royal Society of Chemistry*. (Billing Account Number: 3002468464).

supported the formation of a microvascular network at the wound site, whilst also promoting vascularization and inducing vascular anastomosis between the host and graft. Consequently, wound closure and collagen deposition were facilitated without scar tissue regeneration. The same study group also explored the macrophage status at the wound site and demonstrated that IVET treatment resulted in significantly reduced levels of inducible nitric oxide synthase (iNOS) and a higher percentage of the M2 macrophage phenotype, thereby accelerating wound healing.

6.2. Bone

Large bone injuries still represent a major challenge because of high prevalence rates and the complexity of treatment. Such injuries have often been treated with autologous or allogeneic bone grafts, which carry the risks of infection, immune rejection, and loss of function [155]. The development of bone tissue engineering offers new promise in the treatment of bone injuries, and fibrin scaffolds are known to accelerate bone regeneration [156–158]. Considering the role of bones in the human skeleton, the fibrin scaffolds used in bone tissue engineering must possess a sufficient mechanical strength, stiffness, and flexibility to

match the physiological characteristics of natural bone tissue [159,160]. Importantly, fibrin provides a proper microenvironment for intrachondral formation of mesenchymal stem cells (MSCs), and fibrin-based scaffolds can simply and effectively promote bone formation in bone tissue engineering to achieve indirect ossification. Jeyachandran et al. [161] combined a fibrin hydrogel with porous bioglass-poly (lactic acid-glycol) (Bg-PLGA) composite scaffolds to create a Bg-PLGA@fibrin structure, where the fibrin hydrogel was used to promote cartilage formation, and the Bg-PLGA scaffolds were used to induce hypertrophy and ossification. MSCs were subsequently loaded and cultured in the Bg-PLGA@fibrin structure, and the cartilage and ossification statuses were periodically observed. The Bg-PLGA@fibrin structure inherited the ability of the fibrin hydrogel to mimic the hydration properties of the cartilage matrix, thereby inducing MSC cartilage formation, while simultaneously promoting hypertrophy and matrix mineralization with no exogenous growth factors added; therefore, the system has enormous promise for bone tissue engineering applications. Mesoporous fibrin scaffolds (MFSs) are widely used to repair bone and other injuries because of their high biocompatibilities, biodegradabilities, ease of synthesis, and their ability to promote cell differentiation and adhesion. In this context, Nguyen et al. [162] developed a uniform and scalable fabrication of osteogenic microtissue constructs of MSC spheroids surface-engineered with dexamethasone-releasing polydopamine--coated microparticles (PD-DEXA/MPs) and applied the spheroid-loaded MFSs in a mouse skull defect model (Fig. 5A). This system was found to be highly biocompatible; the MSCs exhibited high cellular activities, and bone regeneration was significantly enhanced in a mouse cranial defect model. Fibrin hydrogels can be strengthened by 3D printing to ensure a high mechanical strength and stability [163]. More specifically, Pitacco et al. [164] mixed fibrinogen, type-A G, hyaluronic acid, and glycerol suspended in human bone marrow-derived MSCs (hBMSCs) as a bioink and bioprinted them into polycaprolactone (PCL) frames to produce mechanically reinforced fibrin structures loaded with cells. These species were then incubated in cartilage medium at five weeks to produce cartilage structures (Fig. 5B). In the final 2 weeks of culture, recombinant protein BMP-2 was also successfully added to initiate early hypertrophy, as evidenced by a marked increase in calcium deposition in the cartilaginous structures. The implantation of these cartilaginous and early hypertrophic structures into a rat femur defect model revealed that the early hypertrophic structures were more supportive of angiogenesis and bone tissue regeneration at the bone injury site, and this was accompanied by a lower degree of ectopic bone formation. Importantly, bone regeneration in the central region of a bone defect was observed for the first time in rats treated with early hypertrophic structures; notably, this has not been observed in the treatment of cartilaginous structures. Therefore, the above study demonstrated that scaffolds 3D printed with fibrin as a bioink support *in-vitro* cartilage formation and the early hypertrophy of hBMSCs, which in turn promote *in vivo* bone defect regeneration. Such approaches are expected to provide a new direction for bone injury treatment.

6.3. Cartilage

Cartilage tissue is not vascularized, and is also known to lack an abundant supply of nutrients and the ability to repair itself [165]. Therefore, cartilage damage is irreversible; cartilage defects due to osteoarthritis, trauma, and other diseases are among the most common causes of disability [166,167]. For the purpose of cartilage reconstruction, autologous chondrocyte implantation is often used clinically; however, this approach is limited due to a lack of chondrocytes and complex chondrocyte processing procedures, in addition to being relatively less effective in elderly patients. Alternatively, cartilage tissue engineering promotes cartilage reconstruction and repair by mimicking the structure and microenvironment of natural cartilage and has been proven to be a reliable means of cartilage tissue healing and regeneration (Fig. 6A) [168–172]. Fibrin can be employed as a scaffold or binder during cartilage tissue engineering to provide a temporary ECM for chondrocytes, thus facilitating cell proliferation, adhesion, and cartilage regeneration. Of note, when fabricating fibrin scaffolds, full consideration should be given to its mechanical properties, such as its elasticity, extensibility, as well as compression resistance. Such properties are required to ensure that the produced cartilage meets the required shock absorption, compression resistance, and lubrication performances. Additionally, to ensure adequate cell adhesion, proliferation, and cartilage repair, the mechanical properties of the scaffolds can be adjusted by modifying the pore sizes and cross-link densities using 3D printing or through combination with a variety of polymers [173]. Xu et al. [16] combined 3D inkjet printing with electrospinning to construct cartilage tissue models from fibrin, collagen, PCL, and rabbit chondrocytes. The resulting hybrid scaffolds exhibited enhanced mechanical properties, tensile strengths, and structural stabilities compared with fibrin-collagen hydrogels, and were also able to withstand greater tensile stresses.

The capacity of fibrin to promote cell angiogenesis, proliferation, and cartilage regeneration can be enhanced by combining it with other bioactive substances. For example, de Melo et al. [174] prepared fibrin-HA semi-IPNs by mixing leukocyte- and platelet-rich plasma (L-PRP) with high molar mass (HMM) HA and low molar mass (LMM) HA, respectively. The effects of the network structure on the cell activity and degree of cartilage repair were evaluated by implanting human adipose tissue-derived mesenchymal stem cells (h-AdMSCs) into the semi-IPNs and stimulating chondrogenesis. Semi-IPN was found to efficiently capture leukocytes, delay fibrin polymerization, and produce thicker and shorter fibers, while also exhibiting an increased degree of swelling and a reduced viscoelasticity. In contrast, fibrin-LMM HA was more angiogenic and secreted significantly higher quantities of vascular endothelial growth factor (VEGF) than fibrin-HMM HA. Both semi-IPNs demonstrated greater abilities to promote h-AdMSC differentiation and chondrogenesis than fibrin alone, with the effect of fibrin-LMM HA being more pronounced (Fig. 6B). The presence of reactive oxygen species (ROS) in the extracellular microenvironment is known to stimulate glycosaminoglycan secretion, which in turn enhances BMSC proliferation and differentiation into chondrocytes. In this context, Wu et al. [175] loaded thrombin, a sono-photosensitizer (PpIX), and the non-toxic drug kartogenin (KGN), which significantly promotes the expression of cartilage-specific genes in BMSC, onto thioketal (TK)-based liposomes. Subsequently, they constructed a novel fibrin-based nanocomposite hydrogel under ultrasonic stimulation (Fig. 6C), which was found to control KGN release and ROS production *in situ*, thereby facilitating the healing of cartilage injury. In their work, the hydrogel precursor was injected into a rat articular cartilage defect model, and under ultrasonic stimulation, PpIX produced ROS, which caused the rupture of TK-based liposomes and promoted the release of thrombin and KGN. Consequently, the released thrombin induced the cross-linking of fibrinogen to form a fibrin hydrogel that filled the vacant cartilage tissue. In contrast, the presence of ROS and KGN in the nanocomposite hydrogel microenvironment promoted BMSC differentiation through the Smad5/mTOR signaling pathway, and significantly facilitated cartilage repair in the rat articular cartilage defect model. However, the excessive accumulation of ROS in the body may cause oxidative damage to the surrounding tissues; therefore, further studies are required to achieve the controlled release of ROS from composite hydrogels to avoid adverse effects on the body. FG exhibited a high tensile strength and good adhesive properties, rendering it suitable for use as a fixation material in cartilage tissue engineering. Moreover, Galarraga's team [176] used the melt electrowriting (MEW) technique to prepare norbornene-modified hyaluronic acid (NorHA) hydrogels loaded with porcine mesenchymal stromal cells (pMSCs). The obtained MEW-NorHA composites encapsulated with pMSCs were immobilized in a full-thickness cartilage defect model of porcine knees using FG. It was observed that the FG promoted filling of the cartilage defects in the composites and improved the quality of the regenerated cartilage tissue.

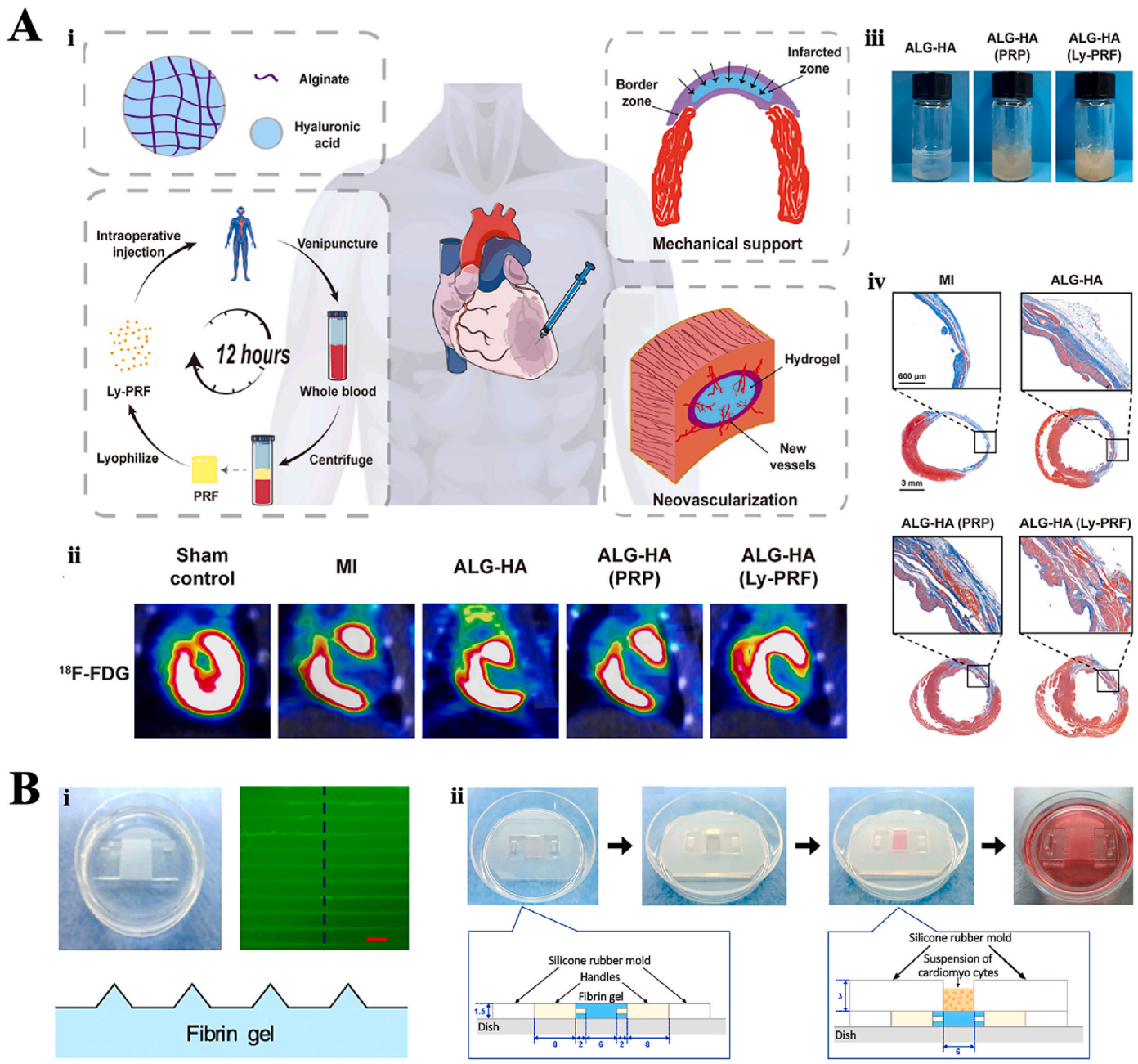

Fig. 7. Application of fibrin in cardiac tissue engineering. **(A)** (i) Schematic diagram of the construction of a composite hydrogel for the treatment of myocardial infarction (MI); (ii) Representative image of 18 F-FDG positron emission tomography-computerized tomography (PET-CT) scan after 28 days; (iii) Alginate and hyaluronic acid (ALG-HA) hydrogels containing platelet rich plasma (PRP) or lyophilized platelet-rich fibrin (Ly-PRF); (iv) The ALG-HA hydrogel with Ly-PRF attenuated left ventricle (LV) remodeling, improved angiogenesis, and reduced apoptosis of cardiomyocytes (CMs). The Figure is reproduced with minor adaptations from Ref. [108] with permission, based on Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Public License (CC BY-NC-ND 4.0), *Copyright © 2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.* **(B)** (i) Fibrin gel with inverted V-shaped ridges; (ii) Fabrication of human-induced pluripotent stem cell-derived CM (hiPSC-CM)-derived cardiac tissue. The Figure is reproduced with minor adaptations from Ref. [188] with permission, *Copyright © 2022 Elsevier Ltd. All rights reserved.* (License number: 5,824,060,527,818).

6.4. Heart

The regenerative capacity of cardiomyocytes (CMs) is extremely limited, and lost CMs are often replaced by scar tissue, which lacks the original contraction, electrical conduction, and other bioactivities of CMs [178,179]. Current treatments for heart damage, including cardiac stenting, have limited applications and are unable to completely repair the myocardium to a healthy level [180,181]. Cardiac tissue engineering may provide a reliable treatment for repairing cardiac defects through the use of functional CMs to fill the scar area [182–184]. Fibrin scaffold mimics the microenvironment in which CMs reside, thus promoting the recovery of damaged cardiac structure and function. In this context, Bei et al. [108] lyophilized platelet-rich fibrin, alginate, and HA to prepare a composite hydrogel that was applied to a rat myocardial infarction (MI) model. This composite hydrogel provided mechanical support to the damaged heart and enabled controlled release of the drug, significantly promoting angiogenesis, reducing ventricular dilatation and cardiomyocyte apoptosis, and improving cardiac function (Fig. 7A). Lou et al. [185] used thrombin to promote fibrinogen cleavage and generate fibrin monomers, which were then cross-linked to form a fibrin network.

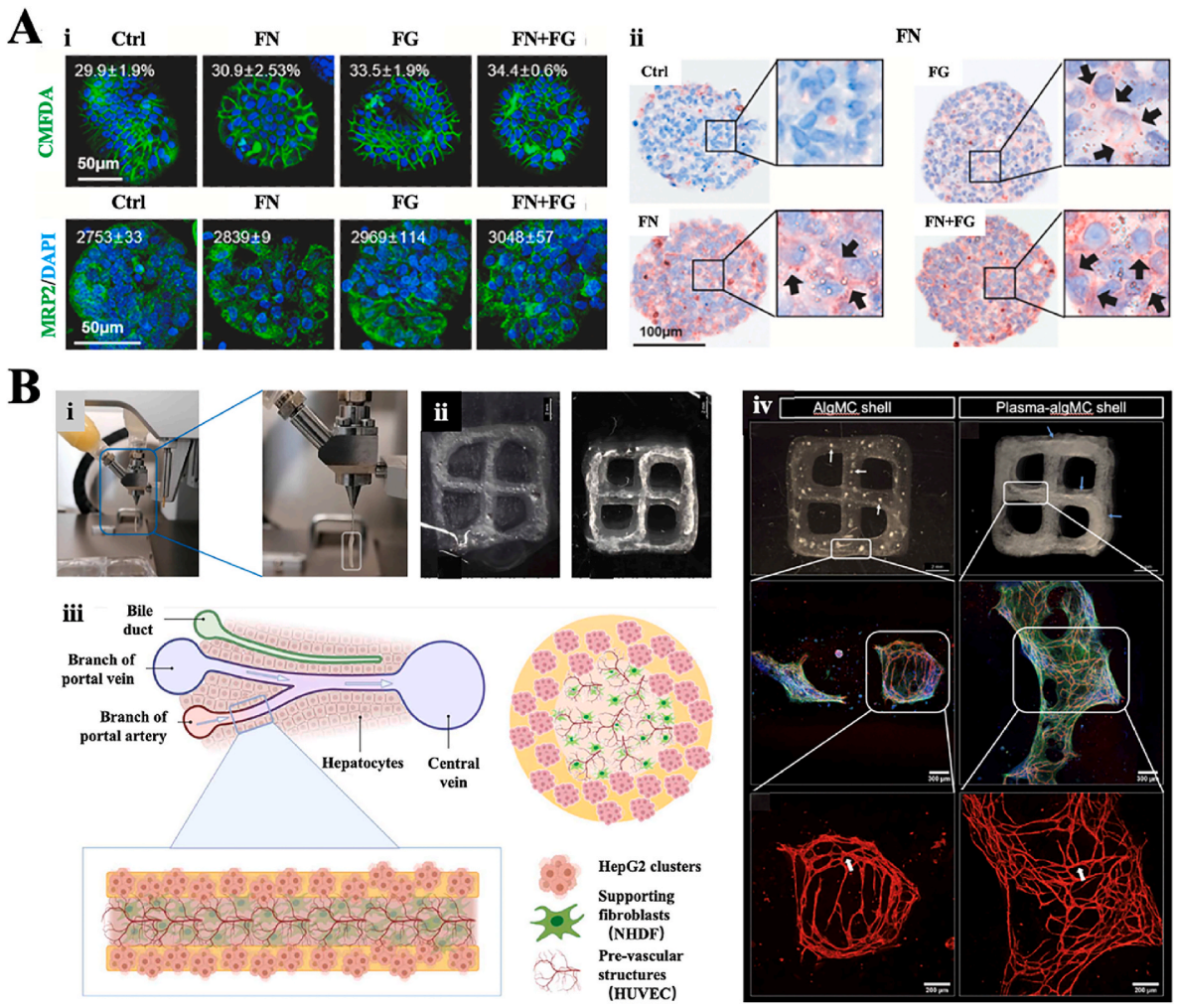

Fig. 8. Application of fibrin in the liver. **(A)** (i) Fibronectin promotes hepatic tissue maturation and liver function; (ii) Fibrinogen increases the assembly of extracellular matrix (ECM) protein fibronectin. The Figure is reproduced with minor adaptations from Ref. [201] with permission, *Copyright © 2021 Elsevier Ltd. All rights reserved.* (License number: 5,824,060,726,537). **(B)** (i) Construction of coaxial extrusion (bio)printing module; (ii) Images of the scaffold after printing and after 10 days of incubation in co-culture medium (CCM); (iii) Schematic diagram for constructing a biological model of the liver; (iv) Images of the core-shell biological model after 10 days of incubation. The Figure is reproduced with minor adaptations from Ref. [200] with permission, *Copyright © 2022 The Author(s). Published by IOP Publishing Ltd.*

Subsequently, human pluripotent stem cell (hPSC)-derived CMs, endothelial cells (ECs), cardiac fibroblasts (CFs), and smooth muscle cells (SMCs) were implanted into the generated fibrin network to construct human cardiac muscle patches (4TCC-hCMPs), in which the fibrin scaffold's porous structure provided favorable conditions of cell adhesion as well as proliferation. It was found that CM maturation markers were highly expressed, and proliferative migration was enhanced in the 4TCC-hCMPs. Importantly, 4TCC-hCMP implantation in the mouse MI model significantly reduced the degree of cardiac infarction, reduced the scar size, enhanced cardiac contraction, and improved cardiac function.

The CMs present in cardiac tissue exhibit a high degree of cellular alignment and layer specificity, wherein the structural and organizational arrangement of CMs determines the specific morphologies and functions of the different cardiomyocyte layers [186]. In recent years, artificial heart patches with 3D-aligned cellular organizations similar to those of the heart structures have been constructed using high-resolution electrohydrodynamic (EHD) printing. In this approach, the unique fast-gelling properties of fibrin can be adapted for 3D printing, promoting uniform cell distribution and the formation of highly aligned cardiac structures. For example, Han et al. [187] co-cultured CMs, rat aortic endothelial cells (RAECs), and fibrin in microfibrous structures printed using EHD technology, wherein the recombination and orientation of the cells were promoted to form a multidirectional cell-aligned 3D cardiac structure with layer-specificity. The resulting cardiac patch effectively inhibited left ventricular remodeling, promoted the formation of microvascular networks, improved the systolic and diastolic functions of the infarcted myocardium, and exhibited tremendous application potential for repairing the damaged myocardium. Sasaki's team [188] implanted human-induced pluripotent stem cell-derived CMs (hiPSC-CMs) into a micro-processed fibrin gel (MFG) with inverted V-shaped ridges to prepare aligned cardiac tissue structures (Fig. 7B). The contractility, contraction velocity, and diastolic velocity were significantly improved, and exhibited more unidirectional and synchronized contractions than in the case of non-aligned cardiac tissues. However, the slow formation of vascular networks limits the application of cardiac tissue engineering. Although the interactions between fibrin and the endothelial cells are conducive to the vascularization of artificial cardiac tissues, the obtained structures lack a certain degree of mechanical strength and stability that is not conducive to the construction of tissues. However, this system can be combined with other polymers for the construction of high-strength cardiac tissue-engineered scaffolds. For instance, Lu et al. [189] used 3D bioprinting to print heart tissue engineering scaffolds using a blend of GelMA, fibrinogen, human umbilical vein endothelial cells (HUVECs),

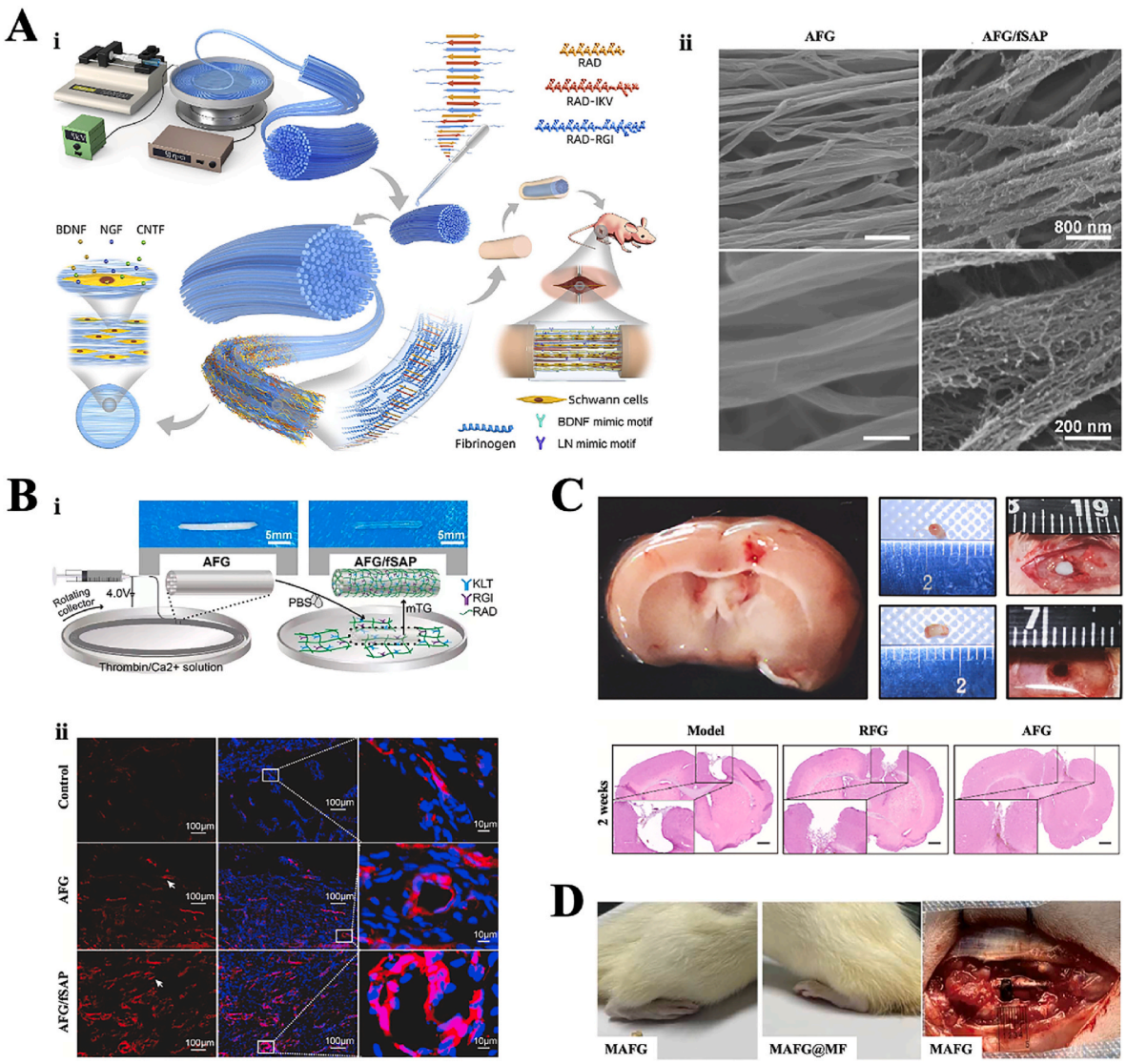

Fig. 9. Application of fibrin in nerve tissue. **(A)** (i) Schematic diagram of the construction and evaluation of an aligned fibrin nanofiber hydrogel (AFG)/functionalized self-assembling peptide (fSAP) interpenetrating hydrogel; (ii) SEM images of the hydrogel's longitudinal fracture surfaces. The Figure is reproduced with minor adaptations from Ref. [209] with permission, based on Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Public License (CC BY-NC-ND 4.0), *Copyright © 2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.* **(B)** (i) The fabrication of the AFG/fSAP hydrogels; (ii) AFG/fSAP implantation facilitates angiogenesis. The Figure is reproduced with minor adaptations from Ref. [210] with permission, *Copyright © 2021 Published by Elsevier Ltd.* (License number: 5,824,061,142,336). **(C)** Implanted AFG evokes endogenous neurogenesis. The Figure is reproduced with minor adaptations from Ref. [211] with permission, *Copyright © 2021 Published by Elsevier Ltd.* (License number: 5,824,061,377,355). **(D)** Magnetically responsive AFG (MAFG) @ magnetic field (MF) implantation promotes recovery of locomotor function. The Figure is reproduced with minor adaptations from Ref. [212] with permission, *Copyright © 2023 IOP Publishing Ltd.* (Billing Account Number: 3002468464).

and hiPSC-CMs as a bioink. The obtained scaffolds exhibited adjustable mechanical properties and suggested the capacity of fibrin to function with endothelial cells to stimulate capillarogenesis and enhance vascularization. Under the action of a high-intensity electric field, endothelial cell angiogenesis was significantly promoted in the scaffold, contributing to the *in vitro* formation of a microvascular network in the artificial heart. Based on the knowledge that fibrin scaffolds lack bioactive factors that promote cardiomyocyte proliferation, and that fibrin itself exhibits a limited therapeutic capacity [190], Chang's team [191] formed a fibrin-based cardiac patch containing the biologically active factor neurogulin-1 (NRG-1) for the treatment of MI in mice. The addition of NRG-1 improved the comprehensive performance of the patch, which supported cardiomyocyte proliferation and maintained cellular activity. Consequently, this patch simultaneously promoted angiogenesis, inhibited post-MI fibrosis, enhanced ventricular contraction in MI hearts, and facilitated the repair and regeneration of damaged hearts.

6.5. Liver

As one of the largest organs in the body, the liver has many important features, such as filtering the blood, excreting waste products, and producing plasma proteins and clotting factors [192]. The liver is the only organ that can regenerate itself, and liver cells are known to possess an excellent regenerative capacity [193]. Nevertheless, under the influence of severe drug-induced injury, chronic alcohol abuse, and chronic viral hepatitis, the liver's regenerative capacity can be impaired, leading to liver failure, accounting for approximately 2 million deaths per year worldwide [194,195]. Hepatic transplantation is currently the sole effective and authoritative therapy for the treatment of liver failure [196]; however, the shortage of liver transplant donors and possible immune rejection remain ongoing challenges. As tissue engineering techniques develop and mature, liver tissue engineering is emerging as a promising solution for the treatment of severe liver disease [197,198].

As a natural multimer, fibrin provides a proper microenvironment for hepatocyte migration and proliferation and promotes liver tissue regeneration (Fig. 8A). Simultaneously, 3D printing can be used to accurately print complex structures that resemble liver tissue, thereby promoting cell differentiation, proliferation, and migration, ultimately leading to the repair of liver damage [199]. For example, Taymour et al. [200] constructed a vascularized liver tissue model based on core-shell 3D bioprinting. The shell was produced from a bioink consisting of a 3 wt% alginate and 49 wt% methylcellulose (algMC) blend, loaded with HepG2 (possessing characteristics similar to those of human hepatocytes). The core consisted of collagen, fibrinogen, and G, which were blended to yield the desired bioink for printing. The core structure was loaded with HUVECs and normal human dermal fibroblasts (NHDFs). Consequently, hepatocyte proliferative capacity, cellular activity, albumin secretion, and in-scaffold vascular network formation were enhanced (Fig. 8B). To compensate for the lack of mechanical strength of the fibrin scaffolds, Rajalekshmi's team [19] combined fibrin with alginate dialdehyde (ADA) and G to construct an ADA-G-FIB hydrogel system, which greatly enhanced the stability and mechanical strength of the fibrin hydrogel, as well as its capacity to promote cell proliferation, adhesion, and regeneration of the liver tissue. Moreover, hepatocytes (HepG2 cell line) grown in the ADA-G-FIB hydrogel exhibited a high cellular activity, with an enhanced cellular metabolism and increased albumin secretion.

6.6. Nerves

Neural network damage caused by neural tissue tears, drug toxicity, and trauma presents a significant challenge [202–204], as nerve tissue typically lacks the ability to repair itself, and scar proliferation at the injury site limits nerve cell regeneration [5,205]. Historically, nerve autografts were employed to recover the function and structure of the nervous system; however, increased postoperative complications, donor site damage, and donor-recipient mismatch of the donor and recipient diameters has limited the application of autografts [206]. Moreover, the complex hierarchical structures of natural neural tissues complicate synthetic regeneration. Neurotissue engineering techniques work well in circumventing these problems and are gradually becoming one of the preferred methods for treating nerve injuries [207,208]. Fibrin is a natural biopolymer that promotes axonal regeneration following nerve injury. Zhu et al. [209] leveraged the ability of fibrin to interact with various cells and biologically active factors to combine an aligned fibrin nanofiber hydrogel (AFG) with a functionalized self-assembling peptide (fSAP) consisting of synergistic laminin-derived peptide (IKVAV) and brain-derived neurotrophic factor (BDNF)-mimicking peptide RGIDKRHWNSQ motifs, which added cell adhesion sites while retaining AFG's original aligned structure. This AFG/fSAP interoperable hydrogel contributed to the secretion of nerve growth factor and BDNF and was successfully used as an intraluminal filler material for chitosan nerve conduits to promote the repair of 15-mm sciatic nerve defects in rats, promoting nerve conduction, axon growth, and motor function recovery (Fig. 9A). In another study, Man et al. [210] selected three bioactive peptides, namely RADA16-I (to simulate the function and structure of the native ECM), KLTWQELYQLKYKGI (KLT; a helical sequence from VEGF), and RGIDKWNSQ (RGI; a helical sequence from BDNF), to introduce a SAP and generate fSAP hydrogels. Combining AFG with RAD/KLT/RGI to form a composite AFG/fSAP hydrogel and subsequent implantation of this hydrogel into a rat model of Brown-Séquard syndrome demonstrated that this material could promote axonal regeneration, angiogenesis, astrocyte migration, and neural repair, while also improving motor function in rats with spinal cord damage (Fig. 9B). Furthermore, using electrospinning and molecular self-assembly, Chai's team [211] prepared a longitudinally aligned AFG with nano-to macro-level hierarchically oriented structures with low elasticities, as well as longitudinal channels that fully mimicked the natural neural ECM. Their findings suggested that AFG was able to induce neural stem cells to differentiate into neuroblasts and promote axonal and neuronal regeneration during brain nerve injury (Fig. 9C). However, due to the lack of stimulation by the corresponding bioactive factors, AFG was less effective in long-distance nerve injury repair, suggesting that incorporating active substances, such as growth factors, is necessary for effective nerve regeneration.

Yang et al. [212] combined magnetic stimulation (MS), which is known to facilitate neurogenesis, neuroprotection, functional recovery, and axonal regeneration, with AFG to develop magnetically responsive AFG (MAFG) by electrospinning magnetic nanoparticles (MNPs) into a fibrin solution. The prepared MAFG possessed an excellent directional topology, which significantly promoted PC12 cell migration and proliferation, axonal growth, and neuronal cell differentiation. Importantly, the MAFG@MFs promoted vascular network generation and axonal and neuronal regeneration at the injury site in a rat spinal cord transection model and contributed to the restoration of motor function in rats after spinal cord injury (Fig. 9D). However, when the body is subjected to MS, the local temperature, pH, etc. may be altered and tissues and cells may be damaged. Therefore, the application of this technique to the human body requires optimization of magnetic field strength to avoid damage to the organism. Notably, the potential of fibrin to promote mimetic nerve fiber construction is often limited by its high degradation rate and weak mechanical strength, thereby rendering its application in neural tissue engineering rather challenging. HA, specifically HA methacrylate (HA-MA), can effectively compensate for this defect in fibrin and enhance hydrogel stability. In this context, Chen et al. [213,214] used microfluidics to construct HA-MA/fibrin bionic microfibers with the assistance of alginate. The nano-orientations of these microfibers were adjusted by varying the fibrin ratio, tensile force, and fluidic state. In addition, the encapsulation of neurons (PC12 cells) and myelinated Schwann cells (RT4-D6P2T cells) in the highly nano-oriented HA-MA/fibrin microfibers were found to promote the aligned elongation of neurons and maturation of the myelin sheaths of Schwann cells. Subsequently, the two-channel microfluidic chip was changed to a three-channel chip to form a core-shell structure for the spatial location of neurons and Schwann cells in bionic nerve fibers. Such systems are advantageous for promoting nerve regeneration and myelin sheath maturation. Moreover, fibrin may act as a delivery system for drugs to enhance nerve regeneration by specifically releasing drugs into damaged nerve tissues. For example, Tajdaran's team [215] utilized fibrin gel as a drug-delivery vehicle, loading it with the immunosuppressive drug FK506, which promotes tissue repair but induces toxic effects in multiple tissues throughout the body [216]. More specifically, FK506 was encapsulated in fibrin gel in the form of microspheres, enabling slow and continuous FK506 release at the damaged nerve sites, while avoiding damage to other vital tissues and organs. However, considering the weaker mechanical properties and faster degradation rate of pure fibrin gels, the study may require further processing of fibrin, such as cross-linking, to enhance its stability, leading to a longer, more consistent release of the drug.

6.7. Cornea

Thermal burns, chemical burns, bacterial infections, or other causes can lead to the destruction of corneal epithelial stem cells at the corneal limbus, resulting in corneal surface vascularization, chronic inflammation, scarring, and ultimately vision loss [217,218]. The primary treatment for blindness caused by corneal disease is corneal transplantation [219], which is the most common transplantation procedure worldwide. However, corneal transplants have several drawbacks, including donor shortages, frequent postoperative infections, allogeneic immune rejection, and the necessity for long-term immunosuppression after surgery, which can lead to high blood sugar levels, high blood pressure, and other complications [220]. Thus, the advent of ocular tissue engineering has introduced new methods for corneal healing and regeneration. For example, Bandeira et al. [221] induced human adipose mesenchymal

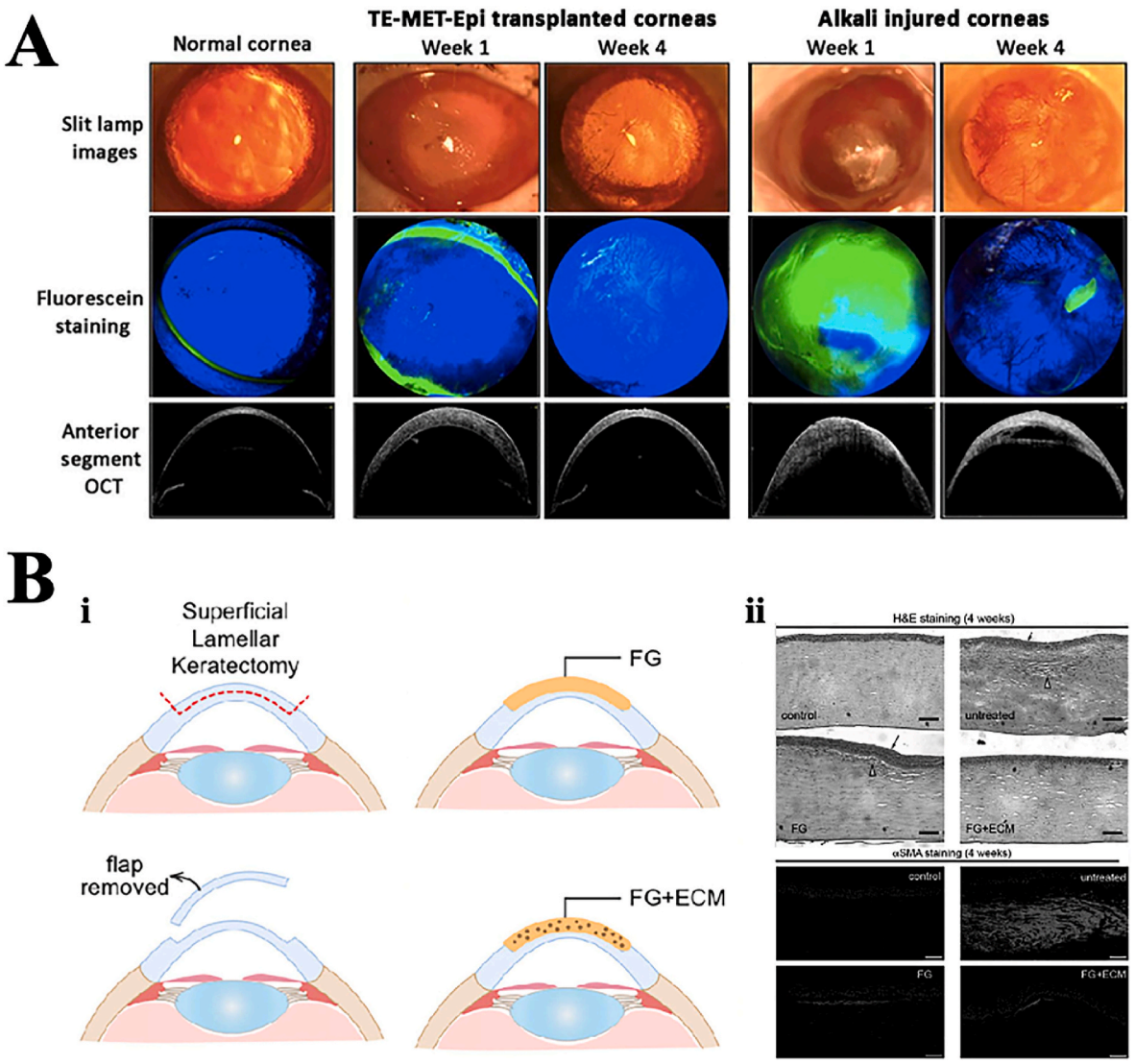

Fig. 10. Application of fibrin in the cornea. **(A)** Transplantation of hybrid hydrogel on the surface of damaged corneas in mice and observation of the therapeutic effect. The Figure is reproduced with minor adaptations from Ref. [221] with permission, based on Creative Commons Attribution 4.0 International License (CC BY 4.0). **(B)** (i) Use of fibrin glue-loaded extracellular matrix (ECM) particles applied to the cornea after keratotomy; (ii) Fibrin glue-loaded ECM applied to corneal injuries is sufficiently anti-fibrotic. The Figure is reproduced with minor adaptations from Ref. [222] with permission, *Copyright © 2018 Published by Elsevier Ltd on behalf of Acta Materialia Inc.* (License number: 5,824,070,557,947).

stem cells (ADSCs) to undergo mesenchymal-epithelial transition (MET) and generate epithelioid (MET-Epi) progenitor cells. These cells were seeded onto the fibrin gel surface and transplanted into a previously prepared rat limbal stem cell deficiency (LSCD) model. Notably, this treatment effectively promoted corneal epithelial healing, enhanced the corneal thickness, inhibited corneal edema, and restored corneal epithelial defects (Fig. 10A). Compared with fibrin scaffolds alone, fibrin/agarose scaffolds possess improved mechanical properties, slower degradation rates, and prolonged scaffold maintenance, with gradual degradation and absorption observed 3–12 weeks postoperatively. Bearing this in mind, González-Gallardo et al. [65] developed an allogeneic tissue-engineered anterior lamellar nanostructured artificial cornea (ATEAHC), employing a nanostructured fibrin/agarose hybrid scaffold as a matrix to encapsulate stromal cells and allogeneic corneal epithelial, calling this model NANOULCOR. Follow-up after the use of NANOULCOR among recruited patients with corneal disease revealed a favorable biocompatibility, significantly reduced likelihood of post-operative ocular complications, reduced corneal inflammation, and a partial increase in corneal transparency. These results confirm the potential of NANOULCOR in promoting corneal epithelial regeneration. Additionally, research has shown that FG can serve as both a wound dressing to facilitate corneal epithelial healing and as a carrier of bioactive substances for ocular tissue engineering applications. More specifically, Yin et al. [222] prepared ECM particles from fresh porcine lymph nodes, corneas, and cartilage, and applied them to a New Zealand rabbit corneal injury model using FG as the delivery agent. This FG-ECM system reduced the degree of corneal injury and scarring compared to FG alone, in addition to reducing inflammation and fibrosis (Fig. 10B).

6.8. Other tissues

Fibrin can also be used for the regeneration of adipose tissue. Adipose tissue mainly serves as a cushioning and insulating agent in the body and exhibits broad applicability in tumor resection and medical aesthetics as a filler for soft tissue defects. Adipose tissue engineering is also a reliable method for fat regeneration [223]. Sawadkar et al. [224] constructed fibrin scaffolds and implanted h-ADSCs into these scaffolds. Their study revealed that these fibrin scaffolds not only promoted a high

Table 2
Tissue-specific applications of fibrin scaffolds.

Tissue/organ to be regenerated	Scaffold	Method of construction	Cells	Animal model	Key Findings	Reference
Skin/wound healing	Fibrin-agarose hydrogel	Self-assembly	Autologous dermal fibroblasts, epidermal keratinocytes	/	A highly differentiated and mature epidermis appears, with increased collagen production in the dermis.	[151]
	Fibrin-PVA Hydrogel	Emulsion molding	MSCs	Mouse full-thickness skin excision defect model	The scaffold promotes collagen fiber formation and angiogenesis, accelerating wound healing.	[83]
	CH:F:SPG-CH:SNP	Electrospinning	Fibroblasts	Albino Wistar rat model of full-thickness dermal excision defects	The scaffold promotes fibroblast proliferation, wound healing, reepithelialization, and prevention of bacterial infection.	[152]
	IVET	Microfluidics	Endothelial cells	Full-thickness skin wounds in mice and rats	IVET supports microvascular network formation at the wound site and promotes vascularization.	[153]
Bone	Bg-PLGA@fibrin	Self-assembly	MSCs	/	Bg-PLGA@fibrin induces mesenchymal cartilage formation, hypertrophy and matrix mineralization.	[161]
	MFS	Microparticle template method	MSCs	Mouse cranial bone defect model	MSCs exhibit high cellular activities and significantly enhance bone regeneration properties in mice.	[162]
	Fibrin/gelatin/ hyaluronic acid/ glycerol scaffold	3D bioprinting	hBMSCs	Rat femoral defect model	The scaffold supports cartilage formation and early hypertrophy *in vitro*, promotes bone tissue regeneration *in vivo*.	[164]
Cartilage	Fibronectin-HA semi-IPN	/	h-AdMSCs	/	The scaffold promotes angiogenesis with h-AdMSC differentiation and chondrogenesis.	[174]
	Fibrin *in situ* nanocomposites	Enzyme reaction	BMSC	Rat articular cartilage defect model	Nanocomposites promotes BMSC differentiation and cartilage repair in the model.	[175]
	Fibrin glue	/	pMSCs	Modeling full-thickness cartilage defects in porcine knees	Fibrin glue promotes filling of cartilage defects in composites and improves the regeneration quality.	[176]
Heart	hCMPs	Enzymatic response	CMs, SMCs, ECs, CFs	Mouse MI model	The patch reduces degree of cardiac infarction, reduces scar size, and enhances cardiac contraction.	[185]
	Layer-specific aligned 3D cardiac structures	EHD printing	CMs, RAECs	Rat MI model	The model inhibited left ventricular remodeling and improved systolic and diastolic function of infarcted myocardium.	[187]
	MFG	Microfabrication	hiPSC-CMs	/	Significant improvement in cardiac contractility, systolic and diastolic velocities.	[188]
	Fibrin Scaffold	3D bioprinting	HUVECs, iPSC-CMs	/	The scaffold promotes endothelial cell angiogenesis.	[189]
	Fibrin patch	Enzyme response	/	Mouse model of MI	It supports cardiomyocyte proliferation, inhibits post-MI fibrosis, and enhances ventricular contraction in MI hearts.	[191]
Liver	Collagen/fibrin/ gelatin core-shell scaffold	Coaxial extrusion 3D bioprinting	HUVECs, NHDF	/	The scaffold enhances hepatocyte proliferation, elevates cellular activity, increases albumin secretion.	[200]
	ADA-G-FIB hydrogel system	Self-assembly	HepG2 cell line	/	It improves the mechanical strength of ADA and G, and enhances the stability of fibrin hydrogels.	[19]
Nerve	AFG	Electrospinning and molecular self-assembly	NSC	SD rat brain injury model	AFG induces neural stem cells to differentiate into neuroblasts and promotes axon and neuron regeneration.	[211]
	AFG/fSAP interactive hydrogel	Electrospinning and molecular self-assembly	Schwann cells	SD rat sciatic nerve defect model	The hydrogel promotes axonal growth, nerve conduction, and motor function recovery.	[209]
	AFG/fSAP composite hydrogel	Electrospinning and molecular self-assembly	/	Brown-Séquard Syndrome Rat Model	It promotes axonal regeneration, angiogenesis, astrocyte migration, and nerve repair.	[210]
	MAFG	Electrospinning, magnetic stimulation	PC12	Rat spinal cord transection SCI model	It enhances neuronal cell differentiation, axonal growth, and recovery of motor function.	[212]
	HA-MA/Fb bionic microfiber	Microfluidics	PC12, RT4-D6P2T cells	/	The model promotes neuronal alignment elongation and myelin maturation in Schwann cells.	[213]
Cornea	Fibrin gel	Self-assembly	Epithelioid progenitor cells	Rat LSCD model	It promotes corneal epithelial healing, enhances corneal thickness, and inhibits corneal edema.	[221]

(*continued on next page*)

Table 2 (*continued*)

Tissue/organ to be regenerated	Scaffold	Method of construction	Cells	Animal model	Key Findings	Reference
	Fibrin-agarose scaffolds	Self-assembly	Allogeneic corneal epithelial and stromal cells	/	Partial increase in corneal transparency and improvement in corneal inflammation.	[65]
	Fibrin glue	Enzyme reaction	/	New Zealand rabbit corneal injury model	Fibrin glue improves corneal injury, reduces scar formation, reduces inflammation and fibrosis.	[222]
Adipose	Fibrin scaffold	Self-assembly	rADSCs	Healthy SD rats	The scaffold improves vascularization at the implantation site and promotes fat regeneration.	[224]
Skeletal muscle	Aligned alginate/ fibronectin microfibril structure	3D bioprinting, EHD-DW	C2C12 cells	Mouse VML model	The model accelerates volumetric muscle repair.	[225]
Rotator cuff tendon	Collagen-fibrin hydrogel	3D bioprinting, self-assembly	hADMSCs	/	It enhances proliferation and differentiation of hADMSCs, facilitates rotator cuff tendon regeneration.	[226]
Salivary gland	Fibrin hydrogel	Self-assembly	/	Head and neck irradiated mouse model	The hydrogel reduces fibrosis and restores vascular and nerve damage at radiation-exposed sites.	[27]

Abbreviations: PVA: polyvinyl alcohol; MSCs: mesenchymal stem cells; CH:F:SPG-CH:SNP: macroporous chitosan/fibrin/silver nanoparticles based smart bandage; IVET: implantable vascularized engineered thrombus; Bg-PLGA@fibrin: lactic acid-co-glycolic acid@fibrin; MFS: macroporous fibrin scaffold; 3D: three-dimensional; hBMSCs: human bone marrow-derived MSCs; HA: hyaluronic acid; IPN: interpenetrating polymer network; h-AdMSCs: human adipose tissue-derived MSCs; BMSC: bone marrow-derived stem cells; pMSCs: porcine mesenchymal stromal cells; hCMPs: human cardiac muscle patches; CMs: cardiomyocytes; SMCs: smooth muscle cells; ECs: endothelial cells; CFs: cardiac fibroblasts; MI: myocardial infarction; EHD: electrohydrodynamics; RAECs: rat aortic endothelial cells; MFG: micro-processed fibrin gel with inverted V-shaped ridges; hiPSC-CMs: human-induced pluripotent stem cell-derived cardiomyocytes; HUVECs: human umbilical vein endothelial cells; iPSC-CMs: human pluripotent stem cell-induced cardiomyocytes; NHDF: human dermal fibroblasts; ADA: alginate dialdehyde; G: gelatin; FIB: fibronectin; AFG: longitudinally aligned fibronectin nanofibrillar hydrogel; NSC: neural stem cell; SD: Sprague-Dawley; fSAP: functionalized self-assembling peptide; MAFG: magnetically responsive aligned fibronectin hydrogel; SCI: complete sectioning spinal cord injury; MF: magnetic field; HA-MA: hyaluronic acid methacrylate; Fb: fibronectin; LSCD: limbal stem cell deficiency; rADSCs: rat adipose-derived stem cells; EHD-DW: electrohydrodynamic-direct-writing; VML: volumetric muscle loss; hADMSCs: human adipose-derived MSCs.

proliferative state in h-ADSCs, but also ensured high cellular activity and induced h-ADSC differentiation. Furthermore, loading rat adipose-derived stem cells (rADSCs) onto scaffolds and their subsequent *in-vivo* implantation significantly increased vascularization levels at the implantation site and promoted adipose regeneration. Fibrin scaffolds can also be applied to skeletal muscle tissues to promote myofibril regeneration and restore motor functions. For example, Yeo et al. [225] prepared aligned alginate/fibrin microfibrous structures by adding fibrin as a bioactive ingredient to an alginate/polyethylene oxide (PEO) bioink and employing the electrohydrodynamic-direct-writing (EHD-DW) approach to encapsulate myoblasts (C2C12). Their findings indicated that this system promoted cell proliferation and differentiation and improved cell metabolic activities, indicating potential applications in skeletal muscle injury repair. Moreover, research indicates that rotator cuff tendon tears can be effectively repaired using fibrin tissue-engineered scaffolds, thereby circumventing the high failure rates associated with autografts and allografts. For instance, Jiang et al. [226] infused a collagen-fibrin hydrogel into 3D-printed PLGA scaffolds using a pipette and observed that the hydrogel was effective in promoting the growth, proliferation, and differentiation of h-ADMSCs. Ultimately, such studies demonstrate the viability of 3D-printed scaffolds for use in rotator cuff tendon regeneration. Finally, it is well known that the ionizing radiation used in the treatment of head and neck cancers is often associated with salivary gland damage, leading to inadequate salivary production and affecting the patients' quality of life [227,228]. To address this aspect, Nam et al. [27] developed a fibrin hydrogel (Ep-FH) incorporating fibroblast growth factors 7 and 10 (FGF-7/10) along with laminin-1 peptide (L_{1p}) to facilitate the functional recovery and regeneration of salivary glands. They reported that injection of the Ep-FH solution into a head- and neck-irradiated mouse model led to the immediate formation of a stable hydrogel loaded with FGF-7/10 and L_{1p} at the injection site. Consequently, this hydrogel reduced fibrosis at the irradiated site, restored vascular and nerve damage, restored epithelial integrity, and increased the degree of salivary secretion.

Fibrin scaffolds have been studied for the regeneration of various tissues, including skin, bone, cartilage, nerves, heart tissue, and more. Different tissues require slightly different microenvironments for growth, e.g., in bone tissue injuries scaffolds are required to have a certain mechanical strength; in cardiac injuries, scaffolds require specific structures to maintain the aligned structure and layer specificity of cardiomyocytes. Fibrin scaffolds perform well in various tissues and are effective in promoting damage repair. Table 2 summarizes the fibrin scaffolds applied in various tissue repair and regeneration processes, along with the main findings.

7. Summary and outlook

Fibrin, a linear protein formed by the aggregation of fibrinogen under the action of thrombin, undergoes processing and folding to form a fibrous structure with a specific stability and strength. As one of the most crucial proteins in the human body, fibrin is integral to the ECM, maintaining the structure and function of tissues, and providing protection. A stable fibrin network promotes platelet adhesion and enhances both platelet aggregation and thrombosis, ultimately resulting in hemostasis. Moreover, it plays unique roles in wound healing, inflammation, infection, and cancer. Fibrin derivatives can be obtained by modifying the fibrin structure through methacryloyl reaction, silylation, physical cross-linking, chemical cross-linking, and other approaches, to enhance its structural strength, slow its rate of degradation, improve its stability, and reduce defect formation associated with uncontrolled shrinkage behavior [75]. In terms of tissue engineering, fibrin hydrogels, FGs, and FMBs are the three most common forms of fibrin. Fibrin hydrogels are hydrophilic, easily extensible and injectable. Conversely, FG is widely used for the fixation of tissue engineering scaffolds at the respective sites due to its high tensile strength and excellent adhesion properties, while the denatured fibrinogen present in FMBs is sensitive to mesenchymal stromal cells and plays a unique role in vascularization. The biofunctionalization of fibrin has been instrumental in expanding its range of applications, and the incorporation of active ingredients, such as growth factors, exosomes, and drugs, has appeared in many studies [132].

Owing to its numerous desirable properties, fibrin has been

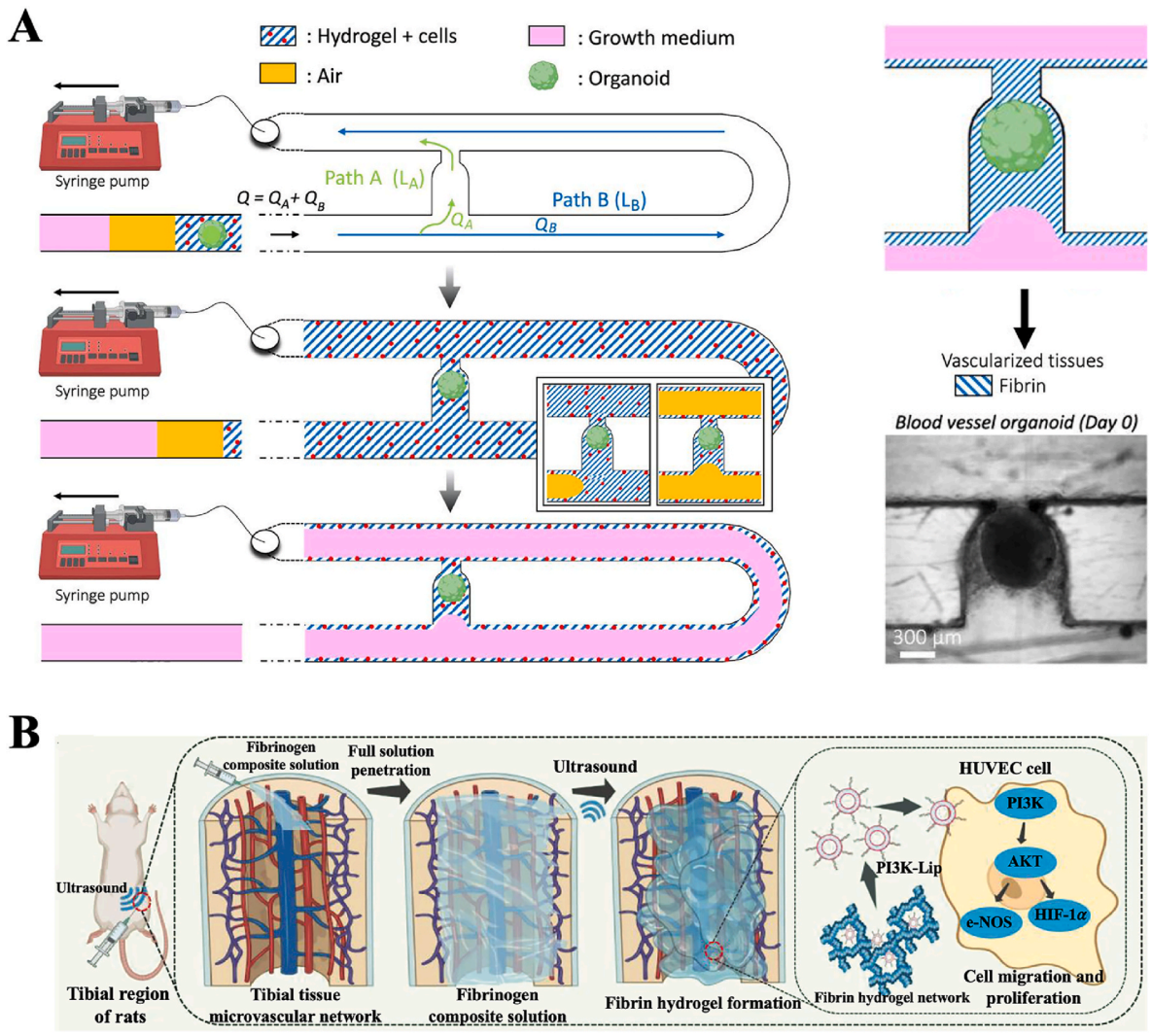

Fig. 11. Cutting-edge research on fibrin-based biomaterials for tissue engineering. **(A)** Cultivation of organoids and vascular spheroids in microfluidic devices using fibrin hydrogels. The Figure is reproduced with minor adaptations from Ref. [115] with permission, based on Creative Commons Attribution 4.0 International License (CC BY 4.0). **(B)** Ultrasound induces *in situ* formation of fibrin networks in damaged tissues. The Figure is reproduced with minor adaptations from Ref. [230] with permission, based on CC BY 4.0 License, *Copyright © 2024 The Authors. Advanced Science published by Wiley-VCH GmbH.*

employed in applications related to skin, bone, cartilage, heart, nerves, and fat; however, its application in tissue engineering is still associated with a number of limitations. Although fibrin is a natural polymer derived from the body, it does not fully mimic the dynamics of the tissue environment and cannot independently change its shape and structure to conform to tissue growth. Currently, four-dimensional (4D) bioprinting, which introduces the time dimension, has gradually become a popular research direction, utilizing external stimuli, such as temperature, light, humidity, and sound waves, to alter the shapes, structures, and functions of fibrin scaffolds to realize their diverse applications [229]. Yang et al. [212] have already taken advantage of the painless and non-invasive deep MS technique to develop magnetically responsive fibrin hydrogels that significantly facilitate motor recovery after a spinal cord injury, thereby highlighting the great potential of 4D bioprinting for tissue engineering applications. Moreover, the important role of fibrin in microfluidic chip technology has attracted growing research interest. Quintard et al. [115] loaded fibroblasts and HUVECs in fibrin hydrogels and introduced them into a pre-designed microfluidic device, thereby facilitating the generation of vascular networks around vascular organoids and contributing to the efficient, gentle and controlled perfusion of vascular organoids (Fig. 11A). In addition, the introduction of ultrasound technology can effectively promote tissue penetration of fibrin hydrogels. Zhao et al. [230] injected the fibrin hydrogel precursor solution into the tibial site of osteoporotic rats to allow full penetration into the tibia and surrounding microvascular network. Ultrasound was subsequently used to induce the release of thrombin and calcium ions within liposomes, which in turn led to the *in situ* formation of fibrin networks. *In vivo* results revealed that ultrasound was able to effectively penetrate the tibia, and the fibrin hydrogel formed *in situ* greatly facilitated the formation of the peri-tibial microvascular network (Fig. 11B).

However, the clinical application of fibrin scaffolds faces several problems. The issues including poor stability, insufficient mechanical strength, and excessive degradation rates limit fibrin scaffolds' application in tissue repair and regeneration [74]. For example, in terms of bone tissue, the scaffold must possess a certain degree of stability and stiffness to match the physiological characteristics of the bone tissue and promote damage repair. The relatively poor stability of fibrin is insufficient to support bone tissue regeneration, and its high degradation rate leads to the relatively rapid breakdown of its mechanical framework prior to complete tissue formation. Consequently, the fibrin scaffold is unable to play a long-term supportive role, rendering it detrimental to tissue repair. Although the mechanical strength and stability of fibrin scaffolds can be enhanced by adjusting the fibrinogen/thrombin ratio, or through modification, cross-linking, or the addition of other

biopolymers, these technologies are still maturing, requiring further research to optimize them for clinical application.

In conclusion, the tissue engineering application of fibrin provides a reliable therapeutic solution for the repair of tissue and organ damage, effectively alleviating limitations associated with the limited self-repairing ability of autologous tissues and a lack of organ transplantation donors. However, various challenges remain, such as insufficient mechanical strength and rapid degradation rate, which limit its application in various tissues. Addressing these challenges through further research is crucial to unlock fibrin scaffolds' full potential in tissue regeneration and functional recovery.

Ethics approval and consent to participate

There are no human and animal subjects in this review and informed consent is not applicable.

Declaration of competing interest

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

CRediT authorship contribution statement

Songjie Li: Writing – original draft. **Xin Dan:** Writing – review & editing. **Han Chen:** Investigation. **Tong Li:** Visualization. **Bo Liu:** Investigation. **Yikun Ju:** Formal analysis. **Yang Li:** Formal analysis. **Lanjie Lei:** Conceptualization. **Xing Fan:** Methodology.

Acknowledgements

This study was supported by Education Department of Shaanxi Provincial Government (No. YJSZG2023134) and Nanjing Medical University Fan Daiming Research Funds for Holistic Integrative Medicine.

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