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Review article

Design principles in mechanically adaptable biomaterials for repairing annulus fibrosus rupture: A review

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ABSTRACT

Annulus fibrosus (AF) plays a crucial role in the biomechanical loading of intervertebral disc (IVD). AF is difficult to self-heal when the annulus tears develop, because AF has a unique intricate structure and biologic milieu *in vivo*. Tissue engineering is promising for repairing AF rupture, but construction of suitable mechanical matching devices or scaffolds is still a grand challenge. To deeply know the varied forces involved in the movement of the native annulus is highly beneficial for designing biomimetic scaffolds to recreate the AF function. In this review, we overview six freedom degrees of forces and adhesion strength on AF tissue. Then, we summarize the mechanical modalities to simulate related forces on AF and to assess the characteristics of biomaterials. We finally outline some current advanced techniques to develop mechanically adaptable biomaterials for AF rupture repair.

1. Introduction

The spine, consisting of hard and rigid vertebrae, ligament, intervertebral discs (IVD) and facet joints, can protect spinal-cord and support upper limbs and head. Twenty-four fibrocartilage intervertebral discs, including 7 cervical, 12 thoracic and 5 lumbar, locate between adjacent vertebrae accounting for roughly one-third of the total spine height [1,2]. The functions of these discs are to withstand biomechanical forces, allow the spine to move and transfer loads associated with exercise [3]. Specially, the discs in the lumbar region play an important role in human activities because they bear the greatest force acting on the spine and maintain the stability of spinal cord.

Spinal diseases, usually rooted from lumbar discs degeneration caused by acute trauma, chronic wear and tear, age-related degeneration, and genetic factors, are now the main causes of disability in the world, especially in developed countries [4]. About 90% of spinal disorders are attribute to intervertebral disc degeneration (IDD). IVD consists of central hydrated nucleus pulposus (NP), circumferential annulus fibrosus (AF) and cartilaginous endplates at the both edges (Fig. 1a), in which all three parts are involved with IDD. For example, dehydration of NP accompanied with reduction of proteoglycans leads to the imbalance loads and induces inflammation [5]. The rupture of AF may result in the protrusion of NP and further compress the nerve [6]. The calcification of cartilaginous endplates affects supply of nutrients to IVD and causes degradation of extracellular matrix [7]. Among these three IDD process, AF rupture is relatively difficult to healing because the protruded NP changes biomechanical environment and further compress surrounding nerves, resulting in the back pain and extremely physical disability [6,8]. Besides, it is a great challenge for IDD to fully recover clinically because the non-vascular and low cellular structures of IVD have a limited healing capacity [9]. Low back pain (LBP), the main clinical manifestation of IDD, is the most prevalent musculoskeletal problem in the world. Many reports indicate the lifetime prevalence rate of the LBP is ~40% [10]. LBP related disease becomes a global public health problem and need all countries to cooperate to address IDD associated issues [10–13]. For treatment of IDD diseases, the key is to effectively seal the AF defects.

Traditional LBP treatments mainly include physical therapy (such as lying down, massage and acupuncture), injection of analgesia, muscle relaxion and surgery [14]. Clinical results show that the majority of

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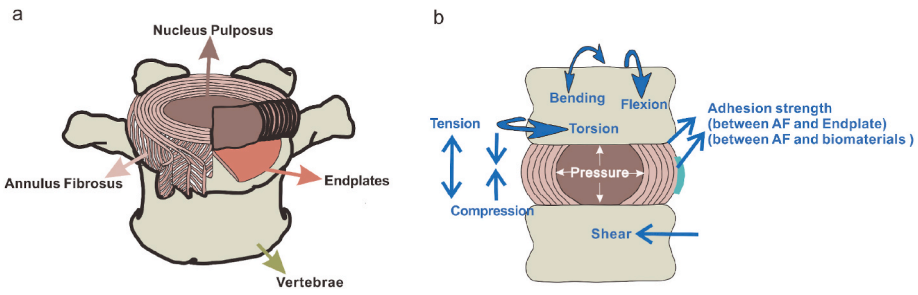


Fig. 1. (a) Schematic structure of IVD. The annulus fibrosus (AF) with concentric rings is arranged in alternating fibers angled at 30-60° from the vertical spine axis. The nucleus pulposus (NP) is located at the center of the disc. The endplates are adjacent to the vertebral body. (b) Scheme of six degrees of freedom (tension, compression, shear, torsion, bending and flexion) and adhesion strength.

patients benefit from a combination of two or more therapies, whereas patients with more extensive disc injury do not respond to conservative measures. In the last few years, discompression and fusion have rapidly evolved into two common surgical approaches for LBP treatment. These surgical treatments, however, are highly invasive and unable to biologically heal or safeguard motion of the operated site. Despite the therapeutic and surgery treatments, many mechanical closure devices, including X-Close tissue repair system, Inclose Surgical Mesh System and Barricaid Ring Closure Device, have been developed to repair AF in preclinical or clinical settings [15]. However, due to low durability and mismatch between natural tissue and these mechanical devices, they are essentially unqualified to reduce the risk of re-protrusion and restore functionally important biomechanical parameters [16–19]. Therefore, there is an unmet need for tissue engineering techniques to mimic the natural structure of AF to overcome the shortcomings of current artificial devices [20,21]. Some studies have suggested that strain-mediated fiber topography can influence mechanobiological response by regulating the cell phenotype to promote AF repair [22–24]. Likewise, using IVD progenitor cells to treat IDD has achieved to first-in-human phase II clinical trial, and this study may determine the ultimate outcome by comparing the function of progenitor cell and mesenchymal stem cell [25]. Scaffolds made of various synthetic or natural materials have also been employed extensively for AF repair [26,27], specially for polymeric hydrogels and stents. These scaffolds can provide mechanical stability while treating AF initially and aid in AF regeneration later on [1,28]. Despite advancements in cell- and scaffold-based strategies for AF repair in a short-term period, these procedures have not yet shown long-term recovery, especially in terms of mechanical qualities [6,29]. The Barricaid scaffold was designed to prevent the disc re-herniation, but this device caused vertebral endplate disruption after 12-months implantation because of the mechanical mismatching, severe inflammation and osteophyte formation [30]. Therefore, it is urgent to develop mechanical adaptable biomaterials and minimally invasive therapies to satisfy the mechanical and biological requirements for successful AF repair [31,32].

Herein, this review summarizes AF repair by addressing three objectives: (1) to review the force implied on the AF and the required mechanical properties; (2) to outline mechanical testing paradigms for the necessary adaptive force-matching property; (3) to overview prospective newly created mechanical-adaptive biomaterials.

2. The structure and load forces of AF

AF is a type of fibrous cartilage, enclosing the gel-like nucleus pulposus (NP) (Fig. 1a). AF includes about 70% water, 15% collagen and 5–15% proteoglycans and elastin [21]. The outer annulus is mainly type I collagen and the inner is type II collagen [33,34]. These collagen secreted from fibroblast cells endows AF a highly anisotropic, multiphase and nonlinear fibrous structure. This special structure results from aligned hierarchical assembly of 15–25 alternating concentric lamellar layers, while the matrix within each lamella is offset by 30–60° from the vertical spine axis [35,36]. Elastin of the layered collagen transfers stress from NP to retain the integrity of IVD and protects AF from bending, stretching and torsion damage [37–39]. Among these three compositions of AF, collagen and elastin proteins have the most significant effect on the failure stress for both interlaminar and intralaminar AF layers. The proteoglycans only have a vital impact on the single layer orientation in terms of failure stress and strain [34]. Besides the compositions, the collagen fiber angles contribute the AF mechanical function. The disorder or decreasing fiber angle can increase the circumferential modulus and compression motion segment stiffness, as well as decrease vertical displacement under compression [34,40].

Six freedom degrees of forces (tension, compression, shear, bending, torsion and flexion) and adhesion strength exhibited from the spinal motion can display force on AF (Fig. 1b) [41]. Tension, especially the circumferential tension, is a main crucial force on AF which can work against the load from the highly hydrated NP. Compression, accompanied with tension as spine moves, is another important factor that helps the IVD remain functional and distribute the vertical load. Shear force can be produced by torsion along the axial direction to measure the viscoelasticity of the tissue [42]. Other types of forces, like bending and flexion, always present together with tension and compression behaviors which are vital for regulating and limiting AF movement. Adhesion strength has a profound impact on providing strong connection between AF and vertebrae. These various forces acting on AF have a substantial impact on the integrity of IVD because any imbalance in these forces can impair the movement of spine and potentially harm AF.

The maintenance of IVD mechanical performance is attributed to the synergy of NP and AF, otherwise the dislocation of NP through the AF defect site will lead to damage of the disc and press the nearby spinal nerves, resulting in low back pain and possibly even disability [43,44]. In order to promote the collaboration of AF and NP, AF must possess extreme mechanical behaviors, such as ~30 MPa tensile moduli, ~1 MPa compression moduli and ~0.2 MPa adhesion strength [45]. However, there are no proper products that can satisfy these strict mechanical behavior requirements. When the AF defect occur, it is necessary to consider mechanical adaptive biomaterials for AF rupture repair.

3. The mechanical designment of engineering biomaterials for AF rupture repair

AF endures repeated joint loads during tension, compression, shear, bending, torsion and flexion [46]. In order to prevent NP from re-protrusion when AF fractured, the defect site must be filled after the discectomy in the clinic treatment. In this situation, suitable filler biomaterials are crucial for AF regeneration, motivating researchers to design proper mechanical-matching biomaterials with a delicate balance among different mechanical forces. Wherein, it is essential for selecting appropriate testing methods to assess these forces. Here, we review testing modalities in term of tension, compression, shear, torsion, bending, flexion and adhesion strength of AF, and summarize recent studies on mechanical properties of AF-repaired materials.

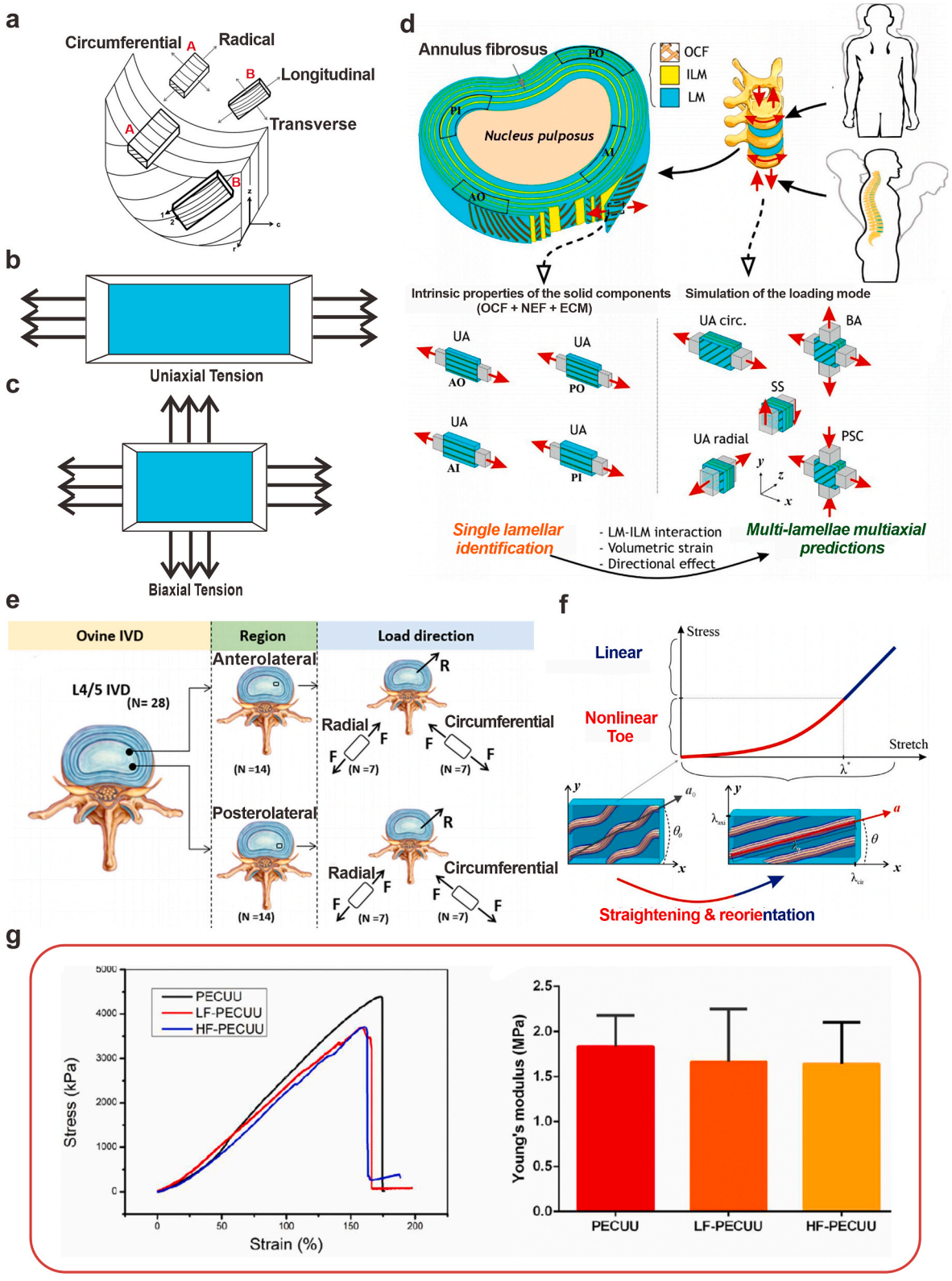


Fig. 2. Tension models and tests for the AF tissue. (a) The orientation of longitudinal and transverse, circumferential and radial tensile of AF tissue [34]. Copyright, 2014 Elsevier (b, c) The schemes of uniaxial and biaxial tensile test. (d) Annulus model of loading modes on single lamellae and multi-layer lamellae [51]. Copyright, 2021 Elsevier (e) anterolateral-radial, anterolateral-circumferential, posterolateral-radial, and posterolateral-circumferential load directions [52]. Copyright, 2022 Elsevier (f) Phenomenon of reorientation of collagen fibers and the strain-stress curve of stretch tension [51]. Copyright, 2021 Elsevier (g) Uniaxial tension test and Young's modulus of poly(ether carbonate urethane) [53]. Copyright, 2022 Elsevier

Table 1
Summary of mechanical properties of various AF-repaired materials.

Species of Model	Materials	Method (s)	Tensile Strength (MPa)	Compression Strength (MPa)	Tensile Modulus (MPa)	Compression Modulus (MPa)	Shear Modulus (MPa)	Torsion	Refs
Bovine	Genipin/fibrin	tensile, compression	2.03	12.4	56.8	10.3	_	_	Chuang et al. (2007) [56]
Rat	Polycaprolactone/Poly(D,L-lactide-co-glycolide)/ Collagen I	tensile, compression	20	0.3	405–1398	_	_	_	Yang et al. (2017) [61]
Sheep	_	cyclic compression	_	_	_	8.66–14.64	_	_	Liu et al. (2020) [62]
Bovine	Genipin/fibrin	compression, shear	_	_	_	0.1–0.2	0.01–0.07	_	Cruz et al. (2018) [63]
_	Polyurethane	compression	_	_	_	3.1–12.4	_	_	Aguol et al. (2018) [64]
_	Poly (trimethylene carbonate) -PEG	compression, torsion test	_	5.9	_	_	_	5°	Long et al. (2018) [65]

-: present no relative data.

3.1. Tension

There are four orientations of tension on the AF tissue: inter-lamellar circumferential and radial directions, intra-lamellar longitudinal and transverse directions (Fig. 2a). These forces usually change with the AF location. Compared with the inner AF area, the outer AF area is harder and effectively bears the load [47,48]. During tension, AF undergoes a large elastic deformation under physiological conditions [49,50]. There are two types of tension tests: uniaxial tension (Fig. 2b) and biaxial tension (Fig. 2c). Typically, uniaxial tension is fordable for materials with significant deformation before yielding, and biaxial tension is suitable for materials with constrained boundaries *in vivo*. In comparison to the biaxial tension, the uniaxial tension is more appropriate for AF-mimic materials since it can be straightforward to identify the most important parameter for tissue characterization when comparing the engineered and native AF [42].

A fully three-dimensional human AF model was developed to predict deformation-induced annulus failure under multiaxial loads (Fig. 2d) [51]. The single lamellae of the annulus was stretched to failure under uniaxial test. The multi-layered lamellar constructed by considering the interactions between neighboring layers was characterized with both uniaxial and biaxial tests along circumferential and radial directions. Similarly, a model used the uniaxial tension test to examine radial and circumferential loading among anterolateral, posterolateral and transition zone regions (Fig. 2e) [52]. The collagen would reflect the reorientation phenomenon when the annulus underwent the loading deformation, revealing the 'toe' and 'liner' regions (Fig. 2f), and showing the strain-stress curves of the materials (Fig. 2g) [53]. It has been reported that the linear circumferential tensile modulus of elasticity in the posterolateral region ranges from 11 to 29 MPa [34,54], which was an order of magnitude larger than the longitudinal modulus (0.42–0.82 MPa) and the radial modulus (0.21–0.45 MPa) [33,55]. Some engineered biomaterials were concluded to improve the tensile properties (Table 1). For example, Shih-Youeng Chuang and coworkers reported that the genipin crosslinked collagen hydrogel enhanced the mean circumferential yield stress to 56.8 MPa and improved ultimate tensile strength to 2.03 MPa, respectively [56]. Junchuan Yang and coworkers developed a concentric ring-aligned polycaprolactone/poly (D, L-lactide-*co*-glycolate)/Collagen I-based AF through electrospinning, achieving the tensile strength to 20 MPa. Likewise, Rose G. Long and coworkers adopted the genipin crosslinked fibrin hydrogel to seal AF defect and the poly(trimethylene carbonate) scaffolds to replace the lost AF tissue. This genipin crosslinked collagen hydrogel endowed the tensile compliance with 4.8 μm/N [57]. Hyaluronan/collagen type I micro/nanofibrous scaffolds with high tensile Young's modulus (30.1–36.4 MPa) and enhanced mechanical strength promoted AF repair after discectomy [58]. Poly(ether carbonate urethane)urea scaffolds regulated the matrix elasticity through cell differentiation, achieving tensile strength of 2.0–16.1 MPa and modulus of 3.8–13.7 MPa [59]. Although the tensile strength of some scaffolds has been developed to satisfy the stress requirement of AF repair, these scaffolds are usually made of synthetic polymers that are lack of biocompatibility for long-term AF restoration *in vivo*. For example, the genipin crosslinker for collagen and fibrosus gels showed cell toxicity [60]. Dichloromethane and span-80 non-biocompatible emulsions were adopted to produce the drug-loaded particles enclosed in the hyaluronan/collagen type I micro/nanofibrous scaffolds [58].

3.2. Compression

A healthy IVD needs to stand up to 5–20 MPa compressive strength within 100 million times a year during normal activities [66,67]. Excessive axial compression can reduce the IVD's height and increase its static pressure [68]. Although the NP receives the majority of the compression and the AF receives very little of it, the compression can transfer to the tension on AF. Thus, the compression test is also a key parameter to estimate the AF strength. There are two types of compression tests: confined compression and unconfined compression (Fig. 3a and b). In the confined model, a compressive load is applied to a confined sample through a porous platen to prevent lateral expansion of the solid phase and restrict fluid flow to the loading axis. This variation of sample in the test process is similar to the expansion of NP in physiological environment. Thus, the confined model can better simulate the expansion restriction of the NP to obtain more accurate data [69,70]. In the unconfined model, the samples are not restricted, which is more suitable for AF variation [71]. However, the majority of studies use the unconfined test for both AF and NP regeneration [60,72,73]. For example, an alginate-based sealants as partially implanted materials to the defect tissue exhibited excellent compressive strength through the unconfined testing and showed the leak-proof property (Fig. 3c) [74]. Also, TPU-based scaffolds for the total disc replacement showed effective stress transfer under unconfined compression, which proved the possibility to reduce the incidence of lumbar dis herniation (Fig. 3d) [75].

People have the pressure in the NP ranged from 0.06 to 0.24 MPa with the posture of prone [76]. Standing and sitting both have higher than prone position, ranging from 0.32 to 1.18 MPa [77,78]. While the average static pressure reported varies from 0.27 to 0.88 MPa [79] and the compressive Young's modulus of non-degraded IVD ranges from 5 to 20 MPa [66,67]. The genipin crosslinked fibrin hydrogel have been employed as an adhesive to regenerate the AF. However, neither the treatment of cell-seeded nor decellularized fibrin resulted in a

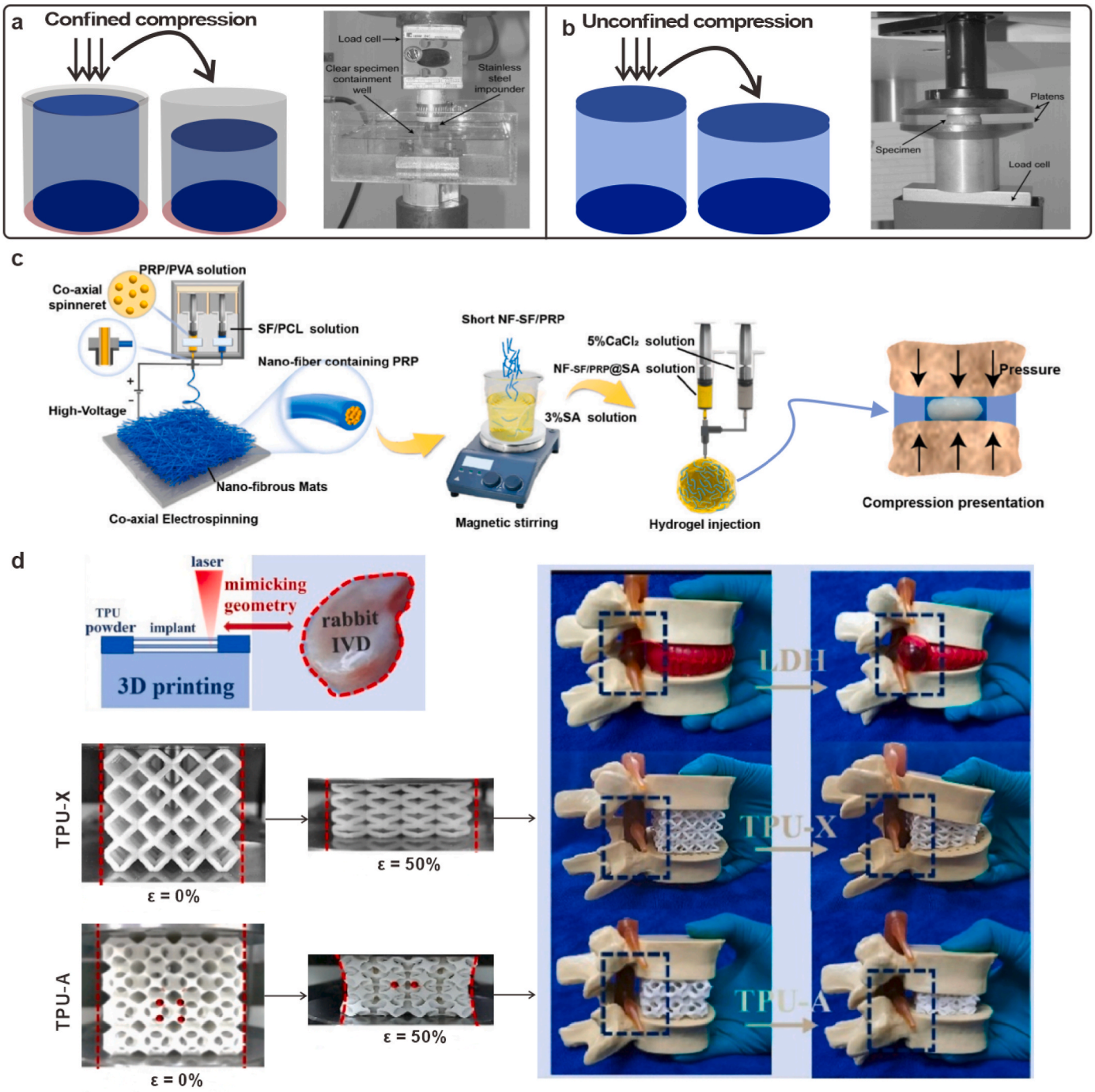


Fig. 3. (a,b) The scheme of confined compression (a) and unconfined compression test (b) [71]. Copyright, 2013 Elsevier (c, d) The unconfined test on the nano-fibrous hydrogels fabricated by electro spinning technique (c) [74] Copyright, 2023 Elsevier and thermoplastic polyurethane (TPU)-based scaffolds fabricated by 3D printing(d) [75]. Copyright, 2023 Elsevier

substantial change in compressive modulus (100–200 kPa) under the unconfined compression [63]. Although the polymerizable polyurethane-based AF adhesive exhibited a compressive modulus reaching to 3.1–12.4 MPa [64], this sealant may attrit the surrounded tissue because of the mismatch of force, further damaging the IVD. Therefore, it's unsatisfied for the therapeutic application of these materials to repair AF in the clinic. Designing novel biomaterials with adequate compressive capabilities similar to the AF restore is a crucial step towards successful AF repair.

3.3. Torsion, shear, flexion and bending

The torsional load generated by axial rotation is a vital load to understand the function of the disc in daily activities, especially when combined with axial compression (Fig. 4a). The vertebral body and IVD equally contribute to the torsional strength of the spine [80,81]. The axial rotation of a single IVD ranges from 0° to 5° under physiological load conditions which can be attributed to the orientation of AF collagen fibers at ± 30°–60°, indicating the IVD's exceptional capacity to endure large rotational deformations before failing [82,83]. In contrast to the increased tension of AF under highly non-linear behavior, linear rotation

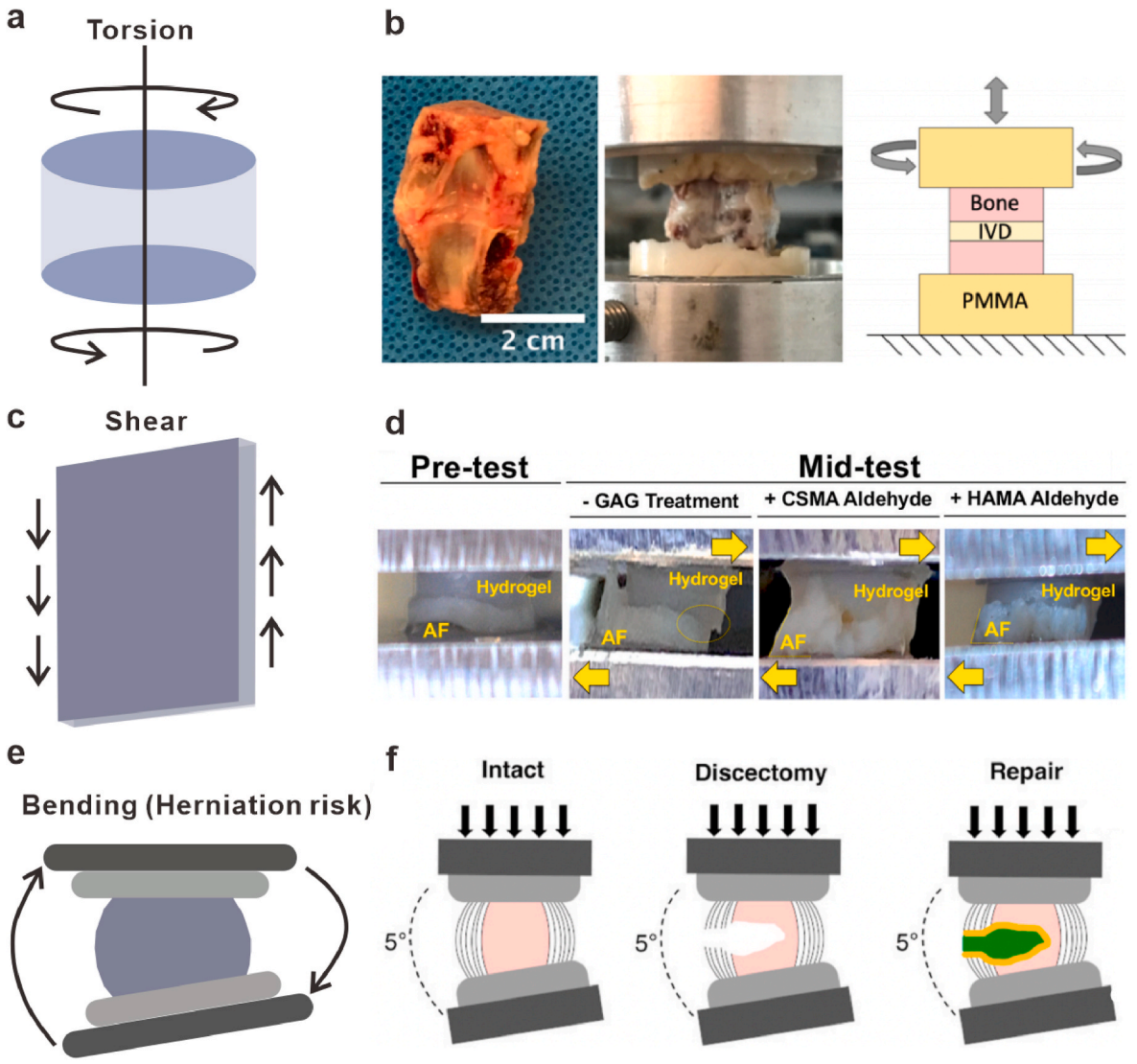


Fig. 4. (a) The test of torsion. (b) Schematics of the mechanical testing with both compression and torsion load frame [85]. Copyright, 2020 American Association for the Advancement of Science(c) The test of shear. (d) Displacement-controlled lap shear test performed at the interface between hydrogel and AF tissue [87]. Copyright, 2020 Elsevier (e) The test of bending (herniation risk). (f) The experimental design to assess herniation risk [87]. Copyright, 2020 Elsevier

of torque is observed because of the preloading from axial compression [83,84]. The compressive strength maintained 0.5 MPa when the torsion varied between ± 4° rotation under the vertebra-IVD-vertebrae motion model (Fig. 4b) [85].

During spinal torsion, AF experiences considerable shear stress (Fig. 4c). Its shear force is significant for regulating and restricting the motion between the vertebrae. Since it is usually difficult to apply pure shear force, researchers use different shapes (cylindrical, cubic, or flat) to get the sample preloaded to mimic the force from each direction [86,87]. As a result, the shear force can contribute to the anisotropy of AF, as well as the viscoelasticity [88]. Displacement-controlled lap shear test was performed on the interface between the hyaluronic acid hydrogel with AF tissue (Fig. 4d), in contrast to the untreated samples, the treated samples remained together until failure occurred, showing the strong adhesion between hydrogel and AF tissues.

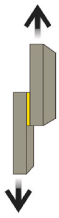
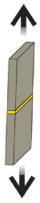
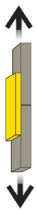
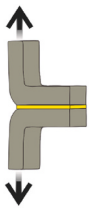
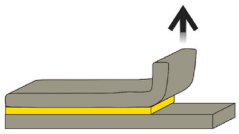
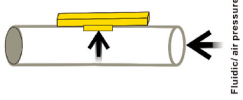
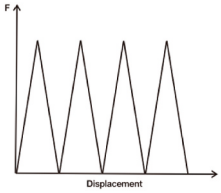
Bending and flexion are also essential for spreading the pressure of IVD. Kelly and coworkers created a realistic disc herniation model featuring compression and bending to analyze the mechanics and microstructure (Fig. 4e) [89]. The results showed compressive deformation under 5° flexion posed a threat of herniation with the failure strength of 5.9 MPa (Fig. 4f) [87].

Table 2
Summary of adhesion properties of various AF-repaired materials.

Species of model	Materials	Method (s)	Shear Modulus (kPa)	Adhesive strength (kPa)	Refs
Bovine	Fibrin/Genipin	Lap shear, Herniation risk	37–60	_	Cruz et al. (2018) [63]
Bovine	Fibrin/Genipin	Lap shear, Herniation risk	10–110	5–35	Cruz et al. (2017) [2]
_	Poly (trimethylene carbonate) -PEG	Lap shear, Herniation risk	220–490	150	Long et al. (2018) [65]
Ovine	High-density collagen/ chondraitinase ABC	Lap shear	_	3.1	Jiang et al. (2019) [86]

-: present no relative data.

Table 3
Adhesion test modalities of the potential biomaterials for AF rupture.

Adhesion Methods	Test Models	Sample Requirements	Mechanical Parameters	Applications on AF Tissue
Lap shear test		The length of tissue should be 1.5 times longer than the length of bond area, and the thickness of the tissue specimen should be 1–2 mm [94].	Shear strength = F_{max}/area	Chondroitin sulfate and hyaluronic acid hydrogels possessed the ultimate adhesion strength of 16 kPa when adhering on AF tissue [87]. The chondroitinase ABC/collagen adhesive had the gel-AF interface strength of 3.1 kPa [86].
Tensile test		The attached area with the length of 2.5 cm and the width of 2.5 cm [95].	Tensile strength = F_{max}/area	–
Wound closure test		Two identical samples (size: ~10 cm × 2.5 cm, thickness, ~5 mm) are bonded with the prepared adhesives. The bonding length is 0.5 cm [96].	F_{max}	–
180° peeling test		The thickness should be less than 5 mm, the width is about 2.5 cm and the length is around 15 cm among which 12.5 cm is bounded [97].	Interfacial toughness = 2F/width	–
90° peeling test		The thickness should be less than 5 mm, the width is about 2.5 cm and the length is around 15 cm among which 12.5 cm is bounded.	Interfacial toughness = F/width	–
Burst test		Circle samples with suitable thickness (less than 5 mm) and diameter (about 3 cm) [98].	P_{max}	Alginate-polyacrylamide hydrogels achieve the restored burst pressure to 12.3 MPa [99].
Fatigue durability test		–	Fatigue threshold = dc/dN, Interfacial toughness = F/width	A hernia model with 100,000 loading hernia compression cycles is carried to prove the stability of the IVD [100].

-: present no relative data.

3.4. Adhesion strength

Adhesion strength is a property to evaluate interface strength of two surfaces. For adhesion between two AF interfaces (or between AF surface and biomaterials), biocompatible adhesives need to seal AF defects and prevent the protrusion of NP. In this situation, the adhesives must retain the NP tissue's stability and establish the surface-to-surface connection with the defect AF. Here, hydrogel-based adhesives have emerged as an important research topic to tissue engineering. Viscous hydrogels are typically injectable and minimal invasive which can be used to treat injury tissues [90–92]. Some viscous hydrogels have been applied for AF adhesion (Table 2). The combination of high-density collagen and chondroitinase ABC hydrogel can stick to the AF tissue through removing proteoglycans and increasing access to cell binding motifs [86]. Also, genipin crosslinked fibrin hydrogels have been utilized to evaluate gelation kinetics and adhesion strength by creating a composite formulation [2]. However, these hydrogels are still far from strong adhesion strength (0.2 MPa). It's necessary to design appropriate adhesives to reach high viscous property for AF adhesion. Evaluation of the adhesion strength is of great significance for designing potential adhesives to effectively seal AF defects and adhere to tissues [31,93]. There are five alternative adhesion characterization methods to evaluate the interfacial strength between the tissue and adhesives: lap shear test, tensile test, wound closure test, 90° or 180° peeling test and burst test (Table 3). Before applying the adhesives into preclinical animal models, researchers should use these criteria as a preliminary assessment of

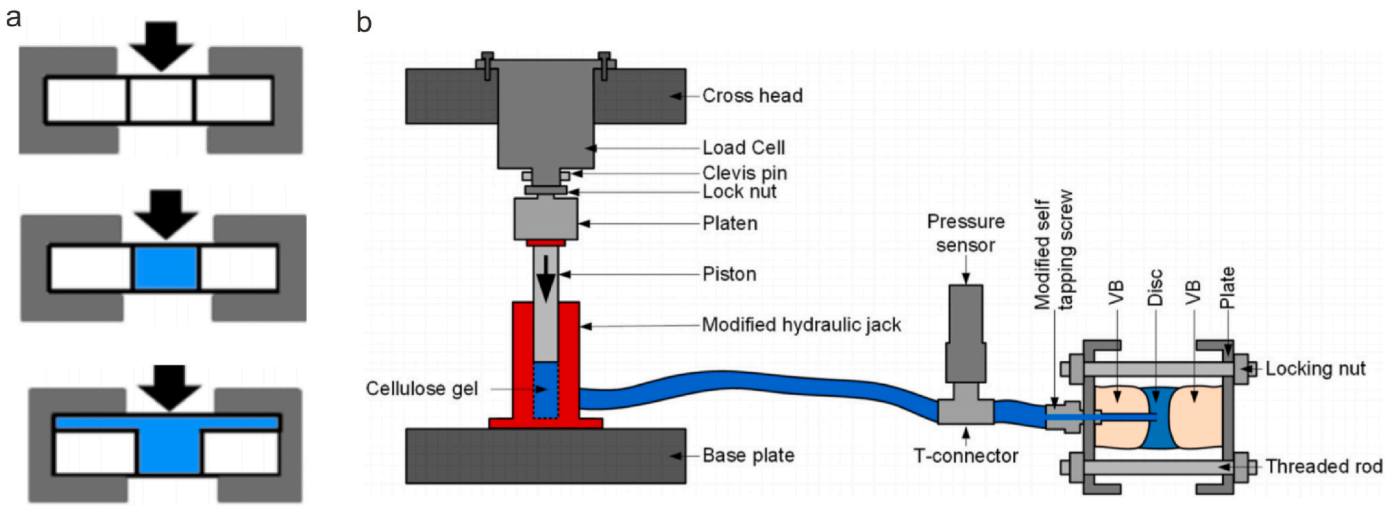


Fig. 5. (a) Pushout test of adhesion [2]. Copyright, 2017 American Society Mechanical Engineering (b) Diagram of the burst pressure test setup to simulate the one-off, high magnitude internal disc pressures [99]. Copyright, 2022 Elsevier

tissue-materials interface adhesion.

The lap shear, tensile, wound closure and peeling tests are universal to characterize materials adhesion property, while the burst and fatigue durability tests are accurate to imitate the AF microenvironment. The pushout test can be seen as the burst pressure test of the materials for the AF characterization (Fig. 5a) [2,101]. Another pressure test methodology is also developed to simulate the one-off, high magnitude internal disc pressures (Fig. 5b) [99]. IVD specimens are placed between two rigid plates, and locking nuts are tightened to keep the IVD height as the cellulose gel is injected into the disc. This device may be very efficient to assess the AF pressure strength, but the device needs to be customized.

These AF forces and mechanical characterizations provide crucial criterion to fabricate AF-repair force-matching materials. However, it is arduous to construct AF-repair materials full of high mechanical properties and biocompatibility. Generally, natural polymers contain inherent side groups and biologically active sites with excellent biocompatibility, but lack mechanical integrity, making it difficult to easily translate into the clinical market. Most synthetic polymers are better suited for mechanical changes but less biocompatible [102]. Therefore, constructing proper AF-repair force-matching biomaterials applied *in vivo* is an urgent need to maintain AF biomechanical and structural properties, as well as to restore its cells biological behavior [103,104].

4. Advanced methods for synthesizing AF-force-matching biomaterials

AF, like other biological tissues in animals (such as muscles, heart valves, tendons, and ligaments), has extremely strong mechanical properties, including high toughness, strength, elasticity, viscosity and fatigue resistance. It has been reported that the AF-matching mechanical properties need to reach the adhesion strength of ~0.2 MPa, compression, shear and tensile moduli of 1 MPa, 0.3 MPa, and 30 MPa respectively [31]. 3D printing is a common and profound method to successfully simulate native AF structures for repairing the AF defects. Most studies focused on printing simulated structures of native AF to promote the cell proliferation [105–107], while the others printed the AF scaffolds for total disc replacement [75,108]. Recently, one work discussed the AF loading changes after discectomy: a honeycomb scaffold printed by poly(ε-caprolactone) (PCL) with *in situ* polymerization of polypyrrole (PPy) could sustain axial spine loading and uniformly diffuse stress under NP swelling and contraction to repair lumbar herniated discs [109]. Electrospinning is an another profound method for fabricating core-shell scaffolds loaded with small drugs or growth factors to regulate the inner inflammation microenvironment [24,58,110]. However, implantation of the core-shell scaffolds is still difficult for achieving robust integration of AF tissue to provide mechanical stability and prevent NP re-herniation.

Table 4
Summary of advantages and disadvantages of the advanced techniques for the AF force-adaptable materials.

Techniques	Advantages	Disadvantages
3D printing	Imitating the native AF structures	Insufficient bionic accuracy The lack of integration of AF tissue The lack of mechanical stability
Electrospinning	Promoting formation of anisotropic structure	The lack of integration of AF tissue The lack of mechanical stability
Mechanical training	Promoting formation of anisotropic structure	High energy dissipation
	High strength and high toughness.	Few studies on AF repair
Directional freezing	Promoting formation of anisotropic structure	High energy dissipation
	High strength and high toughness High fatigue-resistance	Few studies on AF repair
Nanoparticle filler	Promoting formation of anisotropic structure	Difficult to fabricate aligned or oriented materials
	High strength and high toughness	Few studies on AF repair
Slide-ring structure	Low hysteresis	Difficult to mimic the anisotropic structure
	Rapid recovery	Few studies on AF repair

Hydrogels are promising soft materials and have been applied in AF tissue regeneration because of their high-water contents, but they lack the related AF-matching mechanical properties [60,72]. Some synthetic strategies (Table 4) have been proposed to fabricate high-strength or high-adhesion hydrogels for mimicking the native AF structure with anisotropic property, motivating potential application in preparing AF-repair force matching biomaterials. These hydrogels mainly aimed to maintain the balance of AF mechanical properties for stabilizing the IVD microenvironment and preventing the NP re-protrusion.

4.1. Mechanical training

Nature biological tissues, such as muscles, skin, cartilage, ligaments, and tendons, exhibit self-training characteristics. Usually, these tissues'

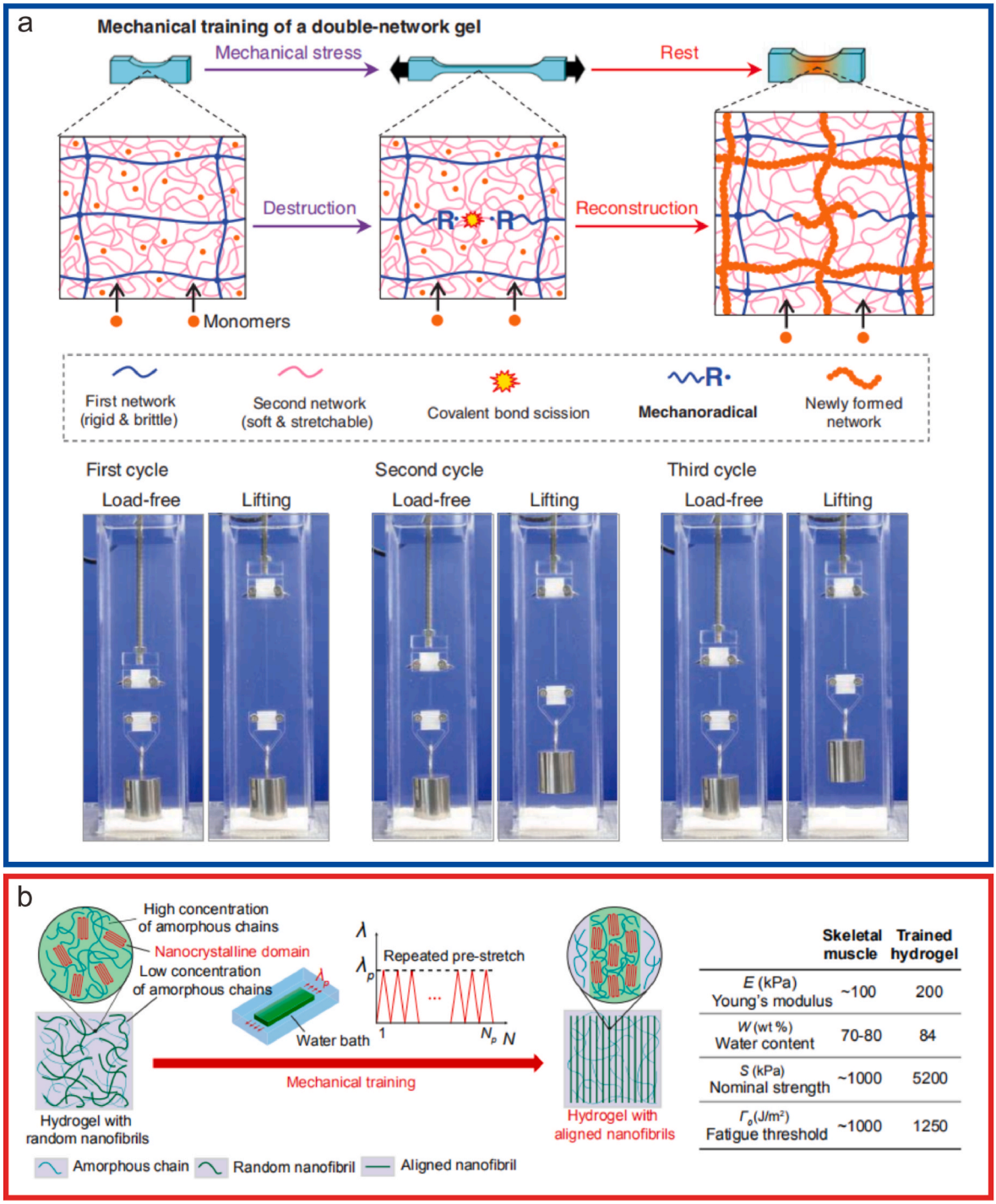


Fig. 6. Mechanical training methods for high tough hydrogels. (a) Self-growing materials induced by mechanical training. Firstly, stress leads to the damage of the brittle network and the stretchable network sustains. Then the mechanoradicals generate at the broken ends of the brittle network stands to trigger polymerization. Finally, the new network form. This process shows the growth in strength and length of the fabricated gels by repetitive mechanical training [111]. Copyright, 2019 American Association for the Advancement of Science (b) Design of muscle-like gels. The microstructure of a PVA hydrogel before (with randomly oriented nanofibrils) and after (with aligned nanofibrils) mechanical training, which is similar to aligned nanofibrillar architectures of human skeletal muscles [112]. Copyright, 2019 Proceedings of the National Academy of Sciences of the United States of America

mechanical properties are self-reinforced with repetitive and constant exercise. Inspired by this tissue remodeling process, researchers have prepared various strain/stress-stiffening hydrogels via using mechanical training method. During the repeated training process, the polymer chain forms a highly oriented anisotropic network matrix, therefore improving the hydrogels' mechanical properties. A "self-growing" double-network *N*-isopropylacrylamide hydrogel is gradually strengthening under mechanical stimuli via a structural destruction and reconstruction process. As a result, the size and strength of the self-growing hydrogels improve with the loading-unloading cycle in the monomer solution. (Fig. 6a) [111]. Similarly, the aligned nanofibrillar polyvinyl alcohol (PVA) hydrogels are constructed via mechanical training, resulting in the muscle-like properties, such as high strength, high fatigue resistance and superior compliance. (Fig. 6b) [112]. In

Table 5
Summary of mechanical properties of potential AF-force-matching materials.

Fabrication methods	Mechanical characteristics	Tensile strength (MPa)	Compression strength (MPa)	Tensile modulus (MPa)	Compression Modulus (MPa)	Shear Strength (MPa)	Refs
Mechanical training	Tensile test	1.-2	–	1	–	–	Mastuda et al. (2019) [111]
Mechanical training	Tensile test	5.2	–	0.2	–	–	Liu et al. (2019) [112]
Mechanical training	Tensile test	25–30	–	–	–	–	Tu et al. (2021) [135]
Directional freezing	Tensile test	24	–	–	–	–	Hua et al. (2021) [115]
Directional freezing	Tensile test	2.5	–	–	–	–	Liang et al. (2021) [116]
Directional freezing	Compression test	–	0.8–1.2	–	–	–	Jiang et al. (2022) [118]
Nanocomposite filler	Tensile test	1215	–	198000	–	–	Zhao et al. (2020) [121]
Nanocomposite filler	Tensile test	900	–	30000	–	–	Dou et al. (2019) [122]
Nanocomposite filler	Tensile test , Compression test , Shear test	0.012	0.027	–	–	0.027	Gan et al. (2019) [123]
Slide-ring structure	Tensile test	5.5	–	–	–	–	Liu et al. (2021) [125]
Slide-ring structure	Tensile test , Compression test	0.87	0.2	–	–	–	Liu et al. (2021) [126]

-: present no relative data.

addition to synthetic polymers, biocompatible natural polymers, e.g., stiff silk material and tough κ-carrageenan hydrogel, can also improve their mechanical properties after repetitive mechanical training [113,114]. These bio-inspired materials with self-strengthen characteristic through tensile testing (Table 5) show great potential for tissue repair, however, their biocompatibility has not yet been verified. For AF tissue repair, it is desirable to construct an anisotropic biocompatible material with multidimensional mechanical-matching properties (such as tensile, compression, shear, bending).

4.2. Directional freezing

Directional freezing method is an effective way to fabricate well-controlled aligned biomimetic porous materials from macro-to nano-architectures and has been considered as a very promising technique to obtain superior mechanical materials when assisting with salting-out or annealing treatment. As an example, shown in Fig. 7a, a highly anisotropic multilayer PVA gel is constructed by directional freezing and salting-out strategy. A honeycomb-like aligned-scale pore wall is formed during the directional freezing process and further a mesh-like nanofibril network is created by the salting-out strategy. This special multiscale structure endows the PVA gel with a high fracture toughness of 210 MJ/m^3, a fracture energy of 170 kJ/m^2 and a high fatigue threshold of 10.5 kJ/m^2 [115]. Another recent study toward the enhancement of directional freezing polymers involves the hierarchically arranged and well-defined crystalline structure after annealing process. This resulting anisotropic gels yield more than 100-fold increase in fatigue thresholds when compared with the original thawed PVA gels (Fig. 7b) [116]. In tissue engineering application, ordered fibrous tough PVA gels as artificial ligaments are constructed and exhibit high strength by combining directional freezing assisted with compression annealing and salting-out treatment (Fig. 7c) [117]. Furthermore, a porous nanocomposite chitosan scaffolds are used for bone defect repair by the modified directional freezing method (Fig. 7d) [118]. Table 5 summarizes mechanical properties of some typical biomimetic structural materials constructed with directional freezing method through tensile and compression test. Wherein, these biomimetic materials have been applied for *in vivo* applications in bone and ligament repair.

4.3. Nanoparticle filler

Hard biological structures, such as teeth and bone, are full of nanocomposites which can contribute to their excellent mechanical strength and toughness. Generally, these nanocomposites can self-assemble into fibrillar structures and then form laminated solids, thus achieving multiscale hierarchical structures from molecular arrangement to macroscopic assembly [119]. It has been reported these functional nanocomposites are bridge to construct macroscale materials and devices [120]. For example, the graphene oxide nanocomposites are assembled to highly ordered layered structures via superspreading strategy (Fig. 8a). The superspreading process provides a strong shear flow force which contributes to in-plane stacked 2D nanosheets and further results in ultrahigh mechanical properties (tensile strength of 1215 MPa and a Young's modulus of 198 GPa) [121]. Apart from the formation of nanocomposite layered architecture, these nanoparticles can also be crosslinked with matrix to provide energy dissipation sites, which can enhance the mechanical performances. Inspired by the spider silks, a hierarchical core-sheath structured fibers are constructed to achieve mechanical properties comparable to spider silk (Fig. 8b) [122]. The core-sheath structure is attribute to the water-evaporation rates of the covalent crosslinked network between the vinyl-functionalized silica nanoparticles and polyacrylic acid. Subsequently, the fiber exhibits a tensile strength of 895 MPa and a modulus of 28.7 GPa under the metal doping and twist insertion strategy. These nanocomposites-based materials not only have excellent tensile and compression priorities (Table 5), but also possess relative interface adhesion strength between tissues and materials. A plant-inspired adhesive and tough hydrogel based on Ag-lignin nanoparticles is developed to apply in surgical operation and biomedical application (Fig. 8c). The Ag-lignin nanoparticles as a dynamic catechol redox system play an import role in mechanical properties and adhesiveness [123]. Other nanocomposites provides a robust interface energy by a unique interlocking mechanism [124]. So far, incorporation of nanoparticles with advanced materials into hierarchical structure, leading to the superior properties, has shown promise for innovation of fabricating AF-force-matching materials.

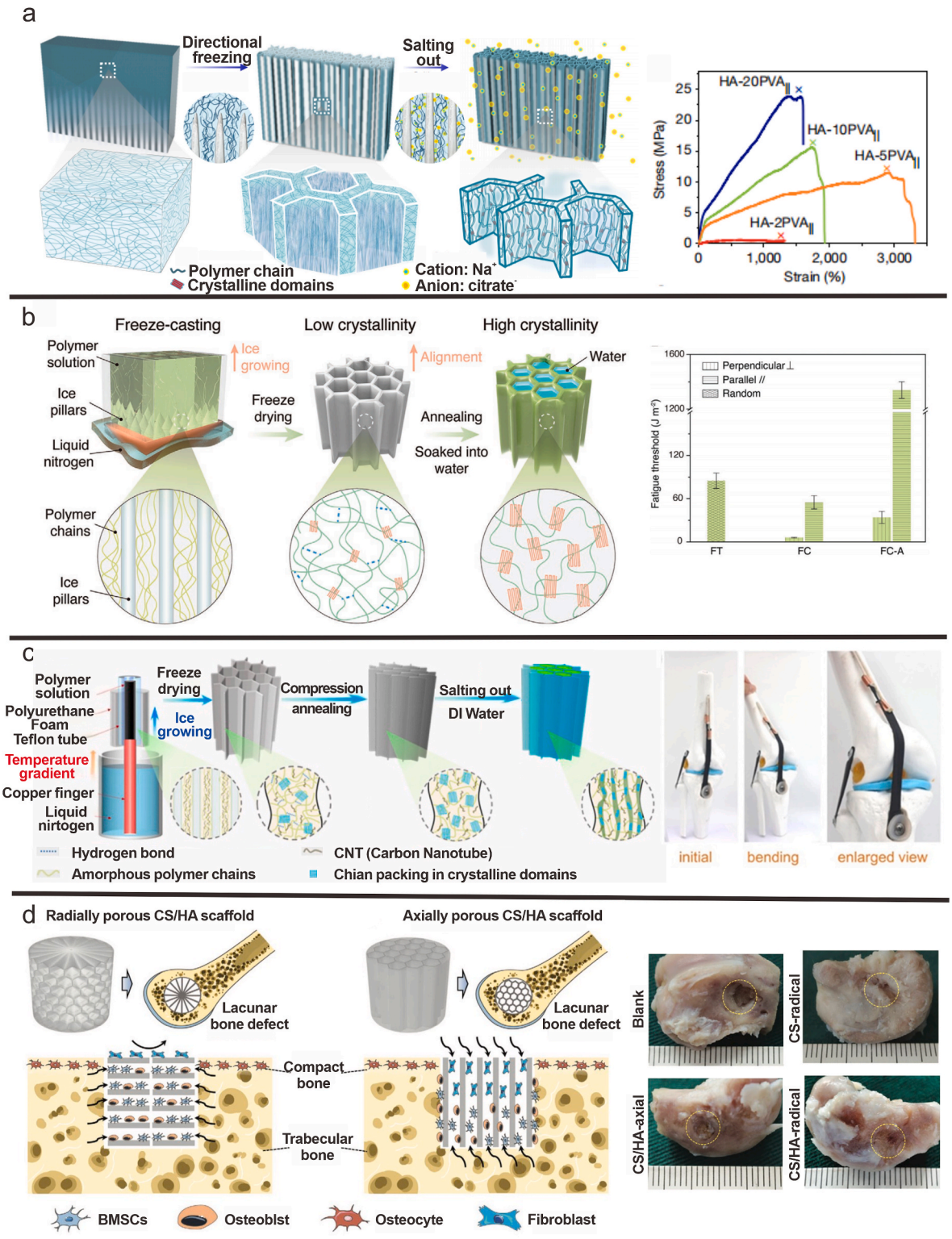


Fig. 7. Directional freezing method for constructing high tough hydrogels. (a) Freezing-assisted salting-out strategy to fabricate HA-PVA hydrogels. The structure changed from microstructure to nanostructure endows the hydrogel high mechanical performances [115]. Copyright,2021 Springer Nature(b) Freezing-assisted annealing strategy to construct a hydrogel system with preferentially-aligned microstructures and nanocrystalline domains. This PVA gels achieve a higher fatigue thresholds of 100 times than conventional gels [116]. Copyright, 2021 John Wiley and Sons (c) Freezing-assisted both annealing and salting-out strategy to prepare strong and tough artificial ligament with arrayed fibrous structures [117]. Copyright, 2023 Royal Society of Chemistry (d) Freezing method to develop the radially and axially porous chitosan/hydroxyapatite scaffold for bone regeneration *in vivo* [118]. Copyright, 2022 John Wiley and Sons

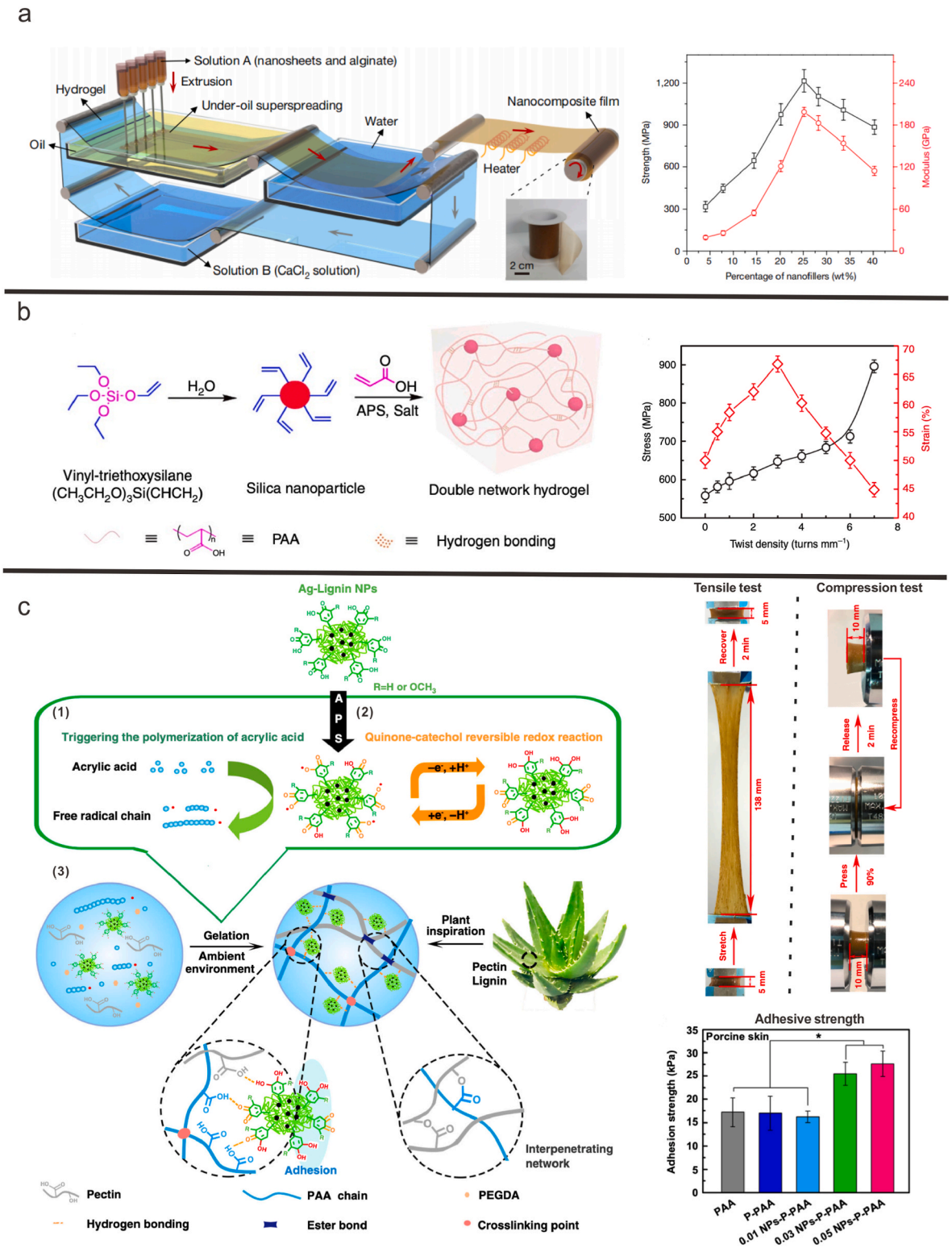


Fig. 8. Nanocomposite filler for constructing high tough hydrogels. (a) Fabrication of the layered nanocomposite films featuring aligned nanosheets to achieve high mechanical properties. The NaAlg/nanosheets solution superspread under oil and crosslink by calcium ions, the oriented nanocomposite gel films are collected after drying [121]. Copyright,2020 Springer Nature (b) Strategy to synthesize tough hydrogels involving vinyl-functionalized silica nano-particles formation and free-radical polymerization. With the twist density increase, the tensile stress improved [122]. Copyright,2019 Springer Nature (c) The fabrication of a plant-inspired catechol-chemistry-based self-adhesive and tough NPs-P-PAA hydrogel. The redox reaction between Ag-Lignin NPs and ammonium persulfate generates the radicals to trigger the gelation of hydrogels, resulting in the hydrogel's elongation, compression and adhesion [123]. Copyright,2019 Springer Nature

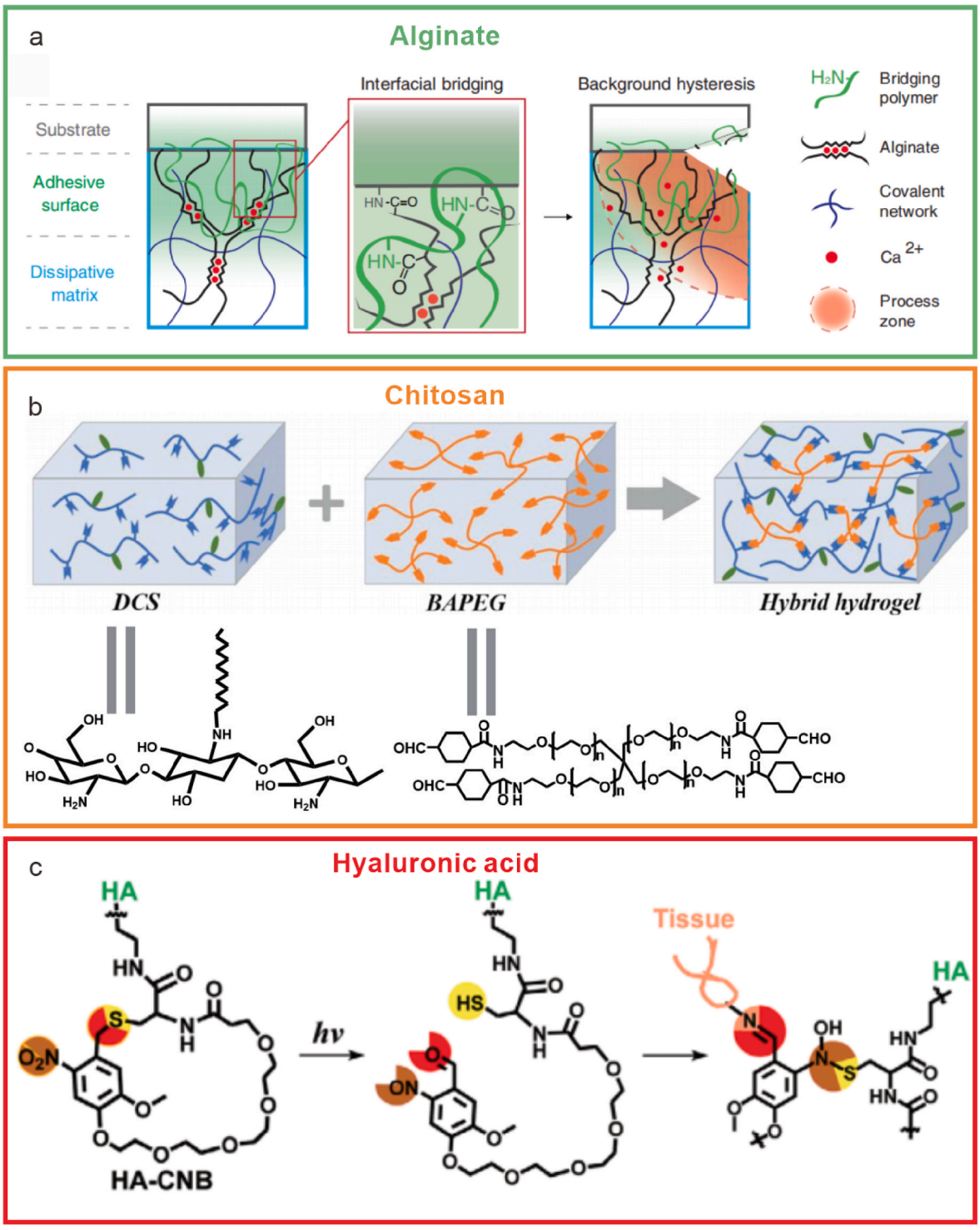


Fig. 9. Potential molecular interaction for tough adhesives. (a) Alginate for TAs consisting dissipative matrix with ionic cross-linking and covalent cross-linking [140]. Copyright, 2017 American Association for the Advancement of Science (b) Chitosan for hybrid hydrogel with bold cell coagulation and hemostasis function [141]. Copyright, 2018 John Wiley and Sons (c) The gelation and tissue integration mechanism for HA-CNB containing cyclic *o*-nitrophenyl-sulfide moieties [142]. Copyright, 2021 John Wiley and Sons

4.4. Slide-ring structure

Slide-ring structural materials are mainly generated by physical bonding to form a high degree of conformational free and mobility structure, similar to a pulley. This structure endows slide-ring materials excellent fracture toughness and low hysteresis, which enables these materials to play a long-term stable role in tissue engineering applications. A slide-ring hydrogel consisting of polyethylene glycol chains and hydroxypropyl-α-cyclodextrin rings sustains almost 100% rapid recovery efficiency of extension energy under repetitive large deformation for artificial small-diameter blood vessels [125,126]. A bioinspired mineral-organic β-cyclodextrin and cholesterol composite hydrogel promotes bone regeneration as self-healable and mechanically robust bone graft [127]. These excellent fatigue properties of the

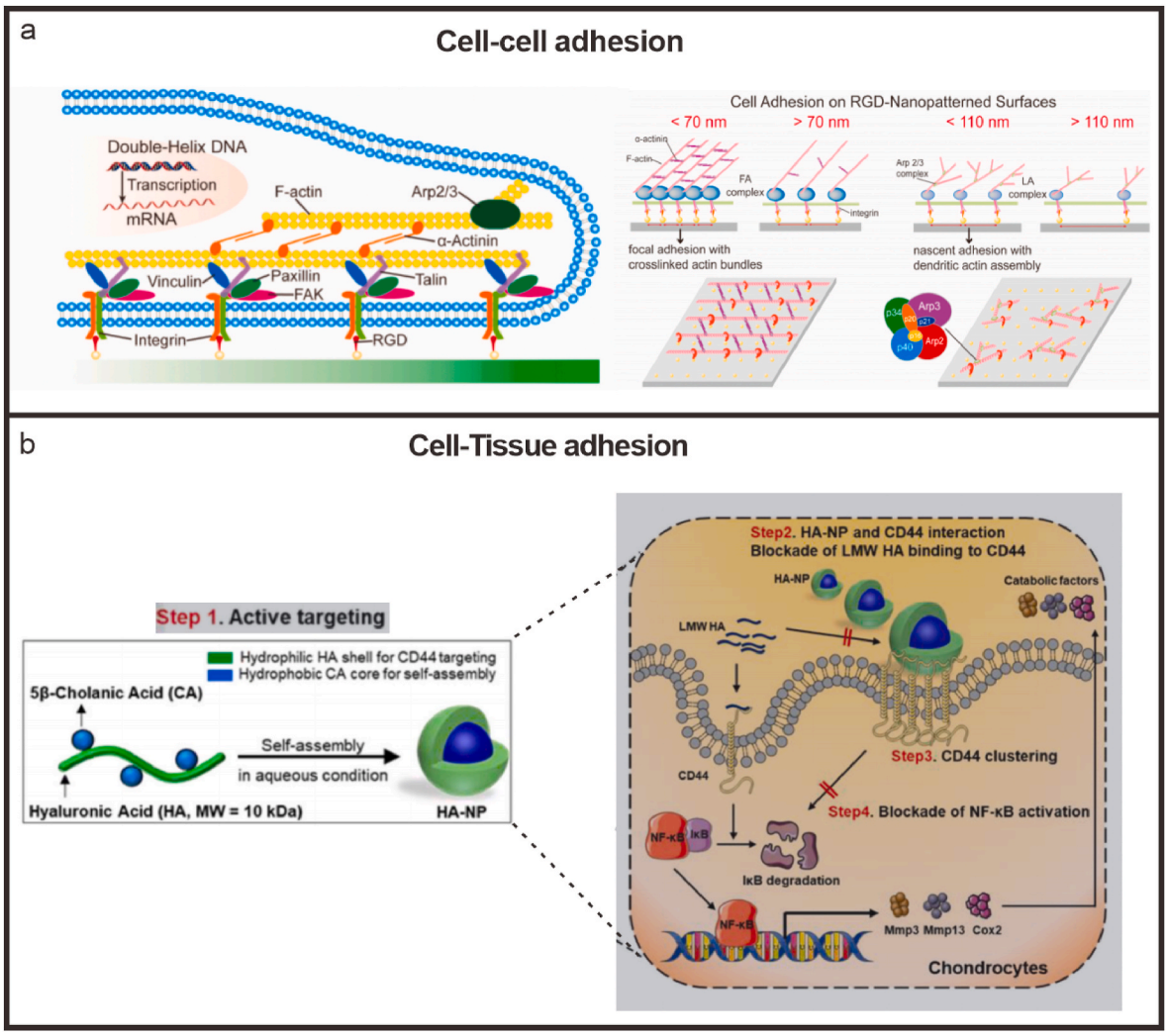


Fig. 10. (a) Potential strategy of cell-cell adhesion for AF repair: the RGD nanoparticles adjust the nano-spacing to meet the adhesive requirements [148]. Copyright, 2020 Elsevier (b) Potential strategy of cell-tissue adhesion for AF repair: the combination of HA and cd44 for enhancing the mechanical properties[149]. Copyright, 2021 Elsevier

slide-ring hydrogels are key for long-term AF repair.

The viscoelasticity of AF is related to the rearrangement of proteoglycans and the remodeling of collagen, forming its special anisotropic layered fiber structure and endowing its superior mechanical properties [128]. The above-mentioned four methods, including mechanical training [112,129,130], directional freezing [115,116,131], nanoparticle filler [121,132] and slide-ring structure [133,134], have improved mechanical properties by introducing some unique structures. However, most works only focus on improving a single dimension mechanical property, such as tensile or compressive strength. There are few studies that can design ideal materials that meet AF tissue's mechanical performances with all six degrees freedom. Therefore, it is desirable to create AF-force-matching biomaterials through the above-mentioned single or mixed methods to meet the requirements of six-degrees-freedom mechanical performances.

4.5. Biomaterial adhesion

The current design principles of tissue adhesives mainly rely on the molecular interaction between adhesive and tissue, cell adhesion and mechanical interlocking methods [136]. Adhesion strength of adhesive depends on its physical and chemical properties, as well as the microenvironment of the tissue [137,138]. The unique and compact anisotropic structure of AF makes molecular interaction and cell adhesion more productive. AF is composed of glycosaminoglycans, collagen and some proteoglycans containing many functional groups, such as primary amines, carboxylic acids, and hydroxyl groups. These functional groups can form amide bonds through carbodiimide chemistry with polysaccharide substances, such as chitosan, alginic acid, hyaluronic acid, agarose and so on [139–142]. Apart from the covalent bond, different tissues have different surface chemistry, providing specifically physical bond to adhesives. For example, the glycosaminoglycans with full of negatively charge can effectively integrate positively charged substances to provide strong adhesion [143]. What's more, relatively low physical reversible bonds can also promote tissue adhesion, such as hydrogen bonding, hydrophobic interaction and van der Waals force [144]. Li and coworkers conducted a covalent-linked polyacrylamide and ionically cross-linked Ca-alginate gel, as well as the primary amine-based polymer. This tough adhesive combined chemical and physical connections at the surface to achieve high adhesion energy to wet tissue (Fig. 9a) [140]. Chen and coworkers presented a hybrid hydrogel through the Schiff base between four-armed benzaldehyde--terminated polyethylene glycol and dodecyl-modified chitosan. This adhesive can promote collagen deposition and macrophage polarization (Fig. 9b) [141]. Also, Zhang and coworkers conducted a light-curing adhesive with cyclic *o*-nitrophenyl-modified hyaluronic acid gel

through coupling reaction (Fig. 9c) [142]. The fabrication of these polysaccharide-based adhesive through chemical and physical cross-linking may be potential to promote the adhesion between AF and surrounded tissues.

Cell-to-cell and cell-to-tissue interactions also play a vital role in tissue adhesion. Cells can diffuse and penetrate the adhesion matrix, promoting to form a certain interpenetrating network with adhesives, thus achieving the integrity of the tissue-adhesion interface and the adhesion matrix [136,145]. Based on the protein of the tissue surface for targeted binding, the studies on cell adhesion have achieved high-precision processes [146,147]. Liu and coworkers investigated the effects of nano-spacing of arginine-glycine-aspartate peptide on cell migration related to cell adhesion. The result proved that the cell adhesion could be tuned by the cell migration through adjusting the nano spacing. (Fig. 10a)[148]. HA in AF, the common substance to investigate with cd44, can also endow the cell-tissue adhesion (Fig. 10b) [149]. Generally, to combine materials and cells is also a feasible approach to promote the strong adhesion, beneficially for AF restoration.

5. Clinical prospects

Current clinical treatments only alleviate pain symptoms and do not alter the underlying pathology or seal AF defects [45,150]. Implanted hydrogels integrating extra cellular matrix and cell may provide a solution to maintain phenotype and preserve AF function. However, mechanical matching is vital for these hydrogels to successful application in AF rupture repair. Therefore, testing paradigms need to be proposed for rapidly screening optimal biomaterials: (1) *in vitro* tests include the cytocompatibility and mechanical modalities (tensile, compression, shear and adhesion tests); (2) *in situ* tests include failure and degradation tests for long-term treatment; (3) animal tests include biomechanical performance monitoring [45,151].

6. Summary

Studies based on AF repair mainly focus on the comparison of the composition, mechanical performances and engineered biomaterials, except the AF-related signal pathway research. Constructing AF-force adaptable biomaterials are desirable to maintain the AF biomechanical behavior and promote the AF structure in a long-term period. In this review, we outline basic composition and anisotropic structure of AF tissue to declare their excellent mechanical properties. Then, we summarize six-degree-freedom AF forces (including compression, tension, shear, bending, flexion, and torsion), adhesion strength and the related characterization modalities, providing guidance for effectively evaluating the AF repair. Finally, we overview different advanced techniques for constructing high-strength and high-toughness hydrogels to promote the interfacial adhesion between AF tissues and biomaterials. These methods aim to design mechanical adaptable biomaterials for the fabrication of clinical suitable devices or scaffolds to maintain the balance of AF mechanical loading and further to promote AF regeneration.

Declaration of competing interest

Decheng Wu is an editorial board member for Bioactive Materials and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

Ethics approval

The review article is no available for Ethics approval and consent to participate.

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