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Mechanobiological insights into ocular nanomaterials: bridging structural design and therapeutic function

Jie Zhang[1,2,†], Min Li[3,†], Yanming Zhu[1,2], Wenyang Xu[1,2], Yanyu Shangguan[1,2], Ruoning Luo[1,2], Yanlong Bi[1,2], Guofeng Liu[4,*] and Bing Li[1,2,*]

[1] Department of ophthalmology, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200065, China
[2] Tongji University Center for Vision Science and Translational Research, Shanghai 200331, China
[3] Department of Ophthalmology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China
[4] School of Chemical Science and Engineering, Tongji University, Shanghai 200092, China

† These authors contributed equally to this work.

* Correspondence authors; E-mails: bing.li@tongji.edu.cn (B.L.); liuguofeng@tongji.edu.cn (G.L.).

Highlights:

- Biomechanics provides a fundamental framework for the rational design of next-generation ocular nanomaterials.
- Region-specific mechanical matching enhances ocular tissue integration, retention, and safety of nanomedicine-based drug delivery systems.
- Biomechanically responsive nanomaterials enable controlled release, protect ocular structure, and improve translational potential in eye disease treatment.

Abstract: Ocular nanomedicines for precise targeted delivery and controlled release in clinical application have expanded. However, developing materials that harmonize with biomechanical properties of various anatomical regions in the eye remains neglected. For instance, biomaterials engineered to mimic the cornea's biomechanical and optical properties can achieve superior integration with ocular surface structures, thereby reducing corneal trauma and extending nanomaterial persistence. Beyond the corneal surface, biomechanically optimized strategies that consider the viscoelasticity and structural integrity of the retina and choroid can significantly improve intraocular drug delivery. Nanomaterials with dynamic biomechanical responsiveness, such as intraocular pressure (IOP)-sensitive behavior, enable controlled drug release and enhance therapeutic efficacy in glaucoma management. Notably, nanomaterials with mechanical stiffness compatible with ocular biomechanics can preserve tissue integrity, stabilize the globe structure, and mitigate trauma-related complications. This review synthesizes current understanding of the biomechanical properties of ocular tissues and provides structural perspectives to inform the development of next-generation nanomaterials for ophthalmic use. We envision that these insights will foster translational innovation and advance biomechanically informed strategies in ocular nanomedicine.

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Keywords: ocular structural properties; nanomaterials; biomechanics; drug delivery strategies; mechanical safety

1. Introduction

Recent years, the rapid advancement of nanomaterials has opened new frontiers in the diagnosis and treatment of ophthalmic diseases. However, ocular applications still encounter substantial challenges, particularly in biomechanical compatibility and long-term safety. Owing to its intricate anatomical architecture and dynamic biomechanical microenvironment, the eye imposes exceptionally stringent requirements on material design [1]. Thus, understanding the mechanical characteristics of ocular tissues can enable the rational alignment of nanomaterials properties with physiological demands. These demands include the elastic modulus of the cornea, the nonlinear viscoelasticity of the retina and choroid, and the dynamic fluctuations in intraocular pressure (IOP). This biomechanically informed design strategy offers significant potential to improve therapeutic outcomes while minimizing adverse ocular reactions [2].

Traditional ophthalmic material design primarily focuses on chemical compatibility and drug release kinetics, overlooking the impact of the biomechanical microenvironment on material performance. From a biomechanical perspective, corneal repair materials are more likely to maintain physiological compatibility and optical transparency when their properties approximate the low-strain quasi-static elastic modulus of the cornea (0.3–1.5 MPa) [3]. Similarly, glaucoma drainage implants need to adapt the dynamic IOP fluctuations (10–21 mmHg, ≈ 1.33–2.80 kPa), to prevent tissue damage or functional failure caused by mechanical mismatches [4]. Tunable mechanical properties in nanomaterials provide the potential solutions in above problems, like high tensile strength, biomimetic viscoelasticity and surface functionalization [5]. Researchers also demonstrated that bioinspired retinal nanodevices can mimic the mechanoelectrical coupling behavior of biological synapses, which enables efficient visual signal processing. This nanodevices can underscore the pivotal role of mechanical biomimicry in functional material design [6]. Also, the integration of biomechanics and nanotechnology can spur innovations in novel drug delivery systems. Surface modifications of nanoparticles can regulate their adhesion to the ocular mucus layer and extend drug retention time [7]. Meanwhile, stress-responsive smart materials enable on-demand drug release in response to IOP variations [8]. Nanomaterials engineered with biomechanical responsive principles (temperature, pH, light, electric fields and mechanical forces) show enhanced potential for precise ocular drug delivery. This review highlights the critical role of biomechanics in designing ocular nanomaterials. We examined diverse mechanical properties of ocular tissues and presented application cases to demonstrate underlying mechano-biological coupling mechanisms. These emerging topics lay the groundwork for the future development of next-generation intelligent nanomaterials with biomechanical adaptability for ophthalmic applications.

2. Biomechanical properties of different ocular tissues

The following equations provide first-order biomechanical insight into ocular deformation, refraction, and aqueous humor flow. Because these formulations are derived largely from continuum-scale assumptions, their application to nano-micro environments requires careful interpretation. Important features of ocular nano-micro systems, including tissue heterogeneity, anisotropy, viscoelasticity,

interfacial effects, confinement-dependent transport, and local material-cell interactions, are not fully represented by these simplified models. Accordingly, in the context of ocular nanomaterials, these equations are better regarded as conceptual biomechanical frameworks than as fully predictive tools.

2.1. The mechanical response of the cornea

As the primary refractive structure of the eye, the mechanical properties of the cornea directly influence its refractive function [9]. The corneal refraction is determined by physical quantities such as corneal curvature and lens refraction. The relationship between refraction and corneal curvature is given by the following Equation (1):

$$D = (n-1) / R \quad (1)$$

(D: corneal refraction; n: corneal refractive index; R: radius of curvature of the anterior corneal surface.)

According to the thin-shell theory, the variation in the radius of curvature can be expressed as Equation (2):

$$\Delta R = (P \cdot R\text{^}2) / (2 \cdot E \cdot t) \quad (2)$$

(ΔR: variation in the radius of curvature of the anterior corneal surface; R: radius of curvature of the anterior corneal surface; P: pressure change; E: corneal elastic modulus; t: central thickness of the cornea.)

The relationship between refraction change and the elastic modulus can be derived with the Equation (3).

$$\Delta D = ((n-1) \cdot P) / (2 \cdot E \cdot t) \quad (3)$$

(ΔD: variation in corneal refraction; D: corneal refraction; n: corneal refractive index; P: pressure change; E: corneal elastic modulus; t: central thickness of the cornea.)

Thus, there is a close mechanical-optical coupling relationship between corneal stiffness and refraction according to the formula [10]. Under a constant pressure, a higher elastic modulus results in smaller changes in curvature and more stable refraction. This modulus is critical for maintaining normal visual function in designing materials. This modulus is critical for maintaining normal visual function and should therefore be considered in material design. Polyacrylate-based nanogels can achieve an adjustable elastic modulus by regulating crosslinking density, improving the shaping effect and reducing corneal epithelial damage [11]. Carbon nanotubes, known for their high mechanical strength and biocompatibility, present promising potential as materials for modulating corneal stiffness [12].

Orthokeratology lenses modify the curvature of the cornea's anterior surface and inhibit axial elongation through their interaction with the lens and tear film in myopia correction. The outcome of orthokeratology lenses, known as the Ogden model, is used to predict the hyperplastic constitutive model of the cornea. The strain energy density W is given by Equation (4):

$$W = \sum_{k=1}^{N} \frac{\mu_k}{\alpha_k} \left(\lambda_1^{\alpha_k} + \lambda_2^{\alpha_k} + \lambda_3^{\alpha_k} - 3 \right) \quad (4)$$

(λ_1, λ_2 and λ_3 are the main elongation ratio (tensile multiple in the main stretching direction), μ_k and α_k are the material parameters, which should be determined experimentally. N is the model order.)

2.2. Nonlinear viscoelasticity and anisotropic behavior of the retina and choroid

The retina and choroid have important biomechanical features, including nonlinear viscoelasticity and anisotropy [13]. The nonlinear viscoelasticity of the retina arises from the layered arrangement of collagen and elastic fibers [14]. Biomechanical features can be described by the generalized Maxwell model, which captures the multivariate relaxation behavior of dielectric elastomers with high accuracy [15]. In retinal mechanics, this model accounts for time-dependent deformation and stress relaxation, demonstrating that the retina exhibits distinct elastic and viscous responses at different stress levels. This viscoelastic behavior is crucial for sustaining the normal physiological function of the eye as described in Equation (5).

$$\sigma(t) = \sigma_\infty + \sum_{i=1}^{n} \left(\sigma_i e^{-t/\tau_i}\right) \quad (5)$$

($\sigma(t)$: the total stress; σ_∞: the equilibrium modulus; σ_i: the elastic modulus of the i-th Maxwell unit; τ_i: the relaxation time of the i^{th} unit; n: the model order.)

The choroid has tenfold higher Young's modulus compared to the retina, suggesting a higher elasticity [16]. Retinal creep is regulated by glial activity, while the choroid is influenced by the pulsatile pressure of blood flow. Despite these differences, both tissues exhibit viscoelastic and anisotropic properties due to their shared physiological location.

Nanomaterials engineered to suit the mechanical environment of the retina provide promising multimodal therapeutic strategies for chorio-retinal diseases. For example, graphene oxide (GO)-based nanomaterials can be used to create biomimetic interfaces for visual repair, for the reason of high conductivity, flexibility and surface modifiability [17]. Carbon nanotube arrays can mimic the laminar structure of the retina, reducing mechanical damage during implantation [18]. Electro-spun nanofiber scaffolds, constructed from polycaprolactone or polylactate hydroxyacetate, create biomimetic 3D environments that promote the directional alignment and functional differentiation of retinal pigment epithelium (RPE) cells [19]. Additionally, liposomal nanoparticles combined with shear-thinning hydrogel carriers adapt to the dynamic viscoelastic environment, prolonging drug retention in macular degeneration treatment while optimizing delivery within choroidal blood flow.

2.3. Mechanical regulation of IOP

IOP undergoes dynamic fluctuations influenced by both physiological and external factors. Abnormal variations in IOP are leading cause of blinding diseases, such as glaucoma. IOP homeostasis relies on the delicate balance between aqueous humor secretion and outflow, a process that significantly impacted by mechanical perturbations at multiple scales. Physiological disturbances include the fluidity of aqueous humor flow and pressure transients from extraocular muscle contractions. The balance between aqueous humor secretion and discharge can be quantified using the Goldman Equation (6):

$$IOP = F / C + P_v \quad (6)$$

(F: the rate of aqueous humor generation; C: the ease of aqueous humor outflow, P_v: the superior scleral venous pressure.)

Recent studies suggest that nanomaterials can intervene in abnormal IOP perturbations by adapting to the dynamics of IOP fluctuations. A biomimetic human trabecular mesh model based on poly-hexanolactone

nanofiber scaffolds has been used to study the biomechanical mechanisms of aqueous outflow. This model quantitatively analyzes the relationship between aqueous outflow resistance and matrix stiffness, as well as the orientation of fiber alignment [20,21]. At the tissue scale, aqueous humor dynamics can be approximated using classical flow equations; however, these formulations do not fully capture nanoscale interfacial transport or local nanomaterial-tissue interactions. The flow rate can be adjusted by the Navier-Stokes equation (7), which ensures that the aqueous outflow rate meets the required antihypertensive targets [22,23].

$$Q = (\pi r^{\wedge 4}\ \Delta P) / 8\mu L \cdot \emptyset(\varepsilon) \quad (7)$$

(Q: the aqueous flow; r: the equivalent radius of the trabecular network gap; ΔP: the pressure difference between the front chamber and the Schlemm tube; μ: the aqueous viscosity; ∅(ε): the porosity correction factor) (Figure 1).

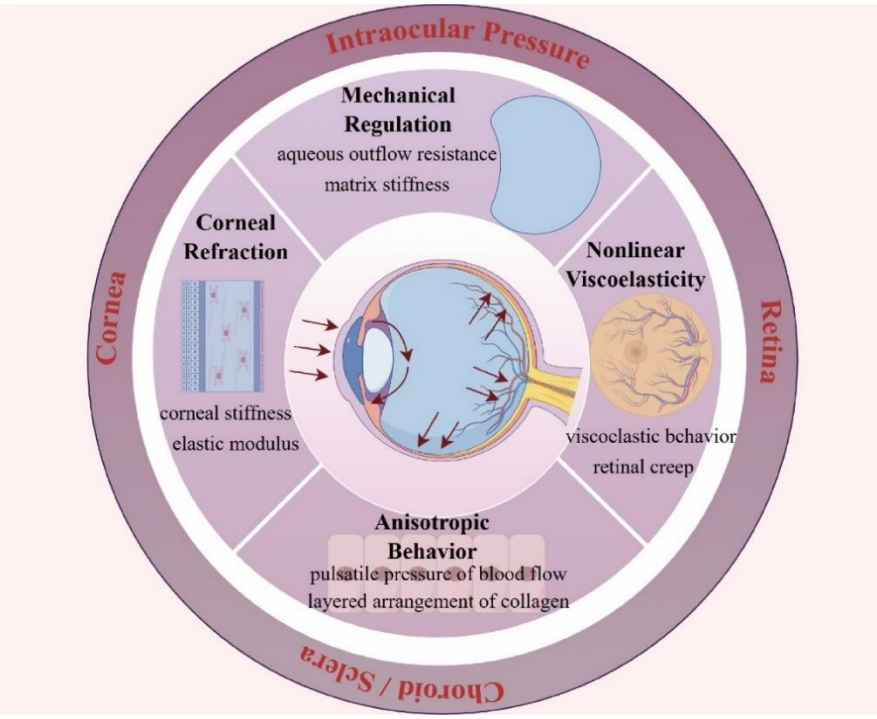

Figure 1. Biomechanical properties of different ocular tissues.

3. Effects of different mechanical conditions on nanomaterials for eye applications

3.1. Static mechanical loads and cellular response

Static mechanical loads, including scleral tension and the inherent weight of the materials, along with the cells' response capabilities, are critical factors influencing the functionality of nanomaterials in ophthalmic applications. Specifically, static mechanical loads can influence focal adhesion formation by regulating integrinβ1, affecting intercellular adhesion, migration capacity, and the stability of the extracellular matrix. This enhances the compatibility between materials and surrounding tissues, and maintains the mechanical balance between nanomaterials and tissues [24,25]. In addition, cellular responses can influence the extent of material strain, ultimately reducing the effectiveness of nanomaterials [26]. Cellular responses also regulate cell behavior through pathways such as the YAP/TAZ pathway, promoting ECM deposition in

localized tissues, which eventually leading to fibrosis [27,28]. Such fibrosis impedes molecular diffusion and may induce immune rejection of nanomaterials. Based on the aforementioned mechanical properties, it is essential to fully consider the effects of static tensile forces when preparing nanomaterials targeting the sclera and other ocular tissues. The relevant materials should possess high stress retention and low creep rates to maintain the integration and stability of the material-cell interface.

3.2. Dynamic mechanical stimulation and ocular development

The dynamic mechanical stimulation, combined with changes of mechanical microenvironment in ocular tissue development, jointly determine the compatibility of nanomaterials with target tissues. Dynamic mechanical stimulation (such as periodic intraocular pressure fluctuations) alters the mechanical properties of nanomaterials by regulating factors like elastic modulus and porosity. Critically, the mechanical properties of nanomaterials must be matched to the specific developmental stage, for stiffness difference existing in the retinal ECM between development and maturity [29]. The mismatch will disrupt pivotal processes such as cellular signaling, communication, and myofibroblast differentiation in the eye [30]. Besides, unsuitable of nanomaterials with issue development can lead to ocular fibrosis and fluctuations in intraocular pressure [31,32], causing adverse effects such as vision impairment and retinal detachment. Therefore, nanomaterials need to possess following dual functionality: adapting their tensile strength to ongoing changes and responding promptly to high-frequency stimuli.

3.3. Mechanical heterogeneity and interface integration

Mechanical heterogeneity and interfacial integration between materials and biological tissues are critical determinants of material biocompatibility. These factors influence cell adhesion and modulate mechanical signal transduction, thereby shaping cellular responses at the material-tissue interface. Mechanical heterogeneity necessitates that ocular nano-scaffolds meet the standards for gradient stiffness design corresponding to ocular tissues, such as the corneal stroma, retina, and sclera [33,34]. Mechanical mismatch can trigger inflammatory responses and even fibrosis within the eye, leading to adhesion between nanomaterials and ocular tissues, which severely affects the biocompatibility of the materials [35]. The integration of the nanomaterial's surface topography (such as nanoscale roughness, porosity, or spike-like morphology) with the spatial interfaces of cell membrane adhesion proteins affects biomechanical integration. The interaction includes adhesion strength and targeting ability of material. Moreover, the proliferation and cytoskeletal rearrangement of target cells also be mentioned [29,36]. Therefore, when designing nanomaterials, it is essential to focus on the surface topography to better promote cell adhesion. Referring the importance of mechanical heterogeneity and interface integration, nanomaterials must meet the elasticity modulus related to changes in eye tissue (Table 1) [37]. Meanwhile, researchers also need to focus on the surface topology of nanomaterials and the density of functional arginine-glycine-aspartic acid (RGD) peptides to enhance the adhesion of nanomaterials in eye tissue and further optimize their mechanical response to target cells [38] (Figure 2).

Table 1. Elastic modulus of key locations in the eye.

Ocular tissue	Elastic modulus (MPa)
cornea	0.69 ± 0.14
superior sclera	2.19 ± 0.43
inferior sclera	1.84 ± 0.30
other scleral locations	Over 4
retina	0.03

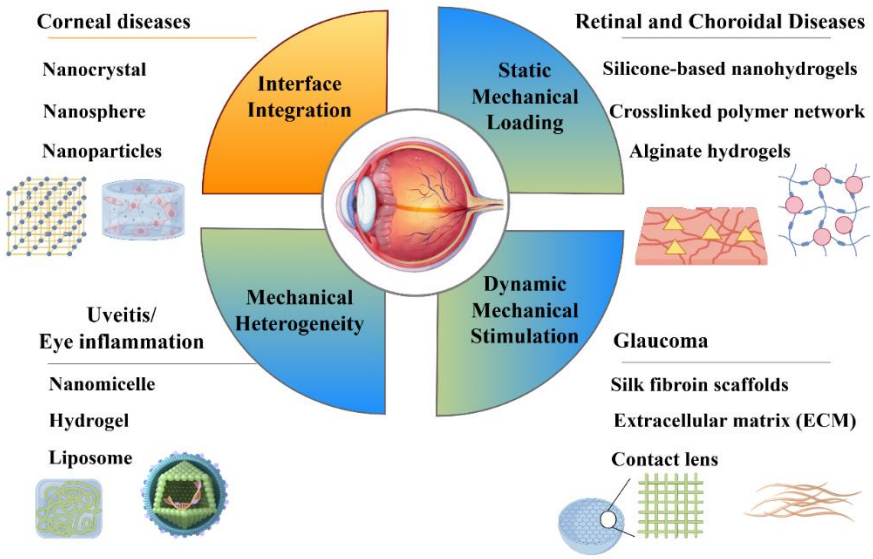

Figure 2. Clinical applications of ocular nanomaterials with different mechanical conditions.

4. Application of nanomaterials in ocular diseases based on biomechanical property analysis

Given the complex biomechanical properties of ocular tissues, considering changes in the mechanical microenvironment of the tissue is vital for nanomaterials [39]. Current ocular nanomaterials can better precisely intervene in pathological processes through the simulation of mechanical properties. For example, hydrogel materials can effectively simulate the physiological microenvironment, with their tunable mechanical properties and stimulus-responsive capabilities [40]. Therefore, they are suitable for constructing smart drug delivery carriers or providing physical support functions [41]. By providing topographical and mechanical cues, nano-fiber scaffolds actively guide directional cell proliferation, thereby fostering a conducive microenvironment for tissue regeneration [42]. Carbon-based nanomaterials leverage their high mechanical strength and ease of modification for use in implantable ocular devices and the construction of high-strength, tough biomimetic scaffolds [43]. Separately, the synergistic combination of metal nanoparticles with inorganic non-metallic nanomaterials can be utilized to construct intelligent perception-response systems for advanced ocular applications [44]. The multifunctional intelligent response nano-system integrates the ability to sense and respond to mechanical environments, enabling targeted drug delivery and prolonged retention in lesion areas [45]. Therefore, we elaborate on nanomaterials based on the type of disease (Table 2).

Table 2. Summary of ocular nanomaterials: types, functions, and applications.

Type	Function	Application
Hydrogel-based materials	High water content, translucency, dynamic responsiveness	Corneal repair, glaucoma treatment, retinal reattachment, and ocular trauma repair
Nanofiber scaffolds	High specific surface area, high precision, high mechanical strength	Corneal injury repair, ocular trauma repair
Carbon-based nanomaterials	High mechanical strength, conductivity, and modifiability	Optimization of contact lenses/glaucoma drainage devices, construction of high-strength and tough bionic corneal scaffolds
Metal/inorganic nanoparticles	Photothermal effect, sensing ability, biomineralization capacity, selective filtration	Intelligent sensing-response closed-loop therapy for glaucoma
Multifunctional intelligent responsive nano-systems	Integrated perception, precise response, precise execution	Dynamic closed-loop regulation of glaucom

4.1. Application in corneal diseases

Nanomaterials engineered to replicate the natural biomechanical characteristics of the corneal limbus effectively preserve epithelial barrier integrity and maintain phenotypic homeostasis [46]. Also, the mechanical microenvironment of the corneal stroma can regulate the phenotypic characteristics and functional activity of corneal epithelial cells [47] (Figure 3A). The mechanobiological coupling mechanism is central to corneal tissue engineering, exemplified by soluble microneedles capable of exosome delivery. Recent advancements have expanded this strategy through the development of microneedle systems incorporating mesenchymal stem cells. By integrating methacrylated hyaluronic acid microneedles with decellularized corneal lenticules, this system facilitates minimal invasion implantation and enables the sustained release of paracrine factors, thereby effectively inhibiting fibrosis and promoting regeneration of the stromal matrix [48]. Nanomaterial design should follow two core principles: replicating the nanoscale mechanical gradient of the limbal basement membrane (hardness gradient of 18–25 kPa) and enabling the coordinated release of bioactive factors to promote corneal barrier reconstruction [49] (Figure 3B,C).

In addition to altering tissue-level biomechanics, mechanical stress imbalance may directly contribute to corneal scarring through nuclear mechanotransduction. In corneal cells, abnormal mechanical loading can induce nuclear deformation and trigger a calcium-dependent adaptive response associated with chromatin reorganization and reduced heterochromatin compaction. This process may initially help buffer mechanical injury to the genome. However, when mechanical stimulation is excessive or persistent, the protective response may become insufficient, resulting in DNA damage accumulation. In parallel, sustained mechanical stress can promote fibroblast activation and myofibroblast transition, accompanied by increased chromatin accessibility to profibrotic genes and enhanced extracellular matrix deposition and remodeling. These changes not only disrupt normal stromal architecture but also reinforce tissue stiffness, thereby creating a feed-forward loop between mechanical stress, cellular activation, and fibrosis. This mechanistic framework provides a biological basis for why biomechanically optimized biomaterials may help suppress scar formation [50].

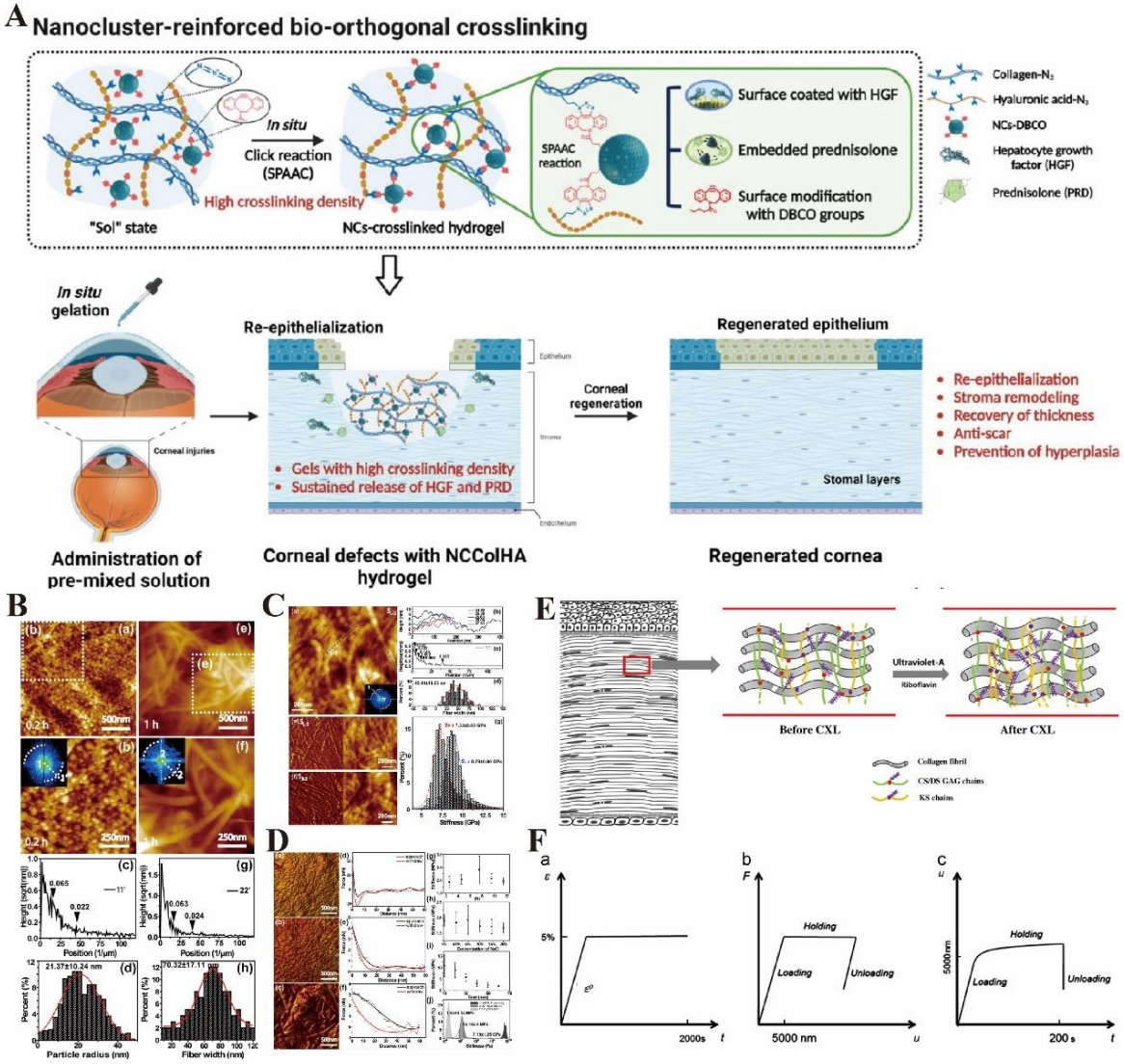

Figure 3. Biomechanical applications of nanomaterials in corneal diseases. **(A)** In Situ-forming, bioorthogonally cross-linked, nanocluster-reinforced hydrogel for the regeneration of corneal defects [51]. Reprinted with permission. Copyright 2024 American Chemical Society; **(B)** The morphologies of the corneal stroma in water and physiological buffer with different hydration time [52]. Reprinted with permission. Copyright 2014 American Chemical Society; **(C)** Periodicity and Young's modulus of the corneal stroma [52]. Reprinted with permission. Copyright 2014 American Chemical Society; **(D)** Stiffness map superimposed with the topography image of corneal stroma [52]. Reprinted with permission. Copyright 2014 American Chemical Society; **(E)** The change of collagen fibers before and after CXL (Corneal cross-linking) [53] Reprinted with permission. Copyright 2018 Elsevier; **(F)** Schematic of stress relaxation and nano-indentation loading schemes [33]. Reprinted with permission. Copyright 2013 Elsevier.

Biomimetic corneal scaffolds designed to simulate the mechanical characteristics of the cornea have overcome the limitations of traditional materials. Supramolecular hydrogels self-assemble into cornea-like stromal fibrous networks, achieving high transparency and water content that closely mirror those of the native cornea. These biomimetic properties establish an ideal biomechanical–optical platform for epithelial regeneration [54]. 3D directional poly (lactic-co-glycolic acid) (PLGA) nanofiber scaffolds

replicate the characteristic collagen alignment of corneal stroma through electrospinning technology, which significantly promotes the oriented proliferation of corneal stromal cells and the secretion of extracellular matrix [55]. Complementing these approaches, an electro-assembly strategy that couples electric field–driven molecular organization with riboflavin-mediated photo-crosslinking has been developed. This method enables the fabrication of dense collagen matrices with hierarchically patterned architectures and has demonstrated effective tissue repair in rabbit corneal defect models [56]. In addition, a Janus artificial corneal stromal substitute has been engineered, comprising a collagen-based multiscale biomimetic framework integrated with a moisture-responsive bio-adhesive coating. This design permits immediate sutureless adhesion through interfacial amidation, promoting rapid corneal epithelialization, stromal integration, and functional visual recovery [57]. Gradient cross-linked nanotube hydrogels simulate the physiological stress distribution of the cornea, reducing the incidence of post-transplant corneal stromal edema compared with traditional materials [58] (Figure 3D). Notably, an electrogenic scaffolding material with controlled fibril density and biomechanical properties has been developed to amplify endogenous wound electric currents when applied to stromal defects, thereby accelerating re-epithelialization and improving optical transparency in preclinical models [59]. In addition, carbon nanostructured materials significantly enhance the deformability resistance of corneal grafts by increasing the tangential elastic modulus by 155% [60] (Figure 3E,F). The collagen fiber reorganization observed after corneal cross-linking in Figure 3E provides a structural basis for this biomechanical reinforcement. In the context of Equations (1)–(3), an increase in corneal elastic modulus reduces pressure-induced changes in corneal curvature (ΔR) and refraction (ΔD), thereby stabilizing optical performance. Thus, the microstructural remodeling of collagen after cross-linking directly supports the mechanical-optical coupling framework described in the text.

Additionally, silicon-doped graphene quantum dots (GQDs) incorporated into hydrogel corneal lenses exhibit oxygen permeability and mechanical strength closely matching those of the native cornea. This biomimetic compatibility enhances oxygen diffusion and effectively alleviates corneal hypoxia during prolonged lens wear [61]. Therefore, researches on nanomaterials in the field of corneal injury mainly focus on two biomechanical aspects: regulating the mechanical microenvironment of the corneal stroma and constructing biomimetic corneal fiber scaffolds.

4.2. IOP regulation and glaucoma management

IOP is a critical regulation in ocular biomechanics for that elevated IOP establishes as a primary pathogenic factor in blindness disease (like glaucoma). Recent developments in nanocarrier design have focused on optimizing corneal permeability [62]. For example, thioether-functionalized hollow mesoporous organosilica nanoparticles enhance diffusion and apparent permeability across the porcine corneal barrier, improving drug delivery to the aqueous humor [63]. Similarly, nimodipine-loaded chitosan nanoparticles increase corneal permeability by 79.41% compared with free drug suspensions and achieve more pronounced and sustained intraocular pressure reduction than timolol maleate eye drops. Specially, innovations in multimodal drug delivery systems have markedly accelerated therapeutic advances in glaucoma treatment. As summarized in Figure 4, nanomaterial-based glaucoma strategies now integrate real-time sensing, pressure-responsive drug delivery, adaptive drainage regulation, and fibrosis-modulating surface design, collectively supporting sustained IOP control in a dynamic mechanical environment. For instance, wireless therapeutic contact lenses (WTCLs) equipped with

integrated flexible sensing and electrically regulated drug-eluting modules enable continuous IOP tracking and on-demand pharmacologic intervention (Figure 4A). Once IOP surpasses 21 mmHg (≈ 2.80 kPa), the embedded system can trigger electro-controlled timolol release, thereby achieving timely pressure reduction [64].

To prevent unintended drug release during physiological IOP fluctuations while enabling rapid activation under pathological pressure elevation, pressure-responsive nanomaterials should be designed with activation thresholds that lie beyond the normal fluctuation range and, where possible, incorporate hysteresis or time-gating features. Such strategies may improve the ability of these systems to discriminate transient pressure variations from sustained pathological surges. In addition, reversibility and stability under cyclic pressure loading are critical for glaucoma applications, as long-term performance depends on reproducible responsiveness during repeated mechanical stimulation [65]. Evidence from IOP-responsive sensing platforms supports this concept: platinum resistor-based sensors have demonstrated stable and repeatable outputs during cyclic pressure loading, while parylene C-protected silver nanowire sensors have shown sustained electrical stability after environmental storage and repeated mechanical challenge [66]. Although these observations derive mainly from sensing studies, they indicate that durable and reversible pressure responsiveness can, in principle, be achieved in ocular nanomaterial-based systems. The incorporation of graphene-based materials has further advanced smart contact lens technology. Owing to their high electrical conductivity and optical transparency, graphene-integrated lenses can function as field-effect transistors, intraocular pressure biosensors, and electroretinography electrodes, enabling continuous ocular monitoring with wireless data transmission while also providing electromagnetic interference shielding and resistance to dehydration [67]. Helical microrobots navigated by external magnetic fields can serve as novel intravitreal delivery vehicles that penetrate the vitreous humor to reach the retina, offering a targeted drug delivery strategy for posterior segment diseases including glaucoma. Additionally, a nanogold near-infrared (NIR) light-responsive drug delivery platform can stabilize IOP within a narrow margin of ±1.5 mmHg via dynamic feedback mechanisms [68] (Figure 4B,C).

Functionalized designs responsive to IOP fluctuations have markedly improved the postoperative ocular microenvironment and the management of refractory glaucoma. A drainage conduit composed of cross-linked hyaluronic acid (HA) nanofibers (45 μm) modulates pore size (50–100 μm) and surface charge, which can significantly reduce fibrin deposition. This adaptive design achieved an 85% medication discontinuation rate within six months after surgery [69] (Figure 4D). Porous architecture of silk fibroin (SF) scaffolds can adapt to IOP variations, improving conformity to the trabecular meshwork anatomy. To reduce the risk of filtering bleb scarring, silicone drainage valves incorporating nano-hydroxyapatite autonomously regulate aqueous outflow in response to IOP changes. To address fibrotic encapsulation, high-throughput TopoChip screening identified immunomodulatory microtopographies on poly(styrene-block-isobutylene-block-styrene) substrates that regulate myofibroblast differentiation and macrophage polarization. When applied to glaucoma shunts in rabbit models, these engineered surfaces significantly altered collagen deposition and density at the tissue–implant interface compared with smooth controls, indicating that rational surface design can attenuate the foreign body response and enhance long-term device performance [70]. Additionally, PLGA nanofiber meshes modified with RGD guide aligned fibroblast growth, significantly elevating the patency rate of aqueous humor drainage pathways [71]. Moreover, polymethyl methacrylate (PMMA)-reinforced GO drainage devices exhibit an increase in elastic modulus and compressive strength, which can substantially improve their efficacy in

IOP control [72]. These sophisticated materials enhance trabecular meshwork drainage through pressure-responsive closed-loop mechanisms while concurrently mitigating postoperative fibrosis via optimized biomechanical compatibility. This synergistic functionality highlights the potential of integrating mechanosensitive design principles with biomimetic materials to achieve personalized and long-lasting glaucoma management.

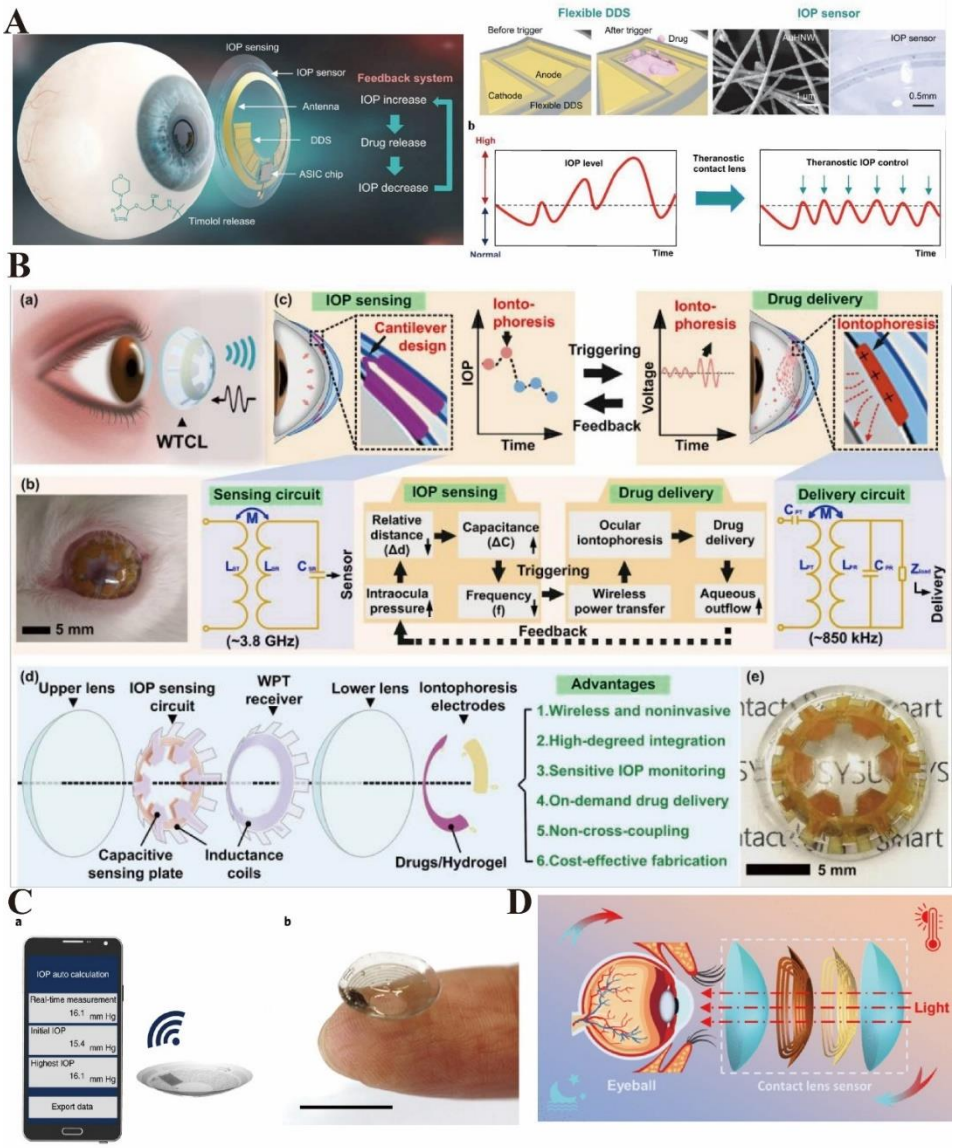

Figure 4. Biomechanical applications of nanomaterials in glaucoma and intraocular pressure regulation. **(A)** Schematic illustration of a theranostic smart contact lens for glaucoma treatment [73]; **(B)** Schematic of the WTCL for real-time and *in situ* IOP monitoring and drug administration [64]; **(C)** Schematic of the NFC-compatible smartphone communicating with the soft contact lens [74]. Reprinted with permission. Copyright 2021 Springer Nature; **(D)** 3D structure of the WMCL in the exploded view [75]. Reprinted with permission. Copyright 2024 American Chemical Society.

4.3. Application in retinal and choroidal disorders

The recurrence of retinal detachment is closely tied to vitreoretinal biomechanics combined with postoperative postural requirements of patients. Recent integration of novel hydrogels with

nanomaterial-based delivery platforms has introduced innovative approaches for treating fundus disorders. Figure 5 highlights the diverse biomechanical functions of nanomaterials in posterior segment diseases, spanning biomimetic structural support, tissue engineering, pressure-related morphological regulation, and mechanically optimized therapeutic delivery. Together, these examples underscore that effective posterior segment nanomaterials must be designed in close alignment with the local mechanical environment and tissue-specific microenvironmental demands. A prominent example is the 3E-OX hydrogel, which undergoes a liquid-to-gel transition driven by shear-thinning behavior. Its gelled state replicates the elastic modulus of the natural vitreous and offers effective support for retinal reattachment [76] (Figure 5A,B). This biomechanical compatibility reduces the need for rigorous postoperative positioning and improves patient adherence. The design of hydrogels for fundus therapy has evolved from a primary focus on safety to a holistic strategy integrating multimodal performance. This shift further unites structural control with biological activity. For instance, hydrogels exhibit ultra-low polymer content for relieving mechanical stress on the retina by adapting to retinal tensile forces [77] (Figure 5C). Likewise, hyaluronic acid nanocellulose composite networks can mimic the vitreous elastic modulus, while their shear-thinning properties accommodate dynamic ocular movements [78]. The biomimetic hydrogel crosslinked by deacetylated HA and 4-arm-polyethylene-succinimidyl-carboxymethyl ester (PESCE) holds potential as an artificial vitreous substitute. After loading the antibiotic meropenem, the drug interacts with the gel matrix via hydrogen bonding, which not only preserves the original viscoelasticity but also further enhances the storage modulus, achieving the dual optimization of antibacterial function and biomechanical performance [79]. Additionally, nanoporous oxide systems demonstrate that tuned porosity and chemical composition can significantly improve compressive strength, this will give new avenues for mechanical stability of artificial vitreous implants [80].

Posterior segment biomechanics show great potential in overcoming drug delivery challenges. Metal nanoparticle based photothermal hydrogels achieve mechanical compliance of choroidal basement membrane by tuning their elastic modulus, which effectively reduces drug clearance and sustains localized therapeutic retention [81] (Figure 5D). Notably, the pore size of the internal limiting membrane, combined with static mechanical loading, critically governs nanoparticle retention and concentration in the posterior choroid and retina. Smaller nanoparticles (20 nm) migrate and diffuse more effectively through the vitreous, enabling efficient delivery to retinal and choroidal tissues, whereas larger nanoparticles (250 nm) are cleared more rapidly (Figure 5E). Nano-delivery systems can be optimized with the above phenomenon. For instance, larger constructs, like liposomes and microspheres, can prolong intravitreal residence time, thereby extending visibility during vitrectomy [82] (Figure 5F). Bisphosphonate-based nanocomposite hydrogels exhibit pronounced shear-thinning and self-healing behavior driven by dynamic metal-ligand coordination [83]. Their storage modulus can be precisely tuned by varying metal ion species and bisphosphonate grafting density, enabling mechanical compatibility with diverse posterior segment tissues. Meanwhile, *in situ* self-assembled nanoparticles strengthen interfacial interactions between the hydrogel network and drug carriers, enabling a reversible gel–sol–gel transition under shear. This property preserves mechanical stability within the vitreous cavity while modulating drug release through a dynamic network, thereby reducing rapid clearance [84]. With the continued integration of materials science and biomechanics, fundus disease therapies are expected to become safer, more efficient, and increasingly personalized [85].

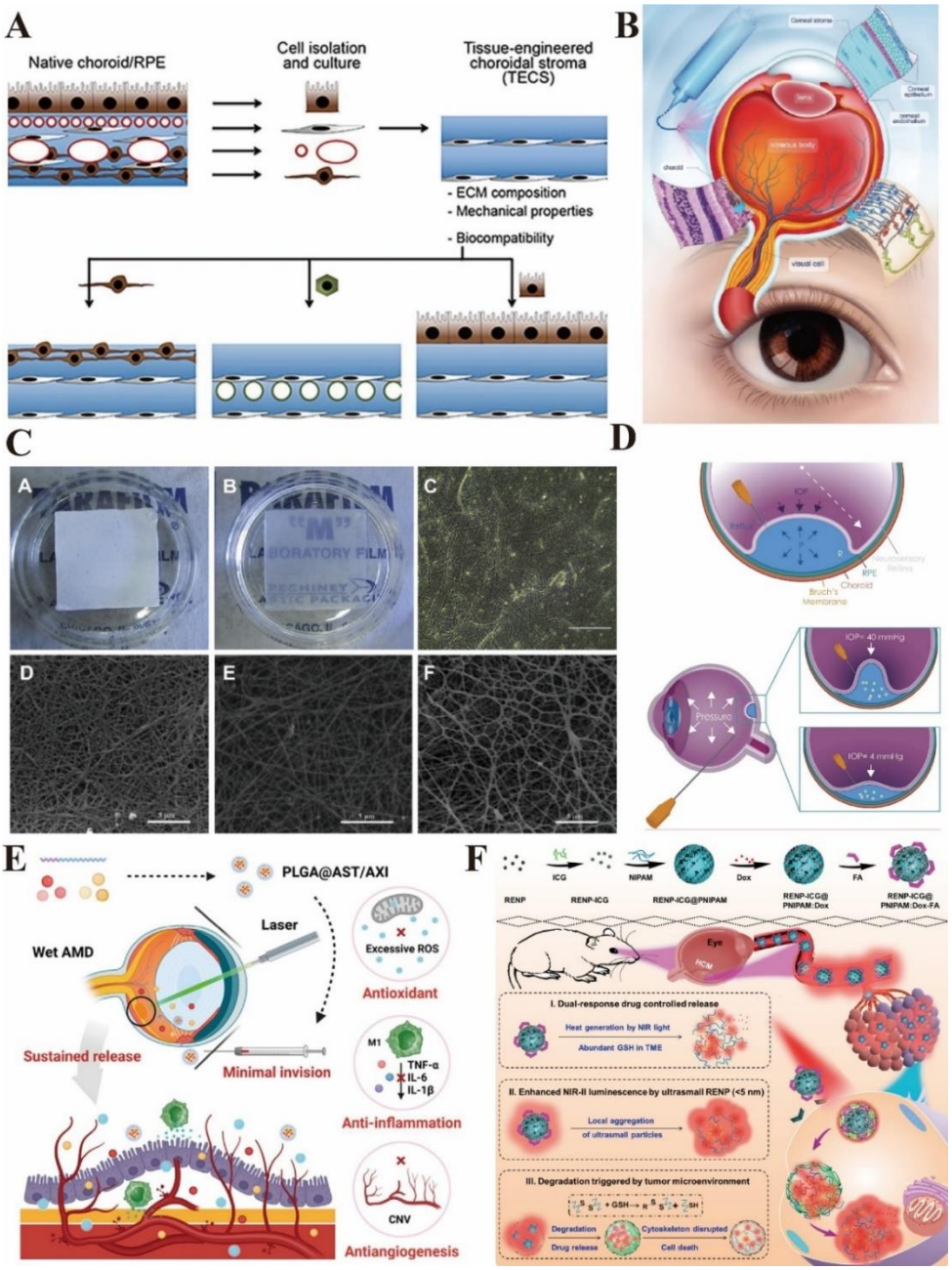

Figure 5. Biomechanical applications of nanomaterials in posterior segment diseases of the eye. **(A)** Characterization of a tissue-engineered choroid [86]. Reprinted with permission. Copyright 2018 Elsevier; **(B)** Roles of bioprinting in ophthalmology [87]; **(C)** A novel Bruch's membrane-mimetic electrospun substrate scaffold for human retinal pigment epithelium cells [88]. Reprinted with permission. Copyright 2014 Elsevier; **(D)** Effects of IOP on bleb shape. High IOP (40 mmHg) settings result in higher vertical blebs, whereas low IOP (4 mmHg) result in blebs with a shallower configuration [89]; **(E)** Schematic illustration of the processes and mechanisms of the multifunctional PLGA@AST/AXI featured with sustained drug release for treating the laser-induced mouse CNV model [90]. Reprinted with permission. Copyright 2024 American Chemical Society; **(F)** Schematic illustration of the fabrication of dual-response nanocomposites and the application in chemo-photothermal therapy for choroidal melanoma and the degradation reaction of cross-linked PNIPAM hydrogels under the tumor microenvironment (TME) [91]. Reprinted with permission. Copyright 2020 American Chemical Society.

4.4. Ocular trauma repair

Ocular trauma poses substantial clinical challenges, frequently leading to visual loss, blindness, endophthalmitis or eyeball atrophy. Recent novel progress in nanomaterial-based therapies has transformed the management of such injuries for corneal repair and regeneration. For simple corneal defects, silk fibroin/polycaprolactone nanofiber membrane adhere stably to the ocular surface and promote epithelial-stromal regeneration [92]. Meanwhile, chitosan/gelatin hydrogels loaded with induced pluripotent stem cell-derived mesenchymal stem cell (iPSC-MSC) exosomes enable sustained bioactive factor release upon thermo-responsive activation, thus markedly decrease collagen deposition and scarring in corneal alkali burn models [93,94]. The thermosensitive hyaluronic acid hydrogel (THH) rapidly forms a uniform, transparent film on the ocular surface via reversible sol–gel transition (4 ℃ to 37 ℃). The film resists blink-induced clearance and prolongs drug–epithelium contact. Owing to its shear-thinning behavior, THH remains stable under dynamic ocular conditions and serves as a biomechanically adaptive platform for controlled delivery of miRNA-24-3p loaded exosomes, thereby accelerating corneal epithelial repair and suppressing fibrosis [95]. Moreover, the combination of biomaterials with smart medical devices enables multidimensional regulation of corneal healing. In trauma-associated IOP dysregulation, nanomaterial-based smart contact lenses effectively attenuate IOP instability in alkali-injured eyes, this can preserve anterior chamber architecture. These devices integrate a nanofiber network capable of sensing IOP fluctuations and utilizing blink-induced pulsed electric fields to modulate aqueous humor outflow in real time [96]. These advances highlight the transformative role of nanotechnology in restoring function and structure after ocular trauma.

In complex ocular trauma, photosensitive organic nanoparticles enable synergistic controlled antibiotic release and photothermal effects under NIR irradiation. This dual action reduces aqueous humor production and enables bidirectional IOP regulation [85,97]. Concurrently, a transparent alginate-phenylboronic acid/polyvinyl alcohol composite hydrogel (TALPPH) allows precise hydrodynamic modulation, stabilizing vitreous cavity pressure in trauma-related retinal detachment models and promoting retinal reattachment [98]. The biomimetic polydopamine nanocomposite scaffold (GA@PDA) constructs oriented porous channels that mimic the anisotropic structure of the optic nerve via the directional ice-templating method. With a compressive modulus of approximately 33.92 kPa, which can resist the collapse of the optic nerve dura mater and provide a stable mechanical support space for axon regeneration [99]. Furthermore, thermosensitive hydrogels enable mechanical supports at physiological temperature *in situ*, this process mitigates the need for reoperation and risks of intraocular rejection [100]. Therefore, the unique biomechanical properties of nanomaterials, like temperature and photosensitivity, establish a solid foundation for developing precise, personalized, and intelligent therapeutic systems in ocular trauma [101].

5. Biomechanically-guided nanomaterial design strategies

5.1. Simulation of the mechanical microenvironment

Ocular nano-scaffolds play a crucial role in stabilizing the intraocular microenvironment by emulating the mechanical cues of the native ECM. Through this biomimetic design, they can guide and promote the directional extension and growth of neuronal axons, supporting the restoration of neural connectivity.

Moreover, such scaffolds facilitate the formation of a uniform epithelial layer by hESC-derived RPE cells, thereby reinforcing tissue integrity and maintaining the biomechanical homeostasis of ocular structures [102]. Consequently, ocular tissues acquire enhanced capacity for tissue regeneration and repair. Recent studies show that electrospun poly(ε-caprolactone) scaffolds provide topographical cues that promote aligned outgrowth of retinal ganglion cell axons, a key requirement for retinal circuit reconstruction [103]. Extending this approach, poly (glycerol sebacate)/PCL scaffolds with controlled ciliary neurotrophic factor release further enhance RGC neurite extension through biomimetic trophic support, creating a permissive microenvironment for axonal regeneration [104]. Ultrathin parylene C scaffolds have also been applied to transplant induced pluripotent stem cell–derived RPE monolayers. In age-related macular degeneration models, these scaffolds preserve hexagonal morphology, tight junction integrity, and physiological fluid transport, thereby maintaining outer blood–retinal barrier function and supporting photoreceptor survival [105]. Moreover, conductive scaffold designs, including hydrogels incorporating aligned carbon nanotubes, promote photoreceptor precursor differentiation and synaptic integration with host retinal circuits, partially restoring light responsiveness in retinal explants. Collectively, these advances highlight the capacity of multifunctional scaffolds to recapitulate both the structural and functional features of the native retinal microenvironment.

5.2. Development of dynamic responsive materials

Dynamic responsive materials can intelligently adapt to changing external conditions and intraocular microenvironments, including temperature, electromagnetic stimuli, pH variation, and specific biochemical cues [106–108]. Such adaptability is essential for accommodating disease-associated biomechanical changes, including alterations in tissue stiffness, intraocular pressure fluctuations, and ocular geometry. From a mechanobiological perspective, shear-thinning hydrogels behave as fluids under injection shear to enable minimal invasion delivery, yet rapidly recover high viscoelasticity at rest, thereby prolonging drug retention in the posterior segment while matching tissue mechanics. In parallel, biomimetic piezoelectric materials, such as PVDF films, convert ocular mechanical deformation into electrical signals that regulate extracellular matrix remodeling, offering a potential strategy for treating pathological myopia [106]. Regarding biochemical microenvironment responsiveness, smart nanocarriers leverage specific signals in pathological states for on-demand release: for instance, temperature changes at the ocular surface or intraocularly trigger sol-gel phase transitions in polymers like Poloxamer or Poly(N-isopropylacrylamide) (PNIPAM), forming *in situ* depots to resist tear clearance, concurrently, acidic pH environments, highly expressed matrix metalloproteinases (MMPs) , or elevated reactive oxygen species (ROS) levels at infection or inflammation sites trigger carrier degradation or pore size alteration for precise delivery of anti-inflammatory or antimicrobial agents, a mechanism that not only enhances bioavailability but also synergistically modulates the oxidative stress microenvironment by scavenging excess ROS (e.g., using selenium- or boronate ester-containing materials). Exogenous stimuli, including ultraviolet, visible, or near-infrared light, can further activate photosensitive polymers or photothermal nanomaterials such as gold nanorods and black phosphorus, enabling spatiotemporally controlled drug release and photothermally mediated modulation of local tissue mechanics [109]. Collectively, by emulating biological “sense-and-respond” mechanisms, dynamic responsive materials overcome the mechanical mismatch of conventional static implants and

provide adaptive, precision therapeutic strategies for complex ocular diseases, including glaucoma, keratitis, and retinopathy.

In glaucoma, however, pathological changes in the ocular mechanical microenvironment, such as increased corneal stiffness and lamina cribrosa remodeling, may alter the activation behavior and drug release profiles of mechanically responsive nanomaterials. Consequently, materials designed for normal physiological conditions may exhibit premature release, insufficient activation, or reduced responsiveness in diseased tissues. This limitation highlights the need for systems that can adapt to pathological mechanical states rather than rely on fixed response thresholds. Such adaptability may be achieved by incorporating tunable mechanical properties or stress-sensitive structures that shift activation toward higher IOP ranges, while integration with biochemical cues such as reactive oxygen species or matrix metalloproteinase activity may further enhance disease specificity. In addition, because IOP fluctuates over time in glaucoma, these materials should maintain reversible and stable performance under repeated loading-unloading cycles, with minimal fatigue and hysteresis, to support long-term reliability.

5.3. Construction of biomimetic ocular structures based on 3D bioprinting technology

3D bioprinting technology enables layer-by-layer deposition of biomaterials, allowing precise spatial reconstruction of the hierarchical architecture of native tissues. The use of decellularized extracellular matrix as a bioink has made fabrication of biomimetic corneal scaffolds feasible. For example, bioinks derived from decellularized corneal stroma combined with stem cells have been used to print transparent artificial corneas with defined lattice architectures, exhibiting fiber alignment and microenvironmental features comparable to those of native cornea [110]. A 3D vitreous model has been developed using decellularized cartilage extracellular matrix, providing vitreous cells with a microenvironment that more closely recapitulates physiological conditions. Nanomaterials further expand the capability to construct complex biological structures. By modulating material scale and interfacial properties, nanocomponents enhance scaffold mechanics, enable functionalization, and optimize optical and biological performance, thereby supporting the development of high-performance artificial ocular tissues [111]. For example, incorporation of graphene or nanoclay into hydrogel systems improves printing resolution and refines regulation of the cellular microenvironment [112]. In ocular tissue engineering, electrospun micro/nanofibrous decellularized extracellular matrix has been integrated with three-dimensional bioprinting to fabricate bioartificial corneas,where the nanoscale fibrous architecture closely mimics the ultrastructural organization of the native corneal stroma [113].

6. Limitations

Despite the considerable therapeutic potential of ocular nanomaterials, their clinical translation remains limited by several major challenges, including biosafety, long-term mechanical stability, degradation-associated property changes, and manufacturing scalability. Biosafety represents a primary concern. Due to their high surface activity and nanoscale dimensions, nanomaterials can easily penetrate ocular surface barriers, potentially leading to cytotoxicity, inflammatory responses, and systemic immune reactions [114]. For instance, QDs have been found to selectively disrupt the blood-retinal barrier (BRB) via DNA methylation. This disruption allows QDs to permeate and accumulate in the choroid, and multiple studies indicate that QDs can exacerbate retinal degenerative damage [115].

Beyond biosafety, the clinical translation of ocular nanomaterials is further limited by long-term mechanical fatigue, degradation-associated biomechanical changes, and manufacturing barriers. Because the eye is a dynamic environment exposed to blinking, ocular movements, and intraocular pressure fluctuations, nanomaterials must maintain structural integrity and mechanical compatibility under repetitive loading, as fatigue-related damage or loss of mechanical matching may compromise efficacy and induce chronic irritation, fibrosis, or secondary injury [116]. At the same time, degradation-induced changes in stiffness, viscoelasticity, and structural integrity, together with the effects of degradation byproducts, may further disrupt tissue homeostasis [117]. In addition, despite encouraging preclinical results, many nanomaterial systems still fall short of the consistency, reproducibility, and regulatory standards required for clinical use. Therefore, long-term biomechanical safety evaluation and scalable, quality-controlled manufacturing remain essential for the clinical advancement of ocular nanomaterials.

7. Conclusion

This article systematically reviews biomechanical design strategies for ocular nanomaterials. The strategies provide theoretical foundation and design principles for optimizing drug delivery efficiency, improving material biocompatibility and reducing biotoxicity in ocular. Advancing our understanding of biomechanical determinants in nanomaterial design will be essential for bridging the gap between experimental innovation and clinical applicability. Integrating biomechanical modeling with nanofabrication strategies may provide a rational framework for developing adaptive ocular therapeutics with enhanced precision and long-term stability.

Future efforts should consider the altered mechanical microenvironment in ocular diseases such as glaucoma. Elevated and fluctuating intraocular pressure, together with tissue remodeling, may significantly affect the performance of mechanically responsive nanomaterials. Designing systems that can operate across a broader pressure range and maintain stable responsiveness under dynamic loading conditions may improve their reliability in clinical settings. Approaches that incorporate tunable activation thresholds, adaptive mechanical sensing, and improved fatigue resistance are likely to be especially valuable for enhancing translational potential.

Data availability statement

No supplementary or additional data were generated in this study.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used ChatGPT only to improve language and readability. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Jie Zhang: writing—review and editing, writing—original draft; Min Li: writing—review and editing, writing—original draft; Yanming Zhu: writing—review and editing; Wenyang Xu: writing—review and editing; Yanyu Shangguan: writing—review and editing, writing—original draft; Ruoning Luo: writing—review and editing; Yanlong Bi: writing—review and editing; Guofeng Liu: writing—review and editing; Bing Li: writing—review and editing; Min Li, Yanlong Bi and Bing Li: funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no competing financial interests.

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