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Review

Exploring gellan gum-based hydrogels for regenerating human embryonic stem cells in age-related macular degeneration therapy: A literature review

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ABSTRACT

Age-related macular degeneration (AMD) is a progressive ocular disease marked by the deterioration of retinal photoreceptor cells, leading to central vision decline, predominantly affecting the elderly population worldwide. Current treatment modalities, such as anti-VEGF agents, laser therapy, and photodynamic therapy, aim to manage the condition, with emerging strategies like stem cell replacement therapy showing promise. However, challenges like immune rejection and cell survival hinder the efficacy of stem cell interventions. Regenerative medicine faces obstacles in maximizing stem cell potential due to limitations in mimicking the dynamic cues of the extracellular matrix (ECM) crucial for guiding stem cell behaviour. Innovative biomaterials like gellan gum hydrogels offer tailored microenvironments conducive to enhancing stem cell culture efficacy and tissue regeneration. Gellan gum-based hydrogels, renowned for biocompatibility and customizable mechanical properties, provide crucial support for cell viability, differentiation, and controlled release of therapeutic factors, making them an ideal platform for culturing human embryonic stem cells (hESCs). These hydrogels mimic native tissue mechanics, promoting optimal hESC differentiation while minimizing immune responses and facilitating localized delivery. This review explores the potential of Gellan Gum-Based Hydrogels in regenerative AMD therapy, emphasizing their role in enhancing hESC regeneration and addressing current status, treatment limitations, and future directions.

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Abbreviations: AMD, Age-related macular degeneration; hESCs, Human Embryonic Stem Cells; iPSCs, Induced Pluripotent Stem Cells; RPE, Retinal Pigment Epithelium; hESC-RPE, Human Embryonic Stem Cell-Derived RPE Cell; RSPC, Retinal Stem-Progenitor Cell; hiPSCs, Human Induced Pluripotent Stem Cells; RGC, Retinal Ganglion Cell; ESCs, Embryonic Stem Cells; RPC, Retinal Progenitor Cell; VEGF, Vascular Endothelial Growth Factor; 3D, Three-Dimensional.

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1. Introduction

Age-related macular degeneration (AMD) ranks prominently among the primary contributors to global visual impairment. This condition shares the stage with other ocular disorders such as glaucoma, cataracts, and diabetic retinopathy [1]. Within this landscape, AMD emerges as a substantial cause of blindness on a global scale, particularly affecting the elderly population [2]. Presenting as a progressive optic neuropathy centred around the macula, AMD triggers a gradual decline in central vision among the aged [2].

The worldwide impact of AMD is staggering, with approximately 200 million individuals grappling with its effects, rendering it a prevalent source of blindness in developed nations [3]. As the demographic landscape experiences an expansion in the ageing population, there is a pronounced escalation in the prevalence of AMD. Projections put forth highlight the potential for a substantial increase in the count of individuals affected by AMD, reaching an approximate tally of 300 million by the year 2040 [3]. The consequences of this escalating prevalence extend beyond health implications to significant economic and social ramifications [4].

The pathogenesis of AMD primarily arises from the progressive deterioration of retinal photoreceptor cells, resulting in the eventual impairment of central visual perception, visual distortion, and reduced visual acuity [5]. Situated centrally within the retina, the macula constitutes a pivotal anatomical element characterized by a dense aggregation of photoreceptor cells [6]. This intricate assembly establishes a localized domain of heightened light interception, facilitating the efficient capture of an extensive spectrum of incoming photons within a spatially confined retinal expanse. Late-stage visual deterioration in AMD primarily arises due to two processes: neovascular (referred to as wet AMD) and geographic atrophy (termed late dry AMD) [7].

In neovascular AMD, choroidal neovascularization breaches the neural retina, causing fluid, lipid, and blood leakage, ultimately leading to fibrous scarring [7]. Conversely, geographic atrophy presents as a gradual degeneration characterized by progressive atrophy impacting the retinal pigment epithelium (RPE), choriocapillaris, and photoreceptor cells [8]. The progressive accumulation of injurious effects directed at the RPE, Bruch's membrane, and choriocapillaris contributes to their collective impairment, ultimately leading to functional deficiencies and subsequent degeneration of RPE cells [9]. This complex sequence of interrelated processes initiates the progressive deterioration of the superjacent photoreceptor cell layer, thereby playing a contributory role in the advancement of geographic atrophy. Consequently, this intricate series of events leads to subsequent visual impairment [10]. In light of these intricate underlying mechanisms, exploring therapeutic interventions that target these processes offers a promising avenue for addressing the progression of geographic atrophy and mitigating resultant visual impairment.

As seen in Fig. 1, treatments for AMD involve anti-VEGF therapy (Bevacizumab, Ranibizumab, Aflibercept, Conbercept), photodynamic therapy, and laser therapy for wet AMD, while topical agents

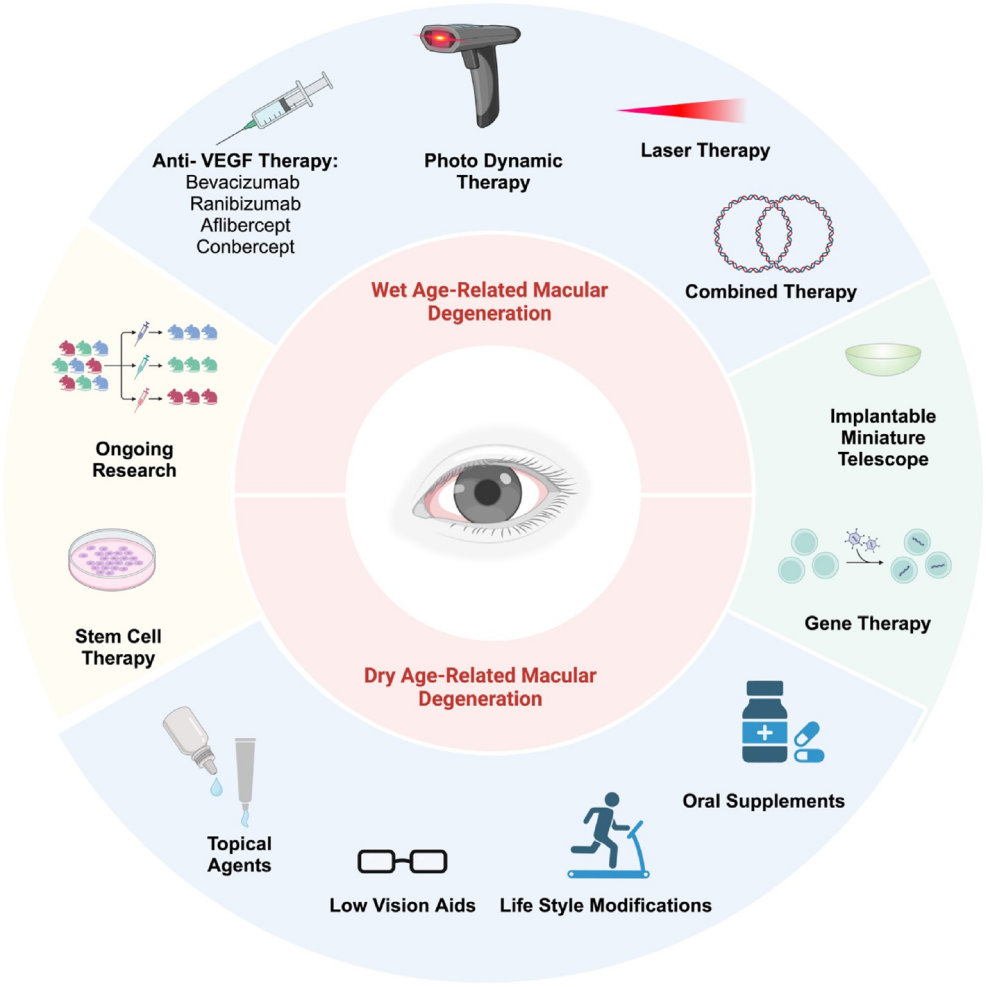

Fig. 1. Treatment options for Age-Related Macular Degeneration.

and dietary antioxidants are commonly used for dry AMD. It's important to note that these treatment modalities are not limited to the ones mentioned here, as ongoing research continues to explore new therapeutic options and combinations for managing both forms of AMD [11].

Table 1 compares the advantages and disadvantages of current treatment approaches for AMD. However, these treatments have limitations. For instance, anti-VEGF therapy requires regular injections and can cause side effects, while laser surgery may not be effective for everyone and may necessitate long-term use. These challenges underscore the need for innovative approaches like stem cell therapy. Stem cell therapy holds promise in overcoming these limitations by offering a potential long-term solution. By replacing damaged retinal cells with healthy ones, stem cell therapy could provide sustained improvement in vision without the need for frequent injections or ongoing treatment. This approach addresses the root cause of AMD and has the potential to restore vision in a more natural and lasting way, making it an effective strategy for combating the disadvantages associated with current treatment methods [12]. Additionally, these treatments mainly alleviate symptoms and do not address the root causes of AMD [13].

A significant advancement in tackling AMD revolves around the substitution of nonviable or expired retinal ganglion cells with viable counterparts, a strategy substantiated to rescue diminishing photoreceptor populations and enhance visual capabilities. This approach has undergone validation via experimentation utilizing animal models characterized by retinal degeneration. The demonstrated efficacy suggests its potential applicability to individuals suffering from AMD [24]. Remarkable progress has been made in the methodology of deriving retinal ganglion cells from human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). This advancement has culminated in the establishment of an expansive and virtually limitless reservoir, offering a promising avenue for replenishing depleted RGC populations [25]. These regenerated cells have showcased their competence to seamlessly integrate into the deteriorating retinal structure, giving rise to enhancements in both structural morphology and functional attributes [26]. Of particular significance is the observation that, despite the intrinsic challenges inherent in acquiring samples of RGCs from living patients before their demise, the human retina presents itself as a favourable physiological entity conducive to the application of modern cell-based therapeutic techniques [27].

Stem cell-based therapies present an opportunity to overcome these challenges by potentially replacing damaged cells with healthy ones, offering a more comprehensive and regenerative approach [28]. However, certain challenges must be surmounted in this endeavour. These challenges encompass intricate facets such as the intricate process of inducing stem cell differentiation into fully operational retinal cells, guaranteeing their viability after transplantation, and effectively managing potential immune reactions [29]. Balancing the benefits and challenges of stem cell-based therapies is crucial for realizing their full potential in

Table 1
Pros and cons of current therapies for AMD.

Treatment Method	Status	Advantages	Disadvantages	AMD Type	References
Low Vision Aids	Established	Improves quality of life by enhancing remaining vision	Does not restore lost vision	Both	[14,15]
Anti-VEGF Therapy	Established	Effective in reducing vision loss, can improve vision in some cases	Requires regular injections into the eye, which may cause side effects such as increased eye pressure or inflammation.	Wet AMD	[16]
Photodynamic Therapy	Established	Can slow the progression of vision loss and stabilize vision in certain cases.	Can cause side effects such as temporary vision changes, and requires multiple treatments.	Wet AMD	[17]
Laser Surgery	Established	Can reduce the risk of severe vision loss, and can be done on an outpatient basis.	Can cause damage to the surrounding retina, and may not be effective for all patients.	Wet AMD	[18]
Implantable Miniature Telescope	Established	Improves vision in some patients with end-stage AMD in both eyes.	Requires surgery and rehabilitation, is not suitable for all patients, and can cause complications such as glare and halos.	Both	[19]
Stem Cell Therapy	Experimental	Potential to restore vision by replacing damaged cells in the retina.	Safety and efficacy not fully established may require immunosuppressive drugs.	Both	[20]
Gene Therapy	Experimental	Potential to slow the progression of AMD by delivering genes that reduce inflammation or promote the growth of healthy blood vessels	Long-term effects are unknown and require further research and development.	Both	[21]
Lifestyle Changes	Established	Low-cost, low risk	Limited effectiveness in advanced stages	Dry AMD	[22]
Vitamin Supplements	Established	Slows progression in some cases	Not effective for everyone, may require long-term use	Dry AMD	[23]

revolutionizing AMD treatment. The challenges in stem cell culture for regenerative medicine include maintaining cell viability and survival due to environmental sensitivity, achieving consistent cell proliferation while maintaining stemness properties, controlling differentiation towards desired lineages, preventing genomic instability, addressing immunogenicity and immune rejection, navigating ethical and legal considerations, managing scalability and cost issues, and achieving functional maturation and integration of stem cell-derived tissues into host tissues [30,31]. Fig. 2 illustrates these challenges. Furthermore, a lack of biomaterials that adequately mimic the extracellular matrix (ECM) can lead to issues such as limited cell adhesion, improper signalling, and poor tissue integration, hindering the success of regenerative therapies. Overcoming these hurdles requires interdisciplinary collaboration and ongoing research to develop biomaterials that effectively support stem cell growth, differentiation, and tissue integration.

The utilization of hydrogels presents a promising avenue in the realm of regenerating RGCs from stem cells [32]. Hydrogels serve as a three-dimensional [3D] structural scaffold, offering support for the proliferation, differentiation, and seamless incorporation of

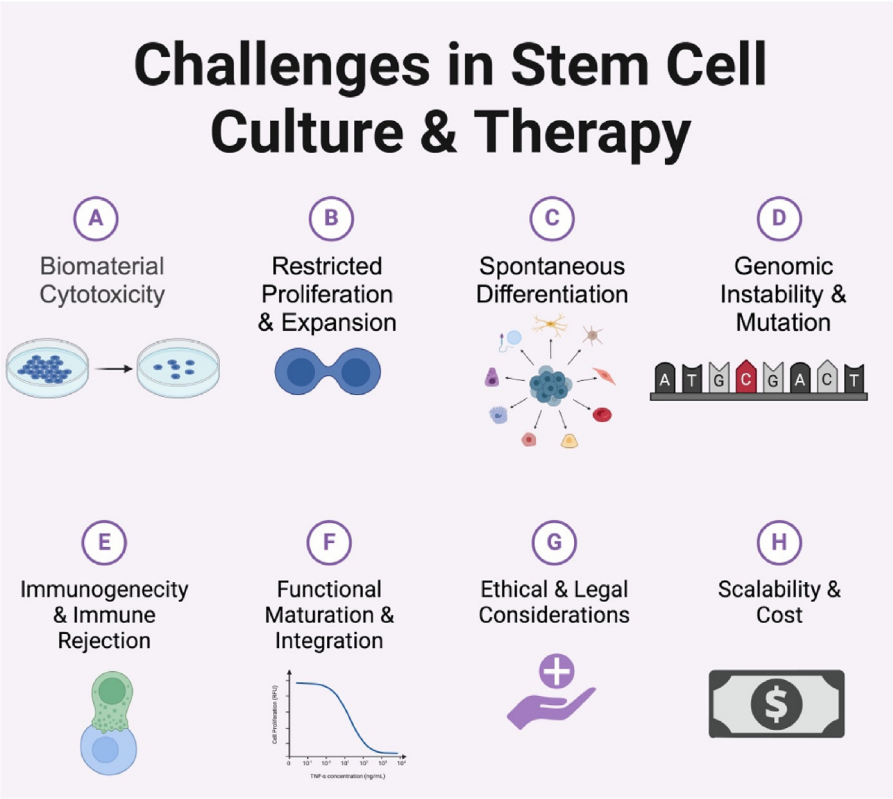

Fig. 2. Multifaceted challenges encountered in stem cell culture for Regenerative Medicine.

stem cell-derived RGCs within the retinal milieu [33]. An intriguing yet relatively unexplored candidate in this context is the utilization of gellan-gum hydrogels, renowned for their biocompatibility and tunable mechanical properties [34]. Additional biomaterials, namely alginate, chitosan, and silk fibroin, have undergone scientific exploration as potential hydrogel matrices in the context of stem cell-centred retinal regeneration endeavours [35–37]. The innate biocompatibility and customizable characteristics of these hydrogels offer the potential to create microenvironments conducive to the development and engraftment of RGCs, holding substantial promise for advancing therapies aimed at restoring visual function in conditions like retinal degeneration [38].

Table 2 highlights the favourable attributes of gellan gum in tissue engineering when compared to other synthetic biopolymers and its superiority over other natural polymers. Gellan gum hydrogels also boast high biocompatibility, with low cytotoxicity and immunogenicity levels, rendering them suitable for diverse biomedical applications. Gellan gum stands out due to its versatile properties, including biocompatibility, tunable mechanical properties, porous structure, thermo-reversible gelation, shear-thinning

Table 2
Favorable properties of gellan gum in tissue engineering.

Properties	Gellan Gum Based Hydrogels	Other Hydrogels	Reference
Mechanical Properties	Tunable stiffness and elasticity, mimicking natural tissues and extracellular matrix	Varied control over mechanical properties is observed among different biomaterials. For instance, silk fibroin typically exhibits high tensile strength, while sodium alginate tends to have lower mechanical strength.	[36,39]
Shear-Thinning Behavior	Exhibits shear-thinning behaviour, facilitating injection, facilitating minimally invasive injection.	Depends on the specific formulation, for example, It is low in κ-carrageenan and sodium alginate and variable in synthetic polymers like Polyethylene Glycol (PEG).	[39,40]
Porous Structure	The porosity of gellan gum can be adjusted and facilitates nutrient and oxygen diffusion, cell migration	In contrast, silk fibroin, gliadin, and Poly (lactic-co-glycolic acid) typically exhibit high porosity. The porosity of sodium alginate varies depending on other components present in the formulation.	[39,41]
Thermo-Reversible Behavior	Undergoes sol-gel transition with temperature change. Enables cell incorporation without compromising viability.	The thermo-reversible behaviour is not universally exhibited across all materials but rather depends on specific formulations. Materials such as silk fibroin, chitin, and pectin do not exhibit thermo-reversible behaviour.	[34,42]
Tunability	Easily tunable through adjustments in concentration, crosslinking density, and composition. Enables precise control over hydrogel properties.	Tunability may be limited, as observed in silk fibroin, chitosan, Polyethylene Glycol, and sodium alginate, which often necessitate more intricate procedures such as crosslinking to achieve desired modifications.	[39,43]
Fabrication & Manipulation	Can be fabricated using simple techniques such as casting or molding. Allows for straightforward and cost-effective production	Fabrication methods vary and can be complex, contingent upon the hydrogel type and its intended application. For instance, Silk Fibroin necessitates electrospinning, while chitosan may require precipitation for gel formation and Poly (lactic-co-glycolic acid) fabrication involves emulsion and solvent casting techniques.	[40–44]
Biocompatibility	Natural origin minimizes the risk of cytotoxicity and immunogenicity	In general, natural biomaterials tend to be more compatible than synthetic counterparts; however, biomaterials such as sodium alginate may necessitate surface modification for enhanced compatibility.	[34,45]
Biodegradability	Biodegradable, gradually replaced by new tissue and supports tissue regeneration.	It varies; for instance, some materials like Polyethylene Glycol (PEG) may necessitate enzymatic degradation.	[40–45]
Biofunctionalization	Can be functionalized with bioactive molecules. Tailors hydrogel for specific cellular responses	Direct biofunctionalization of synthetic polymers like Poly (lactic-co-glycolic acid) compared to naturally derived polymers like gellan gum, silk fibroin, and chitosan may present challenges	[34,46]
Sterilizability	Compatible with various sterilization methods. Ensures safety and sterility for clinical use	Synthetic polymers generally maintain their structural integrity, whereas natural polymers such as silk fibroin, sodium alginate, and chitosan may undergo degradation when subjected to certain sterilization techniques.	[35,47]
Stability	Wide pH and temperature range	The stability fluctuates depending on the composition. Sodium alginate has limited stability, while chitosan demonstrates moderate stability. Synthetic polymers like Polyethylene Glycol exhibit variability in stability.	[39–49]

behaviour, biodegradability, biofunctionalization capability, sterilizability, versatility, and commercial availability [34]. Additionally, their thermo-reversible nature enables straightforward fabrication and manipulation, particularly beneficial for encapsulating sensitive bioactive molecules or cells while maintaining viability. Notably, gellan gum's ability to mimic the ECM of natural tissues makes it an ideal candidate for supporting cellular activities in tissue regeneration [35–37]. Furthermore, its biofunctionalization potential allows for the incorporation of bioactive molecules, such as growth factors or cell-adhesive ligands, essential for modulating cellular behaviour and promoting tissue regeneration. This capability is crucial for creating biomimetic environments in cell culture and tissue engineering applications, where precise control over cellular responses is paramount for successful tissue regeneration. Compared to synthetic biopolymers like polyethylene glycol (PEG) and natural polymers such as alginate or collagen, gellan gum offers a unique combination of properties that make it highly suitable for various tissue engineering strategies, highlighting its promising role in advancing regenerative medicine. In comparison to other hydrogels, gellan gum hydrogels offer distinct advantages that set them apart in various applications [34–38].

2. Gellan-gum-based hydrogels

Gellan gum, distinguished for its pronounced biocompatibility and multifaceted properties, holds a prominent position as a biomaterial of significance within the spheres of tissue engineering and regenerative medicine [50].

Gellan gum exhibits notable characteristics that make it highly suitable for the formulation of hydrogels, establishing it as a favoured biomaterial in the domain of tissue engineering and regenerative medicine [51]. The gelation mechanism of gellan gum is of scientific interest due to its capacity to undergo a sol-to-gel transition in response to variations in temperature, pH, or ion concentration [52]. This dynamic responsiveness allows for controlled and customizable gel formation, offering a precise tuning of hydrogel characteristics [53].

Mechanically, gellan gum hydrogels exhibit a range of stiffness levels, owing to their tunable gelation conditions. This adaptability enables the creation of hydrogel matrices with mechanical properties akin to various tissues, supporting cellular adhesion, migration, and proliferation [54].

Crucially, gellan gum's biocompatibility extends to its capacity for cell encapsulation and cultivation within the hydrogel matrix [55,56]. The hydrophilic nature of gellan gum fosters an aqueous environment conducive to cell viability, and its non-toxicity ensures minimal interference with cellular behaviour [57]. These attributes facilitate the encapsulation and cultivation of various cell types, fostering their growth, differentiation, and tissue-like organization within the hydrogel scaffold [58].

In the interim period, gellan gum has demonstrated remarkable attributes in terms of biocompatibility and biodegradability. In the realm of retinal bioengineering, gellan gum has found utility in the context of endothelial cell sheet grafts, resulting in favourable outcomes within in vivo settings [59]. Gellan gum exhibits a range of compelling attributes that render it a well-suited candidate for utilization in tissue engineering. These attributes comprise pronounced non-cytotoxic characteristics, noteworthy biocompatibility, structural analogies to endogenous glycosaminoglycans, facilitation of processing under mild conditions, and mechanical attributes that closely parallel the elastic moduli observed in conventional tissue matrices [60].

Gellan gum-based hydrogels have garnered notable attention within the realm of biomedical research due to their modifiable characteristics and prospective utility in the domains of tissue engineering and regenerative medicine.

Gellan gum has been investigated as a scaffold conducive to cellular immobilization and proliferation across a range of research endeavours. Notably, gellan gum showcases a pivotal attribute in the form of its capability to create hydrogel matrices. These hydrogels establish an essential 3D milieu, offering robust support for cellular entities.

In contrast to other hydrogels, gellan gum offers distinct advantages that make it a promising candidate for various biomedical applications. For instance, Han et al. (2020)demonstrated that gellan gum hydrogels possess tunable mechanical properties, enabling precise control over stiffness and elasticity, crucial for mimicking native tissue environments [39]. This feature is particularly advantageous in tissue engineering applications where mechanical cues play a vital role in cell behaviour and tissue development. Additionally, the thermo-reversible nature of gellan gum, as highlighted by Alharbi., (2024), facilitates easy fabrication and manipulation, especially for encapsulating sensitive bioactive molecules, drugs or cells while preserving their viability [61]. Furthermore, studies by Vuorenpää et al. (2024) have emphasized the biocompatibility of gellan gum hydrogels, with low cytotoxicity and immunogenicity levels, rendering them suitable for biomedical applications without inducing adverse reactions [62]. Moreover, the stability of gellan gum across a wide range of pH and temperature conditions, as discussed by Stachowiak et al. [2023], enhances its versatility in diverse environments, further broadening its applicability [48]. Overall, the combination of mechanical tunability, biocompatibility, ease of fabrication, and stability positions gellan gum hydrogels as a superior choice compared to many other hydrogel materials for various biomedical applications, as highlighted in the aforementioned studies.

The remarkable properties of gellan gum have spurred significant research interest in this biomaterial. Over recent years, a plethora of gellan-based materials have been developed using diverse fabrication techniques, This breadth of potential applications highlights the multifaceted utility of gellan gum and highlights its significance in advancing diverse field of regenerative medicine [63].

Creating tissue within a 3D microenvironment presents a formidable task, requiring an appropriate biomaterial scaffold to support cell attachment, spreading, proliferation, migration, and differentiation for effective tissue regeneration or organ reconstruction. Polysaccharides, as natural polymers, offer significant promise in crafting a three-dimensional artificial ECM, typically in the form of hydrogels, through diverse processing methods and conditions [64].

Injectable gellan gum hydrogels offer a promising avenue in tissue engineering [65]. These hydrogels possess shear-thinning properties, enabling easy injection and subsequent gel formation at the target site. In a research study by Gantar A. et al., bioactive-glass-reinforced gellan-gum spongy-like hydrogels were introduced. This material showcases promise for potential utilization as scaffolds within the domain of bone tissue engineering. The incorporation of bioactive glass particles led to enhancements in both the material's microstructure and mechanical properties. Notably, human-adipose-derived stem cells exhibited successful adhesion, spreading, and sustained viability within the gellan-gum spongy-like hydrogels fortified with bioactive glass. This outcome bears significance for their potential utilization in bone-tissue engineering [66].

In another study conducted in 2010 by Oliveira, João T., and colleagues, an examination was undertaken to assess the suitability of gellan gum hydrogels as injectable systems. This property facilitates the controlled release and prolonged retention of

chondrocytes, specialized cells crucial for cartilage maintenance. Furthermore, these hydrogels have exhibited a pronounced capacity to sustain chondrocyte cell viability, ensuring the survival and metabolic activity of these cells within the gel matrix. Notably, these hydrogels also possess the capability to induce the generation of extracellular matrix, an essential component of cartilaginous tissue that contributes to its structural integrity and functionality. Dynamic mechanical analysis indicated sustained gel stability over the experimental period, even as mechanical properties gradually decreased, in line with weight measurements. In summary, this investigation establishes the feasibility of gellan gum hydrogels fabricated through uncomplicated methodologies, showcasing their suitability for noninvasive injectable uses. These applications hold particular significance in the advancement of functional constructs for engineered cartilage tissue, thereby contributing to the field of regenerative medicine [67].

3. Stem cell therapy in age-related macular degeneration

Stem cell therapies have arisen as a prospective avenue within the therapeutic landscape for addressing AMD [68]. These therapeutic approaches are directed towards leveraging the regenerative capabilities of stem cells to reinstate compromised retinal cells. The overarching aim is to maintain or enhance visual function through these interventions [68].

Unlike some tissues in the body, the retina has limited regenerative capacity, and once damaged, it does not regenerate fully on its own. Stem cells can be cultured on biomaterials that mimic the retinal microenvironment, allowing them to differentiate into RPE cells or photoreceptor cells. By carefully controlling the culture conditions and biomaterial properties, stem cells can be guided to become functional RPE or photoreceptor cells [69]. Once these cells are generated, they can be transplanted into the damaged retina, where they integrate and potentially restore vision by replacing lost or dysfunctional cells. This approach, as seen in Fig. 3, holds promise for treating AMD by replacing damaged cells in the retina and restoring visual function. However, further research is needed to optimize the differentiation and integration of stem cell-derived cells into the retina for safe and effective treatment.

Diverse categories of stem cells have been systematically investigated in the context of AMD treatment, each characterized by unique mechanisms of action [69].

3.1. Embryonic stem cells (ESCs)

Embryonic stem cells are characterized by their pluripotent nature, signifying their inherent ability to undergo differentiation into a diverse range of distinct cell lineages, including various retinal cell phenotypes [70]. In the realm of AMD, empirical evidence has demonstrated the inherent capacity of ESCs to undergo orchestrated differentiation processes, culminating in the generation of RPE cells. The distinctiveness of these specialized RPE cells is attributed to their fundamental responsibility in upholding the holistic functionality of retinal photoreceptors, thus making a substantial contribution to the preservation of retinal homeostasis [71]. These engineered RPE cells can then be transplanted into the subretinal space to replace dysfunctional RPE cells and support photoreceptor survival [72].

3.2. Induced pluripotent stem cells (iPSCs)

iPSCs represent a class of somatic cells that have undergone a process of reprogramming to reacquire pluripotent characteristics akin to ESCs [73]. iPSCs can be derived through reprogramming a patient's somatic cells, thereby imbuing them with pluripotent capabilities. This approach offers the advantage of minimizing the potential for immune rejection since the resulting iPSCs retain the genetic identity of the individual from whom the somatic cells were obtained [74]. Similar to ESCs, iPSCs also possess the capability to undergo differentiation into RPE cells or various other cell types within the retina. This process of differentiation possesses a substantial capacity for prospective applications within transplantation therapies targeted at ameliorating retinal degenerative

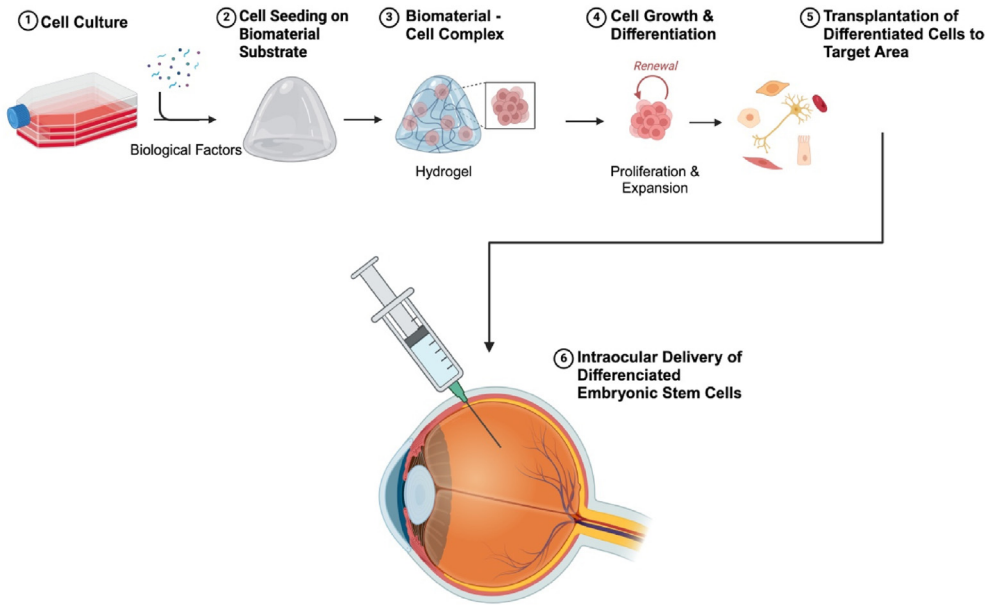

Fig. 3. Stem cell therapy using hydrogels.

disorders [75]. They offer personalized treatment potential and have shown promise in preclinical studies for AMD therapy [76,77].

3.3. Mesenchymal stem cells (MSCs)

MSCs are a class of pluripotent stem cells possessing the capacity to differentiate into a variety of cell lineages. These cells can be derived from diverse reservoirs, including bone marrow and adipose tissue [78]. These compounds exhibit immunomodulatory and anti-inflammatory characteristics, which exhibit promising therapeutic implications within the distinctive microenvironment associated with AMD [78]. MSCs possess the ability to secrete bioactive factors that exert a multifaceted impact on the retinal microenvironment. These secreted factors play a pivotal role in fostering the survival of retinal cells, orchestrating the suppression of inflammatory processes, and facilitating the augmentation of angiogenesis. This inherent biological activity holds significant potential in impeding the advancement of retinal diseases, thereby contributing to the preservation of visual integrity [79,80].

3.4. Retinal Progenitor Cells (RPCs)

RPCs are a class of stem cells that exhibit lineage commitment and are situated within the developing retina [81]. These cells possess the inherent capacity for differentiation into distinct retinal cell lineages, encompassing specialized types such as photoreceptor cells and RPE cells [81]. The objective of introducing Retinal Progenitor Cells into the subretinal space is to initiate the replacement of impaired or absent retinal cells, thereby fostering the potential restoration of visual functionality [82].

The efficacious mechanisms driving the potency of stem cell therapies within the framework of AMD encompass distinct modalities. These modalities are prominently characterized by cell replacement, paracrine effects, and immunomodulation [83].

Stem cells exhibit the capacity to serve as replacements for impaired or deteriorated retinal cells, which encompass photoreceptors and RPE cells. This phenomenon holds the potential to significantly enhance retinal function through the integration of functional stem cell-derived counterparts into the damaged retinal tissue [84]. Stem cells are known to excrete a diverse array of growth factors, cytokines, and various bioactive molecules, collectively contributing to the establishment of a conducive microenvironment [85]. These factors possess the capacity to facilitate cellular survival, mitigate inflammatory processes, and augment angiogenesis. As a result, they hold the potential to confer advantageous outcomes to the compromised retinal microenvironment [85]. Certain types of stem cells, such as MSCs, exhibit immunomodulatory attributes characterized by their ability to regulate immune reactions and mitigate inflammatory processes within the retinal tissue [86].

While stem cell therapies for AMD hold significant promise, challenges remain in terms of optimizing differentiation protocols, ensuring cell integration, and long-term safety [87]. Ongoing clinical trials are currently underway with the primary objective of evaluating the safety and efficacy of these therapeutic interventions. The ultimate aim of these trials is to furnish efficacious treatment modalities that can effectively attenuate or even reverse the progression of visual impairment observed in patients afflicted by AMD [87].

4. Challenges and concerns associated with stem cell transplantation in the eye

The application of stem cell transplantation within the ocular context demonstrates substantial promise in addressing a spectrum of ocular pathologies. However, this avenue is concomitant with a series of intricate challenges and considerations that warrant meticulous attention to ensure favourable therapeutic outcomes. Of particular significance are two primary challenges: the phenomena of immune rejection, where the recipient's immune system targets and responds against transplanted cells and the viability of transplanted cells within the ocular microenvironment. Effective resolution of these challenges is pivotal for the accomplishment of successful therapeutic interventions.

4.1. Immune rejection

Transplanted cells, especially those derived from allogeneic sources, can trigger immune responses in the recipient's body [88]. The ocular environment, while generally categorized as immune-privileged, exhibits a nuanced immunological status. Instances of immune rejection can manifest upon the introduction of foreign cells, indicating that the eye's immune privilege is not absolute. Notably, immune-responsive entities like T cells and macrophages possess the capability to discern and mount an immune response against transplanted cells. Consequently, this immune recognition and subsequent attack can culminate in the deterioration of the transplanted cells, potentially compromising the intended therapeutic outcomes [89]. To address immune rejection, researchers are exploring several strategies, including using autologous cells or generating iPSCs from the patient's cells [90].

4.2. Cell survival and integration

For enduring therapeutic benefits over an extended timeframe, transplanted stem cells must demonstrate persistent viability and effective integration into the recipient tissue [91]. Transplanted cells within the retinal microenvironment often encounter a challenging milieu characterized by inflammation, oxidative stress, and mechanical strain stemming from the transplantation process [92]. The constrained viability demonstrated by transplanted cells could potentially compromise the efficacy of therapeutic interventions [93]. Scientists are actively engaged in the advancement of techniques aimed at enhancing cellular survival and integration. Among these strategies, the utilization of biomaterials, particularly hydrogels, stands out as a promising avenue. Hydrogels offer the dual benefits of furnishing mechanical reinforcement and establishing a meticulously regulated milieu, thus fostering an environment conducive to cellular proliferation and sustenance [94]. Preconditioning cells in vitro before transplantation to enhance their stress tolerance and adaptability to the host environment is another strategy [95]. Moreover, optimizing the timing of transplantation and methodologies can exert a notable influence on both the integration and viability of the engrafted cells [96].

4.3. Tumorigenicity and differentiation control

Transplanted stem cells possess the inherent capacity to initiate tumorigenesis when subjected to unregulated proliferation [97]. In certain instances, the transplantation of pluripotent stem cells may give rise to differentiation processes yielding unintended cellular phenotypes, thereby engendering outcomes that are contrary to the intended therapeutic goals [98]. The mitigation of these risks demands meticulous management to safeguard patient well-being. Stringent quality control measures, comprehensive profiling of engrafted cells, and meticulous differentiation protocols assume pivotal roles in countering the threats associated with tumorigenic potential and incongruous differentiation pathways.

4.4. Long-term effects and monitoring

Monitoring the long-term effects of stem cell transplantation is challenging [99]. The persistent therapeutic outcomes, prospective adverse events, and plausible complexities that may arise over extended periods necessitate meticulous investigation [100]. Sustained surveillance of patients over extended periods and continual vigilance over their ocular well-being play an indispensable role in identifying potential untoward consequences or alterations in visual capabilities [101].

5. Regenerating hESCs in AMD therapy

The justification for incorporating hESCs into the treatment of AMD is rooted in their distinctive pluripotent characteristics and their extraordinary capability to transform into a diverse array of specialized cell types, including those specific to the retina [102]. This pluripotency makes hESCs a promising resource for generating functional replacement cells for the damaged retinal tissue in AMD.

5.1. Pluripotency

hESCs originate from embryos in their early developmental stages and exhibit pluripotent characteristics. This inherent pluripotency signifies their remarkable capability to differentiate into diverse cell types encompassing the entire spectrum of the human body's cellular composition [103]. This attribute presents an unparalleled opportunity to cultivate an extensive spectrum of cell types essential for the advancement of retinal tissue engineering. These encompass RPE cells, photoreceptors, and various other subtypes of retinal cells [104].

5.2. Retinal cell differentiation

Scientists have formulated intricate protocols aimed at directing the differentiation of hESCs into various lineages of retinal cells [105]. By emulating the intrinsic developmental cues inherent to retinal formation, hESCs can be guided through a directed differentiation process to yield RPE cells, photoreceptors, and various other specialized cell types found within the retina [106]. These specialized cells hold the potential to serve as substitutes for impaired or deteriorated cells in the retina, thereby facilitating the restoration of functionality and the recovery of vision.

5.3. Disease modeling and drug screening

Beyond cell replacement, hESCs can be used to model AMD and study disease mechanisms in a controlled laboratory setting. This enables scientists to better understand the disease progression, identify potential drug targets, and test the efficacy of new therapeutic interventions [107]. Moreover, hESCs offer a platform for screening potential drugs and treatments for their ability to rescue retinal cell function and survival, aiding in the development of novel AMD therapies [108].

5.4. Standardized cell sources

hESCs present a standardized and replicable reservoir of retinal cells. This uniformity holds paramount importance in the pursuit of formulating treatments that are both impactful and dependable, applicable across a diverse spectrum of patients afflicted with AMD [109].

5.5. Pioneering clinical trials

Clinical trials centred around the transplantation of hESC-derived RPE cells for AMD have exhibited encouraging outcomes concerning safety and preliminary effectiveness. These positive findings provide impetus for the continued investigation and advancement of hESC-based therapeutic interventions for addressing the challenges posed by AMD [110].

5.6. Optimal differentiation and maturation

The capacity to induce the differentiation of hESCs into retinal cells holds the promise of producing cells at diverse maturation stages. This pivotal capability empowers researchers to meticulously choose the optimal developmental phase for transplantation, thereby effectively attaining the intended therapeutic outcomes [111].

While hESCs use in AMD therapy offers tremendous potential, ethical considerations and challenges related to immune rejection, tumorigenicity, and long-term integration need to be addressed [112]. Continued research and advancements in stem cell biology, tissue engineering, and transplantation techniques are essential to harness the full therapeutic potential of hESCs while ensuring patient safety and ethical compliance [112].

6. Properties of gellan gum hydrogels

Utilizing Gellan Gum-based hydrogels as a cell culturing platform for hESCs offers several potential advantages that can enhance the effectiveness of stem cell therapies [113]. These hydrogels possess unique properties that make them well-suited for supporting hESC viability, promoting differentiation, and enabling controlled release of therapeutic factors [114].

6.1. Biocompatibility and viability support

Gellan gum-based hydrogels have demonstrated notable biocompatibility and non-toxic attributes. These hydrogels establish an environment conducive to the viability and prosperous growth of hESCs [114]. The hydrogel exhibits a pliable and well-hydrated structure that effectively emulates the characteristics of the native extracellular matrix. This emulation significantly fosters cell adhesion, spreading, and proliferation. Consequently, this environment plays a pivotal role in sustaining the viability of hESCs both during the transplantation phase and throughout the ensuing culture period [114].

6.2. Three-dimensional architecture

Gellan Gum hydrogels create a 3D matrix that allows hESCs to be encapsulated like their native tissue environment [115]. This 3D architecture provides physical support and facilitates cell-cell interactions, enhancing cellular communication and differentiation cues [115].

6.3. Tunable mechanical properties

Gellan Gum hydrogels can be systematically engineered to manifest adjustable mechanical attributes, encompassing parameters like stiffness and elasticity. These tailored properties closely emulate the mechanical traits inherent to the native tissue structure [116]. This capacity empowers researchers to engineer hydrogels tailored to closely align with the distinct requirements of the targeted tissue, thereby augmenting the differentiation and integration processes of hESCs [116].

6.4. Promotion of differentiation

Gellan Gum hydrogels can be functionalized with bioactive molecules or growth factors that guide hESC differentiation toward specific lineages [117]. Through targeted alterations in the hydrogel's chemical composition, researchers possess the capability to guide the differentiation of hESCs into specific cell lineages. This controlled differentiation process facilitates the generation of cell types that are pertinent to the treatment of AMD, such as RPE cells or photoreceptor cells [117].

6.5. Controlled release of therapeutic factors

Gellan Gum hydrogels possess the capacity for the encapsulation and controlled release of bioactive therapeutic agents, including growth factors, cytokines, and small molecular compounds [118]. This controlled release can mimic the natural signalling cues in the tissue microenvironment, promoting hESC differentiation and tissue regeneration over time [118].

6.6. Minimized immune response

Gellan Gum hydrogels are considered minimally immunogenic, reducing the risk of immune rejection upon transplantation [119]. This characteristic is crucial when considering the use of hESCs, which can carry the potential for immune reactions in the recipient [119].

6.7. Localized delivery and retention

Gellan Gum hydrogels can be easily injected into target sites and provide localized delivery of hESCs [120]. They can also retain the encapsulated cells at the site of interest, preventing cell dispersion and ensuring a concentrated therapeutic effect [120].

6.8. Ease of handling and processing

Gellan Gum hydrogels are relatively simple to prepare and manipulate, making them suitable for a range of applications [121]. This ease of use is advantageous for both laboratory research and potential clinical translation [121,122].

7. Recent research and findings

Based on our current understanding, there is a conspicuous absence of research within the English literature about the utilization of gellan gum as a hydrogel substrate, specifically in the context of hESCs in the context of AMD. This knowledge gap denotes a distinct area of scientific inquiry. However, extant investigations have indeed explored similar applications, albeit employing alternative biomaterials for the design of hydrogels or focusing on the facet of transplantation.

Table 3 provides the multifaceted nature of research efforts aimed at addressing AMD through the synergistic utilization of cell lines and hydrogel platforms. These approaches encompass strategies such as encapsulating stem cells within different hydrogel types and forms to enhance therapeutic effects [123–142]. Additionally, the table highlights drug delivery systems designed to incorporate therapeutic agents within hydrogel matrices for sustained release, as well as cell-based therapies involving the transplantation of stem cells or iPSC-derived RPE cells. Moreover, it outlines the development of photoreceptor scaffold hydrogels intended to support photoreceptor cells and promote integration within the retinal tissue [123–142]. Overall, the comparative analysis presented in Table 3 underscores the multifaceted nature of research efforts aimed at addressing AMD through the synergistic utilization of cell lines and hydrogel platforms.

Furthermore, these investigations underscore the innate ability of hydrogels sourced from natural origins to promote the smooth integration of differentiated stem cells into the host tissue. It is noted that there is a scarcity of research dedicated to investigating gellan gum-based hydrogels for rejuvenating human embryonic stem cells in AMD treatment. This observation highlights a gap in research and the need for innovative therapeutic approaches to combat retinal degeneration caused by AMD.

8. Challenges and future directions

8.1. Challenges

The utilization of hydrogels based on gellan gum in the context of hESC regeneration for AMD therapy exhibits encouraging potential. However, it is imperative to acknowledge that the progression toward clinical translation is contingent upon the resolution of various challenges and limitations inherent to this approach.

8.1.1. Long-term biocompatibility

While Gellan Gum hydrogels have shown good biocompatibility in short-term studies, their behaviour over extended periods remains uncertain. Long-term exposure to Gellan Gum-based hydrogels might trigger immune responses or lead to unintended reactions within the eye, affecting the safety and efficacy of the therapy [143].

8.1.2. Translation

Transitioning Gellan Gum-based hydrogels from laboratory experimentation to their application in clinical settings necessitates comprehensive regulatory evaluations and safety assessments. The successful advancement of this process entails the rigorous execution of thorough preclinical investigations and meticulously designed clinical trials. These endeavours are crucial for substantiating not only the safety profile but also the effectiveness and sustained advantages of these hydrogels in the context of human subjects [144]. The process of obtaining regulatory approvals and ensuring compliance with clinical guidelines is time-consuming and resource-intensive [144].

8.1.3. Functional integration and maturation

Even if hESCs successfully regenerate damaged tissues, achieving functional integration with the host tissue is a complex task [145]. A fundamental prerequisite for attaining optimal therapeutic outcomes lies in ensuring the accurate differentiation and maturation of hESCs into functional retinal cell types, including photoreceptors and retinal pigment epithelial cells [145].

8.1.4. Ethical considerations

The use of hESCs raises ethical concerns, which can impact public perception and acceptance. Researchers must navigate these ethical considerations while developing and promoting Gellan Gum-based hydrogel therapies [146].

8.2. Future directions

As shown in Fig. 4, exploring gellan gum-based hydrogels for regenerating hESCs in AMD therapy involves several promising future directions. One key area of focus is the optimization of hydrogel properties, such as stiffness, porosity, and degradation rate, to create an ideal microenvironment for supporting hESC growth and differentiation into retinal cells. Enhancing stem cell

Table 3
Comparison of cell sources and hydrogel formulations studied for treating age-related macular degeneration.

Hydrogel components		Description	Cell line	Key components	References
Without gellan gum	Hyaluronan and Methylcellulose	Injectable delivery for in vivo cell transplantation	RSPCs	Supports the survival and proliferation of RSPCs, promoting a more even distribution of cells.	[123]
	Poly (ethylene terephthalate), Poly (lactic acid-co-glycolic acid), poly (glycolic acid) nanoparticles	Synthetic basement membrane design for cultivating RPE cells	ARPE-19	The addition of Poly (lactic acid-co-glycolic acid) and poly (glycolic acid) nanoparticles increased cell metabolism but did not affect cell viability.	[124]
	Poly (lactic acid-co-glycolic acid) nanoparticles of sunitinib malate, methoxy poly (ethylene glycol)-b-copolymers of polycaprolactone (mPEG-PCL) (lactic acid-co-glycolic acid) (PLGA)	In vivo, transplantation of RPE cells encapsulated within hydrogel nanoparticles	ARPE-19	Increased antiangiogenic potential, prolonged inhibition of VEGF activity, stable cell viability	[125]
	Polysulfone, polyethylene terephthalate	Implantation of cells encapsulated within hydrogels	Human RPE, animal model	In situ production of therapeutic biomolecules., stable cell viability	[126,127]
	Methacrylate/methacrylamide	Cell culture on natural and synthetic substrates for future use in RPE monolayer transplantation	RPE	RPE cells formed a monolayer when cultured	[128]
	Betamethasone phosphate (BetP)	Injectable antibody-loaded supramolecular nanofiber hydrogel	ARPE-19	BetP-Gel is nontoxic to cells.	[129]
	Glycol chitosan coated cerium oxide nanoparticles with alginate/gelatin	Design of a novel murine model resembling dry AMD by subjecting mice lacking nuclear factor erythroid 2-related factor (Nrf2) expression (Nrf2−/−) to mild white light exposure.	ARPE-19	Nanoparticles effectively shield the retina from advancing oxidative harm. When combined with an alginate-gelatin-based injectable hydrogel, they exhibited synergistic antioxidant properties, hastening the regeneration of retinal pigment epithelium and photoreceptor cells.	[130]
	Gelatin methacryloyl, hyaluronic acid methacryloyl, alginate, and fibrin	Subretinal transplantation of hESC-RPE	hESC-RPE cells	ARPE-19 and hESC-RPE cells exhibited adhesion and proliferation exclusively on the fibrin. In vivo, assessment with fibrin hydrogels demonstrated excellent short-term biocompatibility in the subretinal region.	[131]
	RGD-alginate, hyaluronic acid	3D generation of laminated neural retina and/or RPE from hiPSCs/hESCs	hiPSCs/hESCs	Alginate hydrogels promoted retinal tissue development from PSCs, while hyaluronic acid-based hydrogels did not demonstrate the same enhancement.	[132]
	Hyaluronic acid	Investigating the encapsulation of cells, their delivery via injection, and subsequent differentiation upon transplantation into the retina.	RPC	Hydrogel degradation facilitated even distribution of RPCs within the subretinal space, and the expressed mature photoreceptor marker, recoverin	[133]
	Alginate/Curcumin	The produced hydrogel was capable of securely anchoring RPE cells within its structure.	Rabbit RPE	The increase of curcumin promotes cell proliferation.	[134]
	Chitosan hydrochloride/ oxidized dextran hydrogels	Cell encapsulation and injection	RPC	Cells can retain a high survival ratio (about 90%) with the protection of the self-healing Chitosan-Odex hydrogels post-injection.	[135]
	IGF-1 loaded Src homology3-binding peptides hyaluronan/ methylcellulose	Injectable hydrogel transplantation strategy to increase the viability of both exogenous and endogenous cells in tissue engineering applications.	RPE, hESCs	substantial enhancement in the viability of RPE cells when subjected to anchorage-independent conditions.	[136]

(*continued on next page*)

Table 3 (*continued*)

Hydrogel components		Description	Cell line	Key components	References
With gellan gum	Polyethylene glycol/gellan gum hydrogels	Cells encapsulated in the hydrogel	ARPE-19	Superior biocompatibility (>90%), cell adhesion and improved cell growth compared	[137]
	Gelatin/gellan gum/glycol chitosan ternary hydrogels	Cell delivery system	ARPE-19	Cell growth, survival, adhesion, and migration were enhanced as the chitosan was incorporated into the matrix.	[138]
	Dopamine-functionalized gellan gum hydrogels	A hydrogel carrier for RPE cell delivery.	ARPE-19	Enhanced biocompatibility with dopamine and gellan gum	[139]
	Gellan gum/hyaluronic acid hydrogels	Optimization of hydrogels for retinal tissue engineering by cell encapsulation in 3D matrix	ARPE-19	The cellular compatibility of the Gellan gum/hyaluronic acid hydrogel was notably enhanced in the fast-relaxing hydrogel during in vitro experiments.	[140]
	Eggshell membrane, gellan gum.	Assessing the impact of incorporating an eggshell membrane into a gellan gum hydrogel matrix	RPE	Enabled the proliferation of the RPE cells devoid of eliciting notable cytotoxic repercussions.	[141]
	Gellan gum and silk sericin	Design of an injectable hydrogel, aiming to serve as a carrier for hESCs	ARPE-19	The introduction of silk sericin into the gellan gum matrix led to enhanced growth of RPE, and cell viability was good	[142]

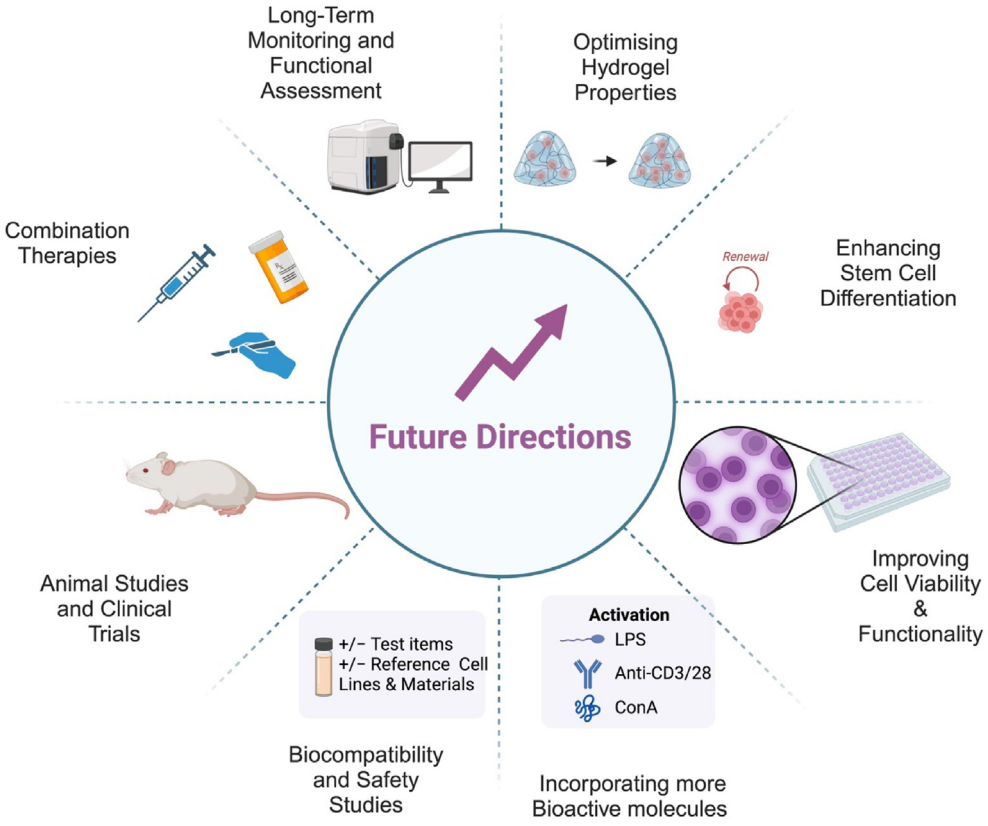

Fig. 4. Future directions of gellan gum research for regenerative therapy.

differentiation within the hydrogel matrix, particularly into specific retinal cell types like RPE cells or photoreceptor cells, is another critical research avenue. Strategies to improve cell viability, functionality, and integration post-transplantation are also being explored, which may involve pre-conditioning cells within the hydrogel or enhancing cell-matrix interactions. Incorporating bioactive molecules into the hydrogel, such as anti-inflammatory agents or neurotrophic factors, is another promising approach to promote cell survival, reduce inflammation, and support retinal degeneration in AMD. Furthermore, comprehensive biocompatibility and safety studies are essential to ensure that gellan gum-based hydrogels are suitable for clinical use, including assessing potential immune responses and long-term effects. As these studies progress, the translation to animal models and eventually clinical trials will be crucial to evaluate the efficacy and safety of this approach in humans. Overall, these future directions hold significant promise for advancing gellan gum-based hydrogels as a viable therapeutic strategy for AMD.

9. Conclusion

In conclusion, the exploration of hydrogels incorporating gellan gum for the regeneration of hESCs in the treatment of AMD presents a promising approach to addressing the challenges of ocular tissue regeneration. Spanning the years 2000–2024, this investigation has synthesized a wealth of scientific literature, providing substantial evidence supporting the potential efficacy of gellan gum hydrogels as a supportive matrix for hESC cultivation, particularly in inducing RPE differentiation.

The targeted differentiation of hESCs within gellan gum hydrogels holds great promise for alleviating the vision impairment characteristic of AMD. By analyzing a comprehensive array of studies, it becomes evident that gellan gum hydrogels create a conducive microenvironment essential for the sustained viability, proliferation, and differentiation of hESCs. This microenvironment plays a pivotal role in facilitating the maturation of crucial retinal cell subtypes necessary for restoring visual function.

By harnessing the unique properties of gellan gum hydrogels, researchers have laid the foundation for a potentially transformative therapeutic strategy in the realm of AMD treatment. The ability of these hydrogels to provide structural support, mimic native tissue properties, and promote cellular interactions underscores their suitability for tissue engineering applications. Moving forward, further research and clinical trials will be essential to fully realize the therapeutic potential of gellan gum hydrogels in ocular tissue regeneration and the treatment of AMD. Through continued innovation and collaboration, this approach may ultimately offer renewed hope to individuals suffering from vision loss due to AMD, significantly improving their quality of life.

Ethical approval

This study, as a literature review, is exempt from Institutional Review Board approval.

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Declaration of competing interest

All authors declare that there is no conflict of interests.

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