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REVIEW

Stem cells and diabetic retinopathy: From models to treatment

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Abstract
Diabetic retinopathy is a common yet complex microvascular disease, caused as a complication of diabetes mellitus. Associated with hyperglycemia and subsequent metabolic abnormalities, advanced stages of the disease lead to fibrosis, subsequent visual impairment and blindness. Though clinical postmortems, animal and cell models provide information about the progression and prognosis of diabetic retinopathy, its underlying pathophysiology still needs a better understanding. In addition to it, the loss of pericytes, immature retinal angiogenesis and neuronal apoptosis portray the disease treatment to be challenging. Indulged with cell loss of both vascular and neuronal type cells, novel therapies like cell replacement strategies by various types of stem cells have been sightseen as a possible treatment of the disease. This review provides insight into the pathophysiology of diabetic retinopathy, current models used in modelling the disease, as well as the varied aspects of stem cells in generating three-dimensional retinal models. Further outlook on stem cell therapy and the future directions of stem cell treatment in diabetic retinopathy have also been contemplated.

Keywords Adipose stem cells · Diabetic retinopathy · Induced models · Mesenchymal stem cells · Type II diabetes mellitus

Introduction

Diabetic retinopathy (DR) is a complex microvascular disease associated with chronic hyperglycemia in patients with diabetes mellitus. It affects the blood vessels in the photosensitive area of the retina and manifests symptoms like blurred vision, flashing lights, and elevated blood sugar levels, with the most common being vision loss [1]. Being the prominent cause of visual loss in the working-age population in developed countries, almost 30 million people suffer from visual impairment associated with DR, as of 2000 [2]. With the exponential surge of increasing diabetic patients per year, with projections of nearly 693 million people suffering from Type II Diabetes Mellitus (T2DM), by the year 2045 [3], the number of patients with DR would also increase over the years owing to the greater expected lifespan of diabetic patients and diabetes' increasing prevalence [4]. It is clinically classified into 2 stages-non proliferative DR (NPDR, subdivided into mild, moderate, and severe stages) with microaneurysms, haemorrhages, venous and intraretinal microvascular abnormalities and hard exudates) [5], and proliferative DR (PDR), with severe retinal ischemia, unregulated expression of proangiogenic factors and proliferation of endothelial cells resulting in rupture-prone and hyperpermeable vessels, pre-retinal or vitreous haemorrhage, fibrovascular proliferation and neovascularization [6]. However, conditions like ischemia and macular edema, which account for the majority of the vision losses due to DR, can occur at any stage [7].

Numerous studies have been performed on DR in both animal models and diabetic patients. However, with the limitations of non-invasive techniques, the underlying pathophysiology hasn't yet been fully understood. Therefore, with the progression of DR amidst the whole world, a robust *in-vitro* model can help elucidate the pathophysiology of DR, thereby providing predictive tools for designing treatment protocols. In this regard, stem cells provide a major role in playing as a viable alternative for both modelling the disease and designing treatment protocols. With the diverse competency of genetically modifying stem cells, they can be further used to model other diabetic-affiliated disorders in vitro.

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Pathophysiology of DR

Recognized as a microvascular diabetic disease for decades, DR is also considered as a neurovascular disease, pertaining to the dysfunction of neurovascular units, neovascularization, axonal degeneration, and for the early involvement of the neuro-retina in its etiopathogenesis [8]. The major pathophysiological factors contributing to DR are hyperglycemia, inflammation, and neural dysfunction, which further stimulate apoptosis, fatty acid metabolism, and advanced glycosylation endproducts (AGEs) interactions. Increased stimulation of varied inflammatory cytokines, free radicals, AGEs, reactive oxygen species (ROS), growth factors [9], advanced levels of chemokines, pro-inflammatory substances, and proangiogenic Vascular Endothelial Growth Factor (VEGF), have been found in the vitreous humor of patients with DR [10]. This has been further correlated with the enhanced expression of glial fibriallary acidic protein in the Muller cells, and its minimal expression in astrocytes, which leads to glial dysfunction. These deformities in the glial cells, contribute towards neuronal degeneration, partly leading to the breakdown of the Blood Brain Barrier (BRB). In addition, escalated levels of polyol pathway flux, formation of AGEs, hexosamine pathway flux, and activation of protein kinase C, due to chronic hyperglycemia, leads to increased production of reactive oxygen species (ROS), also get released in DR, which compromise with the integrity of the Blood Brain Barrier, leading to thickening of the retina, enhanced leukocytosis, endothelial cell damage, mitochondrial dysfunction, thus leading to neovascularization [11]. Elevation of glucose levels also leads to an increase in the production of sorbitol, which has been seen to do damage to retinal cells, via osmotic imbalance in the cells [11].

Thickening of the basement membranes during the initial phases of DR, along with hyperglycemia, hypertension and hypoxia disrupt the pericyte-endothelial cells linkage, thereby causing apoptosis of pericytes, eventually degrading the microvasculature. Loss of the endothelial cells and the pericytes further leads to capillary remodelling, capillary occlusion and generation of microaneurysms, which also act as relevant hallmarks of early DR [12]. Conditions like retinal ischemia are noted in further severe stages of DR, leading to stimulation of VEGF levels, thereby restoring blood supply to the retina. This new process promotes the degradation of the retina, by neovascularization-induced retinal changes, causing the retina to detach or wrinkle, thus being the boundary between NPDR and PDR [13]. Tight junction proteins like occludin and zonula occludens-1 also get phosphorylated due to VEGF, thereby enhancing vascular permeability [14]. Several shreds of evidence have also stated the importance of hypoxia-inducible factors (HIFs) in the regulation of VEGF. Several genes like angiogenin-2, platelet-derived growth factor-B and stromal-derived growth factor-1 which are modulated by HIFs and VEGF have also been seen to play significant roles in the neovascularization of the retina, thereby acting as novel signatures for treating DR [15]. Other angiogenic factors like angiopoietin-1 and angiopoietin-2, in coordination with endothelial receptor tyrosine kinase Tie2 are also seen to be involved in vascular permeability, promoting vascular leakages in in vivo retina models [16].

Modelling the disease

The pathophysiology underlying DR has been performed on models like in vitro cell models, and postmortem retinas of diabetic patients and animals [7]. Loss of selective endothelial and mural cells, acellularity, and microaneurysms were found to be increased in the retinal vessels and capillaries of diabetic patients [17]. Taking into account the complexity of the disease, with several influences from the environment and genes, animal and other retina cell models (have been discussed in this section lately) are preferred subjective to the specifications of the experiment. Induced animal models are generated either through a change in diet, drugs, surgery or chemically. Gene editing and selective breeding also help manifest the required changes in animal models. In virtue of these animal models, several cascades of events post-hyperglycemia like activation of protein kinase C, ROS, AGEs, sorbitol, and upregulation of pathways like VEGF and renin-angiotensin system (RAS) have been discovered [6].

In general, mice have been the most routine in vivo model, accounting for their small size and relatively shorter life span. Mouse models to study DR are usually pharmacologically induced or obtained by inbreeding of mice with endogenous mutations. The availability of transgenic and knockout mice with DR also has appended the list of animal models to a greater extent. Chemicals like alloxan and streptozotocin (STZ), both of which repress or destroy the β-cells of the pancreatic islets have been used to induce diabetes in mice. In addition, appropriate injection methods and dosages can be modulated to induce diabetic complications in the models, like increase in the number of astrocytes, apoptosis of retinal ganglion cells (RGCs), and upregulation of glial fibrillary acidic protein etc. [18, 19]. Galactosemia is also yet another medium, which has been seen to increase the blood aldohexose levels with no changes in levels of insulin, glucose, amino acids, or fatty acids, thereby allowing the study of retinal complications based on the increase of hexose concentration [20]. Endogenous mutations by inbreeding have also been practised with mice models like $Ins2^{Akita}$,

db/db, and KKA^{y} mice [7]. Other models like Wistar Bonn/Kobori rats, Otsuka Long-Evans Tokushima fatty rats, Zucker diabetic fatty rats and Goto Kakizaki rats have also been associated with rat models carrying endogenous mutations [21]. However, with the progression of time, the range of animal models has not just been restricted to rodents, as a single animal model cannot replicate the complications of a human DR, hence other models like dogs, pigs, zebrafish, rabbits, monkeys etc. [21], have been useful in orchestrating the disease.

However, the entire mimicking of DR in humans hasn't yet been achieved with in vivo models only, and other in vitro models have also been synthesized to mimic the same. Most of the in vitro studies have been performed upon human retinal pigment epithelium cell cultures [22, 23], human retinal endothelial cell lines [24, 25], pericytes and, more recently, microglia [26, 27]. In fact, immortalized human retinal pericyte lines cultured in diabetic-like conditions, in association with endothelial cells, have also been in use to understand the cell-to-cell communications and the interactions of endothelial cells with pericytes in the context of proliferation and survival [28, 29]. A similar co-culture approach with human endothelial cells and human retinal progenitor cells has also been practised to elucidate neovascularization responses in DR [30]. Other approaches like retina-in-a-dish or retina-on-a-chip models have been tried, wherein the chip recapitulates varied levels of biological complexity, like pericyte loss in virtue of blood barrier breakdown [31]. But in context to fabricating an entire dynamic model like DR, the research has been limited [32]. However, it has been clearly evident that these 2D cultures aren't sufficient to ensure the discovery of potential drug candidates. In addition to it, the heavy reliance on diabetic retinopathy in animal models also led to the limited clinical fidelity of the subject. Though with the arise of co-culture models, cell-to-cell interactions and advances in the understanding of factors which influence dysfunctions in DR have been enhanced, and exploitable therapeutic avenues have been explored [28], the area of research still needs to be further surveyed. Recent research has shown the influence of stem cells and 3D native environments or retinal organoids in modelling diseases. The ability of iPSCs of differentiating into different cell types has been used to establish iPS cell line for DR, wherein patient Peripheral Blood Mononuclear Cells were extracted and reprogrammed with the Yamanaka factors to induce DR [33]. A similar approach with Muller Glial Cells was incorporated by Courturier et al. to model the features of DR [34]. There have been several reviews eliciting the benefits of retinal organoids to becoming a versatile tool for disease modelling and drug targeting [35–37]. Organoids derived from human or patient stem cells faithfully recapitulate the function and structure of the tissue or organ, thereby paving the way towards personalized medicine and disease modelling. Stem Cells or induced pluripotent stem cells (iPSCs), when embedded on Matrigel, spontaneously generate hemispherical optic vesicles, which upon invagination, form the optic cup. Further refinement in procedure still is in need to develop stringent models for diabetic retinopathy. Thus, the use of iPSCs and retinal organoids in a multifactorial and lifestyle-related disease like DR should be encouraged as they possess the potential to combine laboratory studies with clinically relevant outputs, thus helping to develop a better understanding regarding DR.

Treatment protocols for DR

The basis for the medical management of DR primarily consists of medical interventions like control of glucose homeostasis, lipid homeostasis, blood pressure and insulin therapy. However, the pursuit is challenged when different clinical phenotypes are observed in the later stages of the disease, which are manifested with microaneurysms, haemorrhages, retinal ischemia etc. A combination of several strategies, like laser photocoagulation, intravitreal pharmacological treatment and surgical vitrectomy are thereby adopted for better management of the disease.

Considered as the standard treatment protocol for DR, the efficiency of laser photocoagulation treatment in suppressing vision loss in both patients with NPDR and PDR has been proven to be effective. However, the side effects accompanying this treatment include night blindness, regressed color vision, diminished visual field, acute glaucoma and sometimes vision loss [38]. Intravitreal injections of Food and Drug Administration (FDA) approved Anti-VEGF therapeutics are also used to treat DR and are also commercially available: bevacizumab, ranibizumab, pegaptanib, and aflibercept [39]. However, limitations of anti-VEGF therapy include the short half-life of the drugs leading to increased clinical visits, which increases economic burden. In fact, the risk of tractional retinal detachment has also been associated with VEGF downregulation, thus requiring careful consideration [40, 41]. Corticosteroids, though confer an anti-inflammatory effect but are considered a second-line option, given their increased risk of cataracts and glaucoma [42]. Other treatment options include renin-angiotensin system inhibitors or angiotensin type I and II receptor antagonists also have been associated with reduced retinopathy, but their inhibition leads to Connective Tissue Growth Factor expression, thereby promoting fibrosis in DR [43]. Keeping in view the adverse side effects of using intravitreal therapies, better ways like stem cell therapies can be tested and compared with known treatments.

Stem cells: New players in DR therapy

Stem cell therapies have been acknowledged as one of the most beneficial treatments for most degenerative diseases, including retinal diseases. Affiliated with degeneration and fibrosis, DR is involved with the loss of cells and this loss of cells can be compensated with stem cell therapies. Over the years, scientific literature has strongly supported the potential of regenerative medicine to support abnormal tissues in diseases, which can be extended to DR. As a whole, four basic strategies of stem cell regeneration are in use in the context of DR, namely: (1) Differentiation of Mueller or glial stem cells to retinal glial and/or neurons (2) Retinal stem cells to differentiate into retinal neurons and other damaged photoreceptors and cells (3) Retinal pigment epithelial stem cells that can give rise to photoreceptors and damaged retinal pigment epithelial cells (4) Formation of the retinal vasculature using endothelial, adult or iPSCs [44–48].

Given the potential of stem cells, and the characteristics of DR, cell repair and defence against stress cell damages develop the primary experimental focus. Recent approaches by the use of mesenchymal stem cells (MSCs), obtained from cord blood, adult bone marrow, adipose tissues, dental pulp etc. have shown immense impact on regeneration and recovery of the retina, post damage. Being a potential source of paracrine factors, they have also been shown to promote the regeneration of RGCs and optic nerves in degenerative eye diseases [49].

Adipose stem cells (ASCs)

Rat models with ASCs injected into eyes showed improvement in retinal working (as measured by electroretinogram), reduction in apoptotic cells around the retina, and vascular leakage (known through retinal histopathological evaluation) [50]. In vivo, ASCs have been demonstrated to differentiate into pericytes in both functional and phenotypic aspects, thereby possessing the chances of retinal vasculature repair [46]. They are also found to improve ischemia, promote angiogenesis and provide protection against nerve damage via physical contact with endothelial lining or through paracrine factors [46, 50, 51].

Moreover, these MSCs are also known to pack trophic mediators into extracellular vesicles, transporting not only pro-regenerative factors, like basic fibroblast growth factor, VEGF, Hepatocyte Growth Factor, insulin-like growth factor (IGF), nerve growth factor (NGF), glial-derived neurotrophic factor, brain-derived neurotrophic factor, ciliary neurotrophic factor [52–54], but also microRNAs, mRNAs, and mitochondrial components over long distances, thereby modulating the local microenvironment of injury to a regenerative ambience [55, 56]. However, evidence regarding the dual roles of VEGF and IGF in retinal dysfunction and sustaining retinal and cellular functions stay contentious. Though, overexpression of VEGF plays a vital role in aggravating cell death and retinal neovascularization, if modulated by its niche and relevant upstream pathways, these factors turn out to contribute to tissue regeneration, by irrigating damaged tissues with vascularization [53].

In addition, ASCs also possess ROS-scavenging properties. Hypoxic preconditioning boosts ASC survival in a ROS-dependent manner [57], suggesting that preconditioned ASCs if exposed to hypoxic conditions at right time and in appropriate conditions prove fruitful for cell therapy. The anti-oxidative features of MSCs have also been demonstrated in various mouse models of DR, diabetic nephropathy, and diabetic neuropathy [58–60]. Injection of ASCs in the vitreous humor of STZ-induced T1D mice caused suppression of oxidative damage to the retina, indicating a direct or indirect influence of ASCs on ROS levels [58].

Besides this, ASCs promise a therapeutic approach to mending damaged neurovascular units by demonstrating improved BRB integrity in diabetic animal models by their differentiation into cells similar to glial cells and photoreceptors. ASC injection into the vitreous humor of diabetic rats stimulates a cytoprotective microenvironment by causing a reduction in oxidative damage and accumulative intraocular levels of neurotrophic factors such as NGF (Nerve Growth Factor), glial cell line-derived neurotrophic factor and basic fibroblast growth factor (FGF). It also prevented the loss of RGCs completely, indicating better treatment of the early stages of DR [61]. Recent experiments also suggest a reduction in inflammatory reactions and angiogenesis by targeting of ITGA1 gene by miR-192 from exosomes derived from ASCs [62].

Bone marrow mesenchymal stem cells (BM-MSCs)

BM-MSCs are believed to be of great therapeutic importance in the regeneration of the retina due to the plasticity of Hematopoietic Stem Cells in the bone marrow and their potential role in repopulating bone marrow, repairing vasculature and reception of transplants [63]. Endothelial progenitor cells positive for CD34 + differentiate into endothelial cells and induce vasculature repair in animal models through paracrine methods [64–66]. Intravitreal injection of human CD34 + bone marrow stem cells derived from humans, into mice demonstrated preservation of the vasculature of the retina as compared to the control. The CD34 + stem cells lead to retinal homing and its integration into the eyes of the model [67]. Yet another study showed an improvement in ERG amplitude after injection of BM-MSCs in the vitreous humor, suggesting integration of BM-MSCs in the retina, while in another research no improvement in ERG amplitude was observed [66, 68]. The secretome of BM-MSCs also plays a vital role by containing an array of neurotrophic

factors like NGF, Neurotrophin-3, 4, 5, IGF1, FGF2, etc., which bind to their associative receptors, thereby enhancing axonal outgrowth, neural cell survival and attachment [69]. Nevertheless, on the other hand, research conducted on the long-term effects of BM-MSC therapy on animal models shows their migration to non-target tissue by crossing BRB upon its retinal integration making its efficiency doubtable [70].

Stem cells derived from dental pulp

MSCs derived from dental pulp show clonogenicity, expression of markers, and the property to differentiate into chondrocytes and adipocytes upon induction. They are believed to promote the protection of neurons and axonal regeneration of RGCs after injury to the optic nerve [71, 72].

Stem cells derived from umbilical cord

MSCs derived from the umbilical cord may potentially treat neurodegeneration in DR by enlarging the number of surviving RGCs. RT-PCR and immunofluorescent studies demonstrate their capacity to differentiate into neural stem cells in vitro [73]. Though the mechanism of action is under study, a research conducted by Li et al. indicated a reduction in retinal apoptosis in diabetic mice model by paracrine methods, through targeting of STAT1 gene by micro RNA miR-17-3p carried by UC-MSC-derived exosomes [74]. In an attempt to treat diabetic rats, UC-MSC was used to produce neural stem cells. The study showed morphological and visual improvements, as measured by a focal ERG. Biomarkers such as BDNF and Thy-1 were present in quantities greater than that found in controls indicating their interference with the pathophysiology of DR [71]. UC-MSCs derived from Wharton's jelly cause a reduction in axotomy-induced RGC loss via secreting anti-inflammatory and neuroprotective factors [75].

Endothelial colony-forming cells (ECFCs)

Endothelial colony-forming cells' potential in the treatment of ischemic retinopathies is currently under preclinical evaluation [76]. Intravitreal administration of these cells into a murine model increased the normo-vascular area (30%), through their integration within the neovessels, thereby reducing the avascular area by approximately 41% [77]. These stem cells regulate angiogenesis associated with ischemic retinopathy by releasing extracellular vesicles containing microRNAs [78].

Stem cells derived from the human placenta

Amniotic-membrane derived MSCs have the potential to treat DR via paracrine mechanisms stimulated by the diabetic environment and the retinal angiogenic effects of TGF-β1 [79]. Recent clinical trials have found their administration useful and protective in Asian patients suffering from traumatic optic neuropathy. This indicates their scope in neuroprotection and regeneration in DR [80]. Intravitreal injection of placenta-derived MSCs, overexpressing

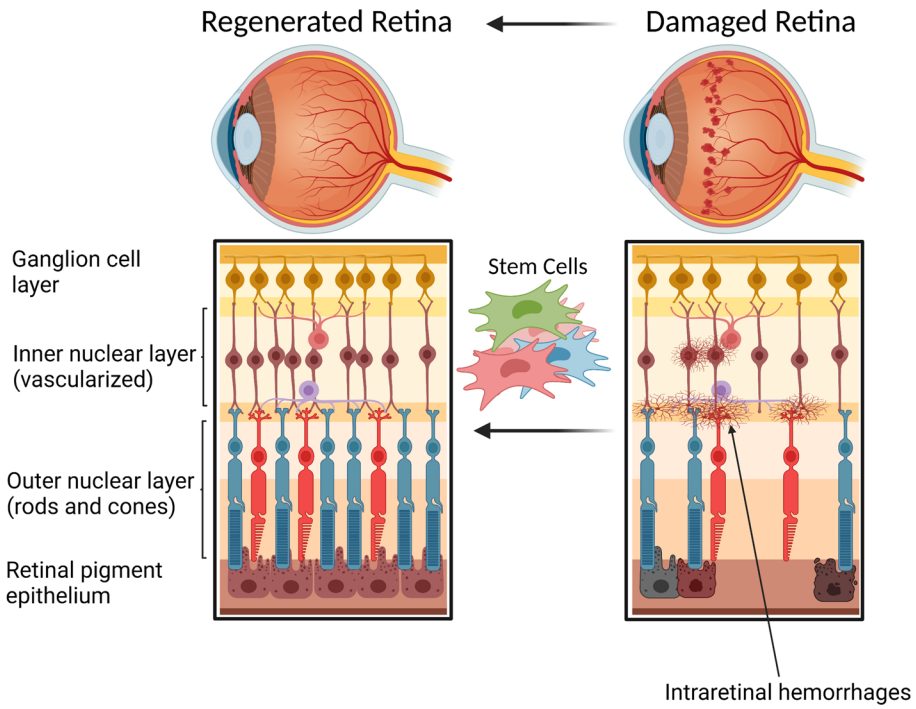

Fig. 1 Diabetic Retinopathy is a multifactorial microvascular disease, caused as a complication of diabetes mellitus. Associated with hyperglycemia and subsequent metabolic abnormalities, advanced stages of the disease lead to fibrosis and subsequent visual impairment and blindness. Current regenerative therapeutics have been in use to cure diabetic retinopathy. The potential for differentiation of a varied range of stem cells like adipose stem cells, bone marrow stem cells, induced pluripotent stem cells and many more have been taken into account to replace the lost cells or provide trophic support. (Created with BioRender.com)

pigment-epithelium derived factor, boosted mitochondrial biogenesis, increased expression of antioxidant enzymes, modulated ROS levels and overall protected the retinal pigment epithelium cells from oxidative stress [81] (Fig. 1).

Pluripotent stem cells

Recent literature has shown the potential of iPSCs to treat various human diseases and endow personalized medicine for future therapy without immunological interventions or ethical issues. In context to DR, several clinical aspects of DR, like retinal vasculopathy, replacement of RPE, and retinal neuropathy have shown improvements when treated with iPSCs. Human iPSC-derived endothelial cells had displayed angiogenic potential and had stimulated vascular recovery, both in vitro and in vivo [82]. Prasain et al. standardized a protocol for iPSC differentiation into ECFCs, wherein they showed 3D tube forming potential, in vivo angiogenesis, thus contributing to vascular repair [83]. Not just vascular repair, iPSCs have also shown potential in expressing characteristic pericyte markers like NG2, CD146, and Platelet derived Growth Factor Receptor-β (PDGFR-β), and restore transendothelial resistance in stressed brain endothelial cells [84]. Recent pre-clinical studies have also stated the benefits of iPSC-derived photoreceptors in in vivo models, wherein these progenitor photoreceptors survived upto three weeks, differentiated into mature photoreceptors and integrated with host retinal neurons [85]. Concerning iPSC derived RPE, successful results were obtained on the basis of gene expression, polarization, secretion of VEGF, membrane potential and ion channel activity, though increased p21 expression and growth arrest were noticed too [86]. However, preclinical trials upon both mice and rat models have shown beneficial effects of hiPSC-RPE cells, including preservation of retinal structures, reduction in inflammations and improvement in visual function [84].

Efficacy of stem cell treatment in DR

As discussed above, MSCs (especially ASCs) exert a dual role in DR, one in a paracrine manner, wherein they acquire perivascular localization and endothelial cell wrapping, thereby resuming pericyte function and its proliferation. Second, they mediate in the secretion of trophic factors which modulate the local environment of injury, by repressing inflammation and ROS. This dual-role help in further modulation of angiogenesis, elevation in skin repair, limitation of tissue loss, and provides a neuroprotective environment against neuronal apoptosis [87, 88]. These studies support the fact that adipose tissues provide us with a novel regenerative therapy for DR. In addition to it, intravenous injections of ASCs have demonstrated an improved BRB integrity [51]. Though the underlying mechanism stays contentious, there have been several favourable hypotheses like ASCs secrete several anti-apoptotic and anti-inflammatory proteins like CCL5, IDO-1, IDO-2, stem cell factor, tumour necrosis factor-inducible gene 6, etc., which further help in mediating some advantageous effects of MSCs in DR [88, 89]. Furthermore, MSCs also exert a strong repressive effect on the proliferation of T cells. Improved Th1/Th2 balance and enhanced numbers of Tregs have been reported in models of T1DM [90]. Inhibition of T cell proliferation has also been linked with MSCs in the context of soluble factors like IL-10, IDO and PD-1 [91, 92].

Thus, keeping in sight the heavy advantages of stem cell-mediated therapy for DR and other ocular diseases, human clinical trials are being conducted using ASCs, bone marrow stem cells, and iPSCs that share morphological features homologous to RPE cells [93]. Intravenous injections of CD34 + BM-MSCs (NCT01736059) have been administered to subjects with irreversible vision loss due to retinal vascular diseases, including DR. In a similar fashion, clinical trials NCT03011541, NCT01920867, and NCT02280135 are also focusing upon using autologous BM-MSCs to treat diabetic retinopathy or associated retinal diseases [94]. Yet another trial, NCT03403699 is undergoing to examine the potential of iPSCs to generate endothelial cells and pericytes in degenerated areas of DR. Autologous bone marrow stem cells also has been seen to reduce levels of C-reactive protein and fasting blood glucose and improved BCVA (best-corrected visual acquity) in patients with DR, thereby affirming the therapeutic window of regenerative medicine against DR [95]. On the other way, some of these trials have also led to macrophage infiltration and retinal foldings in patients [96]. A comparatively recent study wherein lipoaspirate treated ASCs were injected into both eyes, led to a severe vision loss, along with retinal detachment [97]. In this respect, though, favourable results are obtained when such types of therapies are promoted in murine models [67, 98, 99], the underlying mechanism for failure in human DRs needs further research.

Conclusion and future prospects

Keeping in view the promising therapeutic candidature of stem cells (especially MSCs) as a treatment option for DR, with the ability to regenerate pericytes, and modulate angiogenesis and inflammation, the therapeutic potential post-transplantation has been quite poor [90, 100]. Numerous reasons have been cited in conjecture for the negative response of stem cells as treatment, like exposure to the harsh microenvironment, hypoxia, inflammation, oxidative stress, lack of extracellular matrix, mechanical stress, and lack of integration of MSCs post-injection etc. [90, 100]. Moreover, the favourable results in murine models have been accredited to

the disparity in clinical parameters like ocular microenvironments in both murine models and humans [69]. In regard to the differential potential of retinal progenitor cells, they possess limited proliferation and differentiation ability, thus adding up as a challenge. Several unfavourable clinical trials have been attributed to the route of injections, thus this area would also need thorough research to evaluate the relative merits of intravenous versus sub-retinal versus intraorbital injections of MSCs. Emerging data has seen the competence of CD34 + cells, hence a combination of CD34 + and MSCs or other progenitor cells would lead to an increased retinal endothelial cell survival [90]. Similarly, keeping in view the reduced differential potential of retinal progenitor cells, combinational therapies must be promoted to develop effective therapies. Development of ex vivo models should also be expanded to iPSC derived retinal organoids, as they retain tissue identity and genomic stability and can be used as a novel model to explore the avenue of regenerative medicine against DR. Last but not the least, the translation of stem cell research in both the aspects of modelling the disease and regenerative medicine should be scaled up in the context of human usage. Weighing on a benefit versus risk scale, stem cell treatment in DR has shown remarkable progress and will continue over the next few years.

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