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A Review on Mesenchymal Stem Cells for Treatment of Retinal Diseases

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Abstract

Mesenchymal Stem Cells (MSCs) have been studied extensively for the treatment of several retinal diseases. The therapeutic potential of MSCs lies in its ability to differentiate into multiple lineages and secretome enriched with immunomodulatory, anti-angiogenic and neurotrophic factors. Several studies have reported the role of MSCs in repair and regeneration of the damaged retina where the secreted factors from MSCs prevent retinal degeneration, improve retinal morphology and function. MSCs also donate mitochondria to rescue the function of retinal cells and exosomes secreted by MSCs were found to have anti-apoptotic and anti-inflammatory effects. Based on several promising results obtained from the preclinical studies, several clinical trials were initiated to explore the potential advantages of MSCs for the treatment of retinal diseases. This review summarizes the various properties of MSCs that help to repair and restore the damaged retinal cells and its potential for the treatment of retinal degenerative diseases.

Key words Retinal regeneration · cell replacement therapy · exosomes · mitochondrial transfer · anti-inflammatory molecules

Abbreviations

AMD	Age-related macular degeneration
ABCA4	ATP- binding cassette, sub-family A (ABC1), member 4
ACE2	Angiotensin converting enzyme 2
ADSCs	Adipose tissue derived mesenchymal stem cells
AMSCs	Amniotic membrane derived mesenchymal stem cells
APCs	Antigen presenting cells
ASCs	Adipose tissue derived stromal cells
BCL-XL	B-cell lymphoma-extra-large-protein
BCVA	Best corrected visual acuity
BDNF	Brain derived neurotrophic factor
BM	Bruch's membrane
BMSCs	Bone marrow derived mesenchymal stem cells
BRB	Blood retinal barrier
CMSCs	Conjunctival mesenchymal stem cells
CNV	Choroidal neovascularization
CNTF	Ciliary neurotrophic factor
CTLA-2, 4	Cytotoxic T-lymphocyte antigen-2, 4
CXCR4	Chemokine receptor type 4
DAMPs	Damage associated molecular patterns
DPSCs	Dental pulp derived mesenchymal stem cells
DR	Diabetic retinopathy
EFN	Eye-field neuroectoderm
EGF	Epidermal growth factor
ESCs	Embryonic stem cells
FGF2	Basic Fibroblast growth factor
GA	Geographic atrophy
GCL	Ganglion cell layer
GDNF	Glial cell-line derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
HGF	Hepatocyte growth factor
HSPGs	Heparin sulfate proteoglycans
ICAM1	Intercellular adhesion molecule 1
IDO	Indoleamine 2,3- dioxygenase
IFNγ	Interferon γ
IGF1	Insulin-like growth factor1
IL1	Interleukin 1

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IL6	Interleukin 6
IL8	Interleukin 8
IL10	Interleukin 10
IL17	Interleukin 17
IL22	Interleukin 22
IL1β	Interleukin 1β
ILM	Inner limiting membrane
INL	Inner nuclear layer
IOP	Intraocular pressure
iPSCs	Induced pluripotent stem cells
MCP1	Monocyte chemoattractant protein 1
MERTK	Mer receptor tyrosine kinase
MMP-9	Matrix metalloproteinase-9
MSCs	Mesenchymal stem cells
NSCs	Neural stem cells
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NPDR	Non-proliferative stage of diabetic retinopathy
NT-3,4/5	Neurotrophin-3, 4/5
NTFs	Neurotrophic factors
ONL	Outer nuclear layer
PAMPs	Pathogen associated molecular patterns
PAX6	Paired box 6 protein
PDR	Proliferative stage of diabetic retinopathy
PDGF	Platelet derived growth factor
PDL1	Programmed death-ligand 1
PEDF	Pigment epithelium-derived factor
PGE2	Prostaglandin E2
PGE2R	Prostaglandin E2 receptor
PMSCs	Placenta derived mesenchymal stem cells
RGCs	Retinal ganglion cells
rAAV2	Recombinant adeno-associated virus
RP	Retinitis pigmentosa
RPCs	Retinal progenitor cells
RPE	Retinal pigment epithelium
RPGR	Retinitis pigmentosa GTPase regulator
SCOTS	Stem cell ophthalmology treatment study
SD	Stargardt's disease
SDF1	Stromal derived factor 1
SPARC	Secreted protein rich in cysteine
STZ	Streptozotocin
TGFβ1	Transforming growth factor β1
TIMP1	Tissue inhibitor of metalloproteinase 1
TLRs	Toll-like receptors
TM	Trabecular meshwork
TNFα	Tumour necrosis factor α
Treg	T regulatory cells.
TSG6	Tumour necrosis factor-stimulated gene 6
TSP1	Thrombospondin type 1
UMSCs	Umbilical cord blood derived mesenchymal stem cells
VEGF	Vascular endothelial growth factor
VEGFR1, 2	Vascular endothelial growth factor receptor 1, 2
WJMSCs	Wharton's jelly derived mesenchymal stem cells
XLRP	X-linked retinitis pigmentosa

Introduction

Mesenchymal stem cells (MSCs) were successfully isolated from several tissue sources such as bone marrow, adipose tissue, dental pulp, umbilical cord blood, amniotic membrane and considered as promising candidates for therapy to regenerate and repair the degenerated retinal cells in several retinal degenerative disorders [1] . The important reasons for considering MSCs as suitable option for treatment of retinal disorders are, firstly, the paracrine signaling through secretion of neurotropic factors for repair of neuro-retinal cells, secondly, MSCs possess immunomodulatory properties that can dampen the pro-inflammatory microenvironment common to the retinal degenerative diseases and thirdly, their ability to secrete anti-angiogenic factors to inhibit the pro-angiogenesis involved in the etiology of certain ocular diseases [2].

Although, conventional therapies such as surgery and ocular drugs can slow the progression of the ocular diseases, novel approaches including stem cells and gene therapy have the potential to regenerate the damaged retinal architecture. Several cell therapy approaches were aimed to augment endogenous retinal regeneration by retinal pigment epithelium (RPE) cells and müller glia cells, as well as cell replacement therapy with the help of embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and retinal progenitor cells (RPCs) [3]. This review will focus on utilizing MSCs for treating retinal diseases and some of the advantages in utilizing MSCs for therapy. This review includes, firstly, some of the common retinal degenerative diseases and the conventional treatments that are administered for these diseases; secondly, the pre-clinical studies that have tested MSCs for the treatment of retinal diseases and finally, we will discuss the outcome of some of the clinical trials utilizing MSCs, where positive therapeutic outcomes were observed.

Age-related macular degeneration (AMD) and Stargardt's disease (SD)

AMD is a degenerative disease with several genetic and environmental factors contributing to the disease pathogenesis [4]. The advanced stage of AMD comprises of two forms, geographic atrophy (GA) or dry AMD and choroidal neovascularization (CNV) or wet AMD. GA is characterized by the degradation of the retinal pigment epithelium (RPE) layer and Bruch's membrane, the basement membrane, followed by loss of

photoreceptors as the damaged RPE layer fails to phagocytose the photoreceptor outer segments. Incomplete phagocytosis leads to accumulation of a lysosomal protein lipofuscin, which interferes with the proper functioning of the RPE layer. Accumulation of drusen, the cell debris between the RPE layer and Bruch's membrane causes its detachment inducing progression towards CNV or wet AMD. CNV manifests as abnormal and undesired leaky capillaries across the ocular tissue that leads to fluid accumulation and hemorrhage at the macula [5]. Stargardt's disease (SD), a hereditary disease, is characterized by macular degeneration, and occurs within the first two decades of human life [6]. The most common form of this disease involves mutation in the ABCA4 (ATP-binding cassette, subfamily A , member 4) gene [7], the dysfunction of which causes accumulation of N-retinylidene-N-retinyl-ethanolamine, a major component of lipofuscin, which has a detrimental effect on RPE and photoreceptor cells [8]. Molday et al reported that degeneration of foveal RPE, cone photoreceptors and loss of central vision in Stargardt patients is due to ABCR mutations [9]. Anti-VEGF (vascular endothelial growth factor), photodynamic and laser photocoagulation therapy are administered for wet AMD in order to alleviate neovascularization [10, 11]. Gene therapy approaches include recombinant adeno-associated virus (rAAV2) vectors carrying soluble fms like tyrosine kinase 1 (sFlt1) [12, 13] or chimeric protein such as sFlt01 [14, 15], that prevent VEGF binding to endothelial receptors Flt1 (VEGFR1) and Fmk1 (VEGFR2) to reduce neovascularization in wet AMD has been tested by several groups [16, 17]. Song et al reported that subretinal transplantation of human embryonic stem cell (hESC)-derived RPE cells was well tolerated in AMD patients [18, 19] and patients with Stargardt's disease as also reported as Schwartz et al [20, 19]. Although iPSCs have attracted preclinical and clinical studies, autologous transplantation of human iPSCs derived RPE cells resulted in no significant clinical improvement in the AMD patient tested [21, 22].

Retinitis Pigmentosa (RP)

Retinitis Pigmentosa (RP), a hereditary degenerative disorder has autosomal recessive [23], autosomal dominant [24] or X-linked recessive inheritance patterns [25]. While the initial stages of the disease involves destruction of the rod photoreceptors causing loss of night vision and limited peripheral vision, further progression to later stages results in degeneration of cones leading to loss of central and color vision [26]. The degeneration of photoreceptors in RP is usually associated with gene mutations. Until date, ~4500 mutations have been discovered in 70 genes involved in the causation of RP [27]. RP is linked with Usher Syndrome, Bardet-Biedl Syndrome, and can also exist as non-syndromic RP [28]. Pathogenesis of autosomal recessive RP is due to mutation in genes involved in photo-transduction pathway like cGMP phosphodiesterase (PDE6) [29], and intraocular delivery of recombinant Adeno-associated virus (rAAV) containing corrected PDE6 gene, led to disease remission in mouse disease models [30]. Since, mutation in Mer receptor tyrosine kinase (MERTK) is also known to play a role in autosomal recessive RP [31], gene replacement through AAV vector have resulted in improvement in retinal function in RP models as well as human patients [32, 33]. Gene therapy tested for autosomal dominant RP include rAAV carrying ribozymes designed to specifically inhibit mRNA of defective rhodopsin gene [30]. Positive outcomes were reported in X-linked RP (XLRP), caused by mutant retinitis pigmentosa GTPase regulator (RPGR) when treated with AAV8 vectors expressing normal RPGR gene [34]. The first in vivo gene therapy to be approved by Food and Drug Administration (FDA) for RP is, Luxturna, a AAV2 virus carrying the complementary DNA (cDNA) of the gene RPE65, whose biallelic mutation causes recessive RP [35]. FDA also approved transplantation of an artificial retina, resulting in recovery of vision in late-stage RP patients [36, 37]. RP patient-derived iPSCs corrected for mutations in Pro23His variant of rhodopsin (RHO) gene and homozygous Alu insertion in exon 9 of male germ cell-associated kinase (MAK) gene by CRISAP/Cas9 mediated gene editing was proposed for autologous retinal cell replacement. Correction of RPGR gene by CRISPR/Cas9 gene editing also resulted in repair of defective photoreceptors and ciliopathy in the patient iPSC-derived organoids [38, 39].

Diabetic Retinopathy (DR)

Defined as a multifactorial microvascular disease, DR is induced by chronic hyperglycemia and a consequent sequence of abnormal metabolic events [40] bringing about an overproduction of reactive oxygen species (ROS) [41]. Early or non-proliferative stage of DR (NPDR) is characterized by loss of pericytes, endothelial cells and neuronal cells in the retina [42]. Progression to a more severe stage, the proliferative stage of DR (PDR), results in pro-angiogenic and inflammatory responses, forming intra-retinal vasculature abnormalities and hemorrhages [43]. Since PDR is due to neovascularization, standard treatment methods attempt to lessen uncontrolled angiogenesis by anti-VEGF administration [44]. Expression of an array of anti-VEGF molecules such as, sFlt-1 [45], Flt23k [46], endostatin [47], calreticulin anti-angiogenic domain (CAD 180), CAD-like peptide 112 (CAD 112) [48] through viral vectors have resulted in favorable prognosis of DR. Similarly, in a preclinical study, when iris and RPE cells were transfected with pigment epithelium derived factor (PEDF), the CNV reduced by 50% [49]. Other gene therapeutic strategies that resulted in positive outcomes include viral mediated prolonged expression of human erythropoietin gene that protected the blood retinal barrier (BRB) and retinal neurons in experimental DR rats [50], soluble membrane-independent form of CD59 (sCD59) expression leading to 60% reduction in the leakiness of retinal blood

vessels in diabetic mice by blockage of membrane attack complex (MAC) deposition [51] and manganese dependent superoxide dismutase (MnSOD) expression resulting in reduction of intra-ocular ROS levels which prevented progression of DR [52]. Moreover, AAV2 mediated overexpression of retinal angiotensin converting enzyme 2 (ACE2), an intermediate in the renin angiotensin aldosterone system (RAAS) pathway, conferred prevention and partial reversal of the DR associated increase in RAAS signaling as well as the subsequent detrimental effects on the vasculature [53].

Glaucoma

Glaucoma is characterized by a significant elevation in intraocular pressure (IOP), which leads to progressive death of RGCs, degeneration of the optic nerve head and subsequent vision loss [54]. This rise in IOP is related to degeneration and fibrosis of the trabecular meshwork (TM). Under normal conditions, the role of TM is to drain the aqueous humor, the dysfunction of which leads to open-angle glaucoma and the blockade of TM due to abnormal anatomical location of iris leads to angle-closure glaucoma [55]. Other factors that lead to RGCs damage in glaucoma are hypoxia, ischemic insult, deprivation of nutrients and energy, neuroinflammation, reduction in transmission of neurotrophic factors and chronic neurotoxicity which occur as a consequence of neuronal damage associated buildup of extracellular glutamate, free radicals and excitatory amino acids. Glutamate induced exicitotoxicity leads to disruption of anterograde and retrograde axonal transport and axotomy-induced death in RGCs [54].

Reduction of IOP by pharmacological agents or surgical techniques such as trabeculectomy, non-penetrating glaucoma surgery, micro-invasive glaucoma surgery and glaucoma drainage implants have so far been the primary mode of therapy to prevent disease progression in glaucoma [56]. Minimally invasive ab-interno trabeculectomy which involves removal of the TM via an electro-ablative procedure has shown to have long-term effectiveness in lowering IOP in glaucoma patients [57]. Gene therapy methods to reduce IOP and provide neuroprotection by expression of neurotrophic factors has emerged as an alternative therapeutic option, however the major challenge for gene therapy is the multiple pathogenic mutations associated with glaucoma [58]. Although no gene therapy method has resulted in good clinical outcome in glaucoma [59], a novel gene therapy construct expressing brain derived growth factor (BDNF) and it's receptor tropomyosin receptor kinase B (TrkB) [60] exhibited neuroprotection in experimental glaucoma models [61]. CRISPR/Cas9 gene editing method utilized to disrupt aquaporin 1 gene in ciliary body epithelium cells also resulted in lowering of IOP in an experimental glaucoma model [62].

MSCs for treatment of retinal disorders

In this section, we discuss some significant properties of MSCs such as the paracrine factors secreted by the cells, the exosomes and mitochondrial transfer into host cells that facilitate the repair and regeneration of retinal layer.

Paracrine neuroprotective factors

The secretome of bone marrow derived mesenchymal stem cells (BMSCs) contain an array of neurotrophic factors (NTFs) such as ciliary neurotrophic factor (CNTF), BDNF, glial cell derived neurotrophic factor (GDNF), platelet derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin-3, 4/5 (NT-3, 4/5) [63], insulin-like growth factor 1 (IGF1), basic Fibroblast growth factor (FGF2), PEDF and erythropoietin (EPO) [64]. The neurotrophic factors secreted by BMSCs, bind to their cognate receptors on the recipient cells [65] and enhance the neural cell survival, differentiation, axonal outgrowth, neural cell attachment and inhibit neural cell apoptosis [66, 65]. The signaling pathways activated by the NTFs, such as P13K/AKT, P13K/IAP, PLC/IP3/PKC, MAPK/ERK and JAK/STAT3 have neuroprotective effect on the neuro-retinal cells [67, 65]. The neuroprotective role was demonstrated in an ex vivo study by Cui et al, where co-culturing BMSCs with RGCs reduced hydrogen peroxide (H_2O_2) induced injury in RGCs through the expression of neurotrophins, BDNF, CNTF and reduced the expression of pro-inflammatory factors interleukin 1β (IL1β) and tumor necrosis factor α (TNFα) by RGCs [68]. Moreover, Osborne et al and Johnson et al found that PDGF secreted by BMSCs protected RGCs in an ex vivo and preclinical models respectively [69, 67]. Mead et al proposed that NGF, BDNF and NT-3 secreted by BMSCs have protective effects on RGCs [63] and this neuroprotective effect induced by BMSCs was ablated when tropomyosin related kinase (TrK) [70, 71] and PDGF receptor α (PDGFRα) [69] were inhibited on RGCs. Intravitreal transplantation of GDNF and BDNF secreting BMSCs resulted in higher number of RGCs compared to the control group in an experimental optic nerve crush model [72]. Similarly, long-term neuroprotection and axon regeneration of RGCs was observed after transplantation of BMSCs, which was attributed to an increased expression of FGF2 and IL1β in the RGC layer that activated the PI3/AKT signaling cascade and rescued RGCs [73]. Martin et al found a significant increase in neuroprotective (Dll4, Crim-1, Glupican-3, Cntn1), anti-inflammatory (Transforming Growth Factor β and IL10, 13, 11, 4) molecules as well as proteins associated with anti-oxidant (haptoglobin), anti-apoptotic (Apex1) activity and protein homeostasis (Hsp10, Hsp60, Hsp70, Hsp20, Hsp27, Kctd10, Pyk2, clusterin) in the secretome of human BMSCs co-cultured with neuroretinal explants [64].

Similar to BMSCs, adipose derived mesenchymal stem cells (ADSCs) secrete a repertoire of NTFs such as hepatocyte growth factor (HGF), CNTF, IGF [74], FGF2, epidermal growth factor (EGF) [75], VEGF, NGF, BDNF, GDNF, NT-3, and PDGF [76]. Ezquer et al found that intravitreal administration of murine ADSCs resulted in significant increase in intraocular levels of NGF, FGF2 and GDNF, prevented RGC loss and reduced oxidative stress in the retina in a diabetic mouse model. In addition, the injected cells also differentiated into RGCs, astrocytes and pericytes in vivo [77]. Further, conditioned media from human ADSCs protected RPE and photoreceptor cells from oxidative stress mediated cell death [78] and inhibited retinal damage in vitro and in vivo [79]. Progranulin, tissue inhibitor of metalloproteinase 1 (TIMP1), the secreted protein rich in cysteine (SPARC) [79, 80] and HGF [78] present in the ADSCs conditioned media played an important role in neuroprotection. On the other hand, treatment of ADSCs with conditioned media of RPE cells under oxidative stress enhanced the migration rate of ADSCs, through SDF1 and CXCR4 mediated interaction between RPE cells and ADSCs, respectively [78].

Mead et al found that human dental pulp derived mesenchymal stem cells (DPSCs) secreted higher levels of PDGF, NGF and prostaglandin E2 receptor (PGE2R) than human BMSCs and ADSCs [71]. Further, DPSCs transplantation resulted in significantly high number of brain specific transcription factor 3a (Brn3a) positive RGCs, increased retinal nerve fibre layer thickness and improved RGC function in an open-angle glaucomatous preclinical model [81]. Ji et al found that the human umbilical cord blood derived mesenchymal stem cells (UMSCs) mainly exhibited neuroprotective properties through secretion of BDNF and GDNF in an ocular hypertension animal model [82]. In addition, Zhang et al reported that human UMSCs derived neural stem cells (NSCs) when transplanted in a STZ-induced DR model increased the survival of RGCs and reduced the progression of DR [83]. Wharton's jelly derived mesenchymal stem cells (WJMSCs) were reported to delay axotomy-induced death of RGCs when stimulated to release neuroprotective and immunomodulatory factors by the cues present in the microenvironment of the injured retina [84].

MSC derived extracellular vesicles (MSC-EVs)

MSC-EVs or exosomes are secreted, bilipid layered, nano dimensional micro vesicles which encapsulates functional molecules such as proteins, lipids, miRNAs and can provide important therapeutic effects. MSC-EVs were found to be endocytosed by retinal neurons, microglia and RGCs via caveolar mediated endocytic pathway, facilitated by heparin sulfate proteoglycans (HSPGs). Furthermore, the endocytosis of MSC-EVs took place in a dose, temperature dependent manner and saturable interaction of MSC-EVs with proteins of the vitreous humor was responsible for prolonged retention of EVs in the eye [85]. Yu and co-workers showed that intravitreally injected MSC-EVs were as efficient as transplanted MSCs in reducing damage and apoptosis in addition to improving vision in an experimental model of retinal laser injury. Moreover, MSC-EVs ameliorated retinal damage by downregulating the expression of pro-inflammatory mediators, intercellular adhesion molecule 1 (ICAM1), monocyte chemoattractant protein 1 (MCP1), TNFα [86] and VEGF-A [87]. Studies by Mead et al showed that BMSCs derived exosomes prevented death of RGCs and preserved more than 50 % of RGC function in a rat optic nerve crush model [88]. This was found to be orchestrated by miRNA dependent mechanism where the positive effects on RGC declined when Argonaute2, a protein necessary for miRNA biogenesis was knocked out in experimental models of glaucoma [89, 90]. Safwat et al reported beneficial role of micRNA-222, shuttled in ADSCs derived exosomes, for retinal repair in a diabetic rabbit model. Hyperglycemia, which leads to decreased expression of micRNA-222, is associated with acute retinal damage and substantial hemorrhage in different layers of retina. Injection of EVs through intravenous (IV), sub conjunctival (SC) and intraocular (IO) routes increased the expression of micRNA-222 in the retina, leading to retinal regeneration [91]. MSCs derived EVs can negate the demerits of cell-based therapy like transplantation failure, immunogenic, oncogenic risks and opens further opportunities to engineer artificial, function specific EVs to achieve neuroprotection and retinal regeneration.

MSCs dampen inflammatory responses

The ability of the eye to prevent intraocular inflammation in order to protect the visual elements from damage and thus, conserving visual acuity, is defined as ocular immune privilege [92]. This highly complex phenomenon is maintained by the BRB which efficiently separates the eye from the immune system along with local inhibition of both innate and adaptive immune responses by the ocular microenvironment, and ocular-specific mechanisms cause systemic activation of immunosuppressive regulatory T cells [93]. Ocular fluids contain suppressors of natural killer (NK) cell function, namely, macrophage migration inhibitory factor (MIF) and transforming growth factor β (TGFβ); neuropeptides, alpha-melanocyte stimulating hormone (α-MSH) and calcitonin gene-related peptide (CGRP) which dampen the activation and the function of macrophages; complement factor H (CFH), decay accelerating factor (DAF) and Crry, proteins involved in regulation of the complement system [94]. Further, expression of molecules such as Fas ligand (CD95), programmed death-ligand (PDL1), cytotoxic T-lymphocyte antigen-4 (CTLA-4) and CTLA-2 by ocular cells, especially the ciliary body, iris and RPE cells, control the adaptive

immune cells, hence generating an immunosuppressive ocular microenvironment [95]. However, pathological conditions such as AMD, glaucoma and DR, are characterized by an abundance of proinflammatory cytokines in addition to infiltration of immune cells leading to breakage of the BRB [96].

The inflammatory response involved in the etiology of AMD, has a significantly small magnitude and tempo, a phenomenon broadly known as "para-inflammation". The adaptive immune system is involved in the development of AMD, where complement C5a promotes Th17 mediated inflammation. High levels of IL22 and IL17 in the sera of AMD patients demonstrates the prominence of T-cell involvement [97]. In case of glaucoma however, neuroretinal damage occurs, which is not only due to the amino acid glutamate, but also by a distinctive neuro-inflammatory response via activation of astrocytes and microglial cells, as a consequence of recognition of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs). Toll-like receptors (TLRs) expressed by astrocytes and microglial cells, activate the secretion of cytokines of the IL1 family, which in turn promotes the production of a secondary cascade of inflammatory cytokines, such as secretion of IL6 by astrocytes and TNFα by microglia, which leads to a heightened inflammatory response [98]. Hyperglycemic condition in DR activates a number of glucose metabolic pathways, which indirectly results in an upregulation of pro-inflammatory and angiogenic factors, leading to an aberrant inflammatory response and endothelial dysfunction. Activation of retinal glial cells including astrocytes, müller cells and microglia play a significant role in the onset of inflammation at the later stages of DR [99]. Several studies have shown that MSCs have the ability to selectively suppress immune responses, only when placed within a pro-inflammatory microenvironment and hence have been suggested for therapy for patients with severe immunological disorders [100]. The mechanism of immunosuppression by MSCs involves cell-cell contact mediated repression of function and maturation of T cells (CD4+ and CD8+ cells), B cells, dendritic cells (DCs), NK cells, neutrophils and macrophages [101]. Functional regulation of these immune cells and anti-inflammatory responses by MSCs is triggered by secretion of immune-modulatory cytokines such as, nitric oxide (NO), indoleamine 2,3- dioxygenase (IDO), tumour necrosis factor-stimulated gene 6 (TSG6), prostaglandin E2 (PGE2), thrombospondin type 1 (TSP1), interleukins 6, 10 (IL6, IL10), TGFβ1, and HGF [102]. Further, MSC derived exosomes modulate inflammation by promoting polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, activation of regulatory T (Treg) cells, inhibition of B lymphocytes and prevention of neutrophil mobilization [103, 104].

Studies have shown that intravitreal and periorbital administration of BMSCs resulted in significant reduction of inflammatory cytokines in the retinal microenvironment, infiltration of macrophages [105] and $CD4^+$ T cells [106]. Moreover, when stimulated with IL17 and IFNγ (Interferon γ), the high expression of pro-inflammatory factors observed in organotypic cultures of the posterior segment of the eye was significantly thwarted in the presence of murine BMSCs [107]. Further, injection of rat BMSCs impeded the Th1/Th17 mediated inflammation, regulated the equilibrium between Th17 and Tregs, and decreased the function of antigen presenting cells (APCs) in an experimental autoimmune uveitis model [108]. Transplantation of rat ADSCs in an experimental ocular hypertension model led to reduced expression of pro-inflammatory cytokines, IFNγ, TNFα and increased the expression of anti-inflammatory cytokines, prostaglandin E2 receptor and IL1Ra [109]. Ji et al found that intravitreally injected human UMSCs attenuated retinal neuroinflammation by downregulation of TLR4 signaling pathway in a glaucomatous rat model [110]. Moreover, intravitreally administered rat BMSCs decreased the levels of pro-inflammatory cytokines TNFα, ILβ1 and IL6 and abrogated ischemia-induced damage in the retina in a preclinical model reported by Mathew et al [111]. Holan et al and Cejkoa et al reported a marked suppression in the infiltration of T lymphocytes and levels of pro-inflammatory cytokines after transfer of rabbit derived MSCs onto an alkali-injured ocular surface [112, 113]. Millan-Rivero et al reported that human WJMSCs expressed a higher level of immunomodulatory factors TGFβ, IDO, PGE2 than BMSCs and elicited neuroprotection [84].

MSCs modulate angiogenesis

Pathological retinal angiogenesis, unlike vasculogenesis and physiological angiogenesis, leads to disorderliness and creates physiologically deficient blood vessels that disrupt the neuronal histology. These newly formed blood vessels intrude into the outer retina and the macular pit, where absence of vascularity is essential for human vision. Retinal diseases like AMD, diabetic retinopathy, uveitis and retinal vasculitis are characterized by pathological angiogenesis leading to permanent loss of vision [114]. Kim et al reported that intraperitoneal injection of human placental amniotic membrane derived MSCs (AMSCs) in a mouse model of oxygen induced retinopathy resulted in significant abrogation of neovascularization through TGFβ1 expression, which was blocked when AMSCs were transfected with TGFβ1 siRNA [115]. Ghazaryan et al reported that sub-conjunctival injection of BMSCs encouraged corneal wound healing and significantly reduced the neovascularization by downregulating VEGF and matrix metalloproteinase-9 (MMP-9) expression [116]. When murine ADSCs were intravitreally administered in a diabetic mouse model, although the intraocular levels of VEGF and PDGF was unaffected, the expression levels of TSP1 increased significantly [77]. TSP1, primarily produced by RPE, choroid and müller glial cells in the healthy eye prevents

VEGF receptor 2 (VEGFR2) activation by disrupting the receptor's association with CD47 and terminates the VEGF signaling to AKT- endothelial nitric oxide synthase pathway [117, 118]. TSP1 also binds to CD36 and recruits Src homology 2 domain- containing protein tyrosine phosphatase (SHP1) to the CD36-VEGFR2 complex in the microvascular endothelial cells, which in turn dephosphorylates VEGFR2 and inhibits angiogenesis [119]. Several studies have suggested that the successful reconstruction of damaged ocular tissues by MSCs was more dependent on the release of paracrine anti-inflammatory and anti-angiogenic factors than differentiation into ocular cells [120–122]. Thus, when human BMSCs were intravitreally implanted in an oxygen induced retinopathy mouse model, it significantly reduced retinal neovascularization [123]. When engineered to secrete therapeutic dose of anti-angiogenic factor PEDF, BMSCs were recruited to CNV lesions and inhibited neo-angiogenesis in vivo [124]. Although MSCs secrete pro-angiogenic factors VEGF and PDGF, which in fact can accelerate pathological angiogenesis in retinal diseases, it was found that MSCs exert either pro- or anti-angiogenic effect depending on the tissue microenvironment into which they were transplanted [77, 125].

MSCs donate mitochondria

Several studies have reported that MSCs transfer healthy, functional mitochondria via tunneling nanotubes (TNTs) [126], gap junctions [127] and exosomes [128, 129] to the damaged cells for its regeneration [130]. Numerous studies have demonstrated enhancement of mitochondrial bioenergetics by MSCs in the injured cells in spinal cord [131], bronchial epithelia [132, 133], corneal epithelia [134], cardiomyocytes [135, 136] and cells affected by neurotoxicity [137, 138]. Ndufs4 knockout mouse model, characterized by mitochondrial complex I dysfunction, suffer from RGC degeneration, a condition which is strongly linked to pro-inflammatory and innate immune responses. When induced pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSCs) were injected intravitreally into Ndufs4 knock out mouse, MSCs donated mitochondria to damaged RGCs via TNT formation and rescued its function. Although, injected MSCs do not pass through inner limiting membrane (ILM) of the retina, the mitochondria donated by the MSCs efficiently permeated the ILM and limited the RGC death [139]. Mitochondrial dysfunction is involved in many retinal diseases such as AMD, DR, glaucoma and mitochondrial transfer therapy might have profound impact for the treatment of these diseases [140].

MSCs replace pericytes

Pericytes are a heterogenous population of cells in the blood vessels [141], embedded in the basement membrane of the vasculature, provides protection and stabilize the retinal microvasculature [142]. Vasoregression caused due to loss of pericytes induced by hyperglycemia, is a major cause of pathogenesis in DR [143]. Several studies have suggested that MSCs could replace pericytes [77, 144], due to the morphological and functional similarities of MSCs with pericytes [145] and thus MSCs can provide therapeutic advantage in the early stage DR [146]. Adipose tissue derived stromal cells (ASCs), isolated from the stromal vascular fraction of the adipose tissue, shares cell surface markers expression with both MSCs and pericytes [147]. ASCs were found located at perivascular locations in the adipose tissue and expressed genes characteristic of pericytes [148], stabilized the vasculature and prevented apoptosis of endothelial cells. NOTCH2 was found to be essential for ASCs to acquire pericyte position in the retinal microvasculature in vivo whereas its regenerative capacity was unaffected by NOTCH2 downregulation [149]. Mendel et al found that intravitreal injection of ASCs in oxygen induced retinopathy mouse model and Akimba diabetic mice models resulted in integration of the injected cells in the retinal microvessels and exhibited pericyte like function. The injected cells normalized retinal microvasculature and prevented capillary loss in these disease models [144]. Further, Rajashekhar et al found that intravitreally injected human ASCs in a chronic hyperglycemia DR model aligned themselves with the host vasculature, rescued the neural retina degeneration and improved visual function, suggesting pericyte-like function of the injected cells [150].

The property of human ADSCs to stabilize retinal vasculature remains unaltered, in the hyperglycemic or diabetic environment generally found in DR [151–153]. Fiori et al found that ADSCs supported angiogenesis under hyperglycemic conditions while their differentiation ability and cell surface marker expression remain unaffected. In agreement with the angiogenesis supporting ability, the ADSCs acquired pericyte-like function when co-cultured with endothelial cells [151]. However, treatment with ADSCs might be beneficial only in the early stages of DR during vasoregression and can be detrimental in the late stage of DR characterized by neo-angiogenesis.

Differentiation of MSCs into retinal cells

BMSCs, ADSCs, DPSCs and UMSCs have been found to efficiently differentiate into various cells of retinal lineages in vitro and express genes related to retinal cells. Some studies also tested the functionality of the differentiated cells in in vitro systems. Autologous MSC transplantation could be a promising strategy for cell replacement therapy in retinal

diseases, however, further preclinical studies are required to understand the safety, immunogenicity and function of the transplanted cells in vivo.

BMSCs

When cultured in the presence of retinal extract and supernatant from T-cell mitogen Concanavalin A-stimulated splenocytes, murine BMSCs differentiated and expressed genes related to several retinal cell types such as photoreceptors (rhodopsin, S antigen, recoverin), horizontal and bipolar cells (calbindin2), RPE cells (retinaldehyde binding protein) and müller cells (retinaldehyde binding protein, retinal pigment epithelium 65) [154]. Further, rat BMSCs cultured in conditioned media from neonatal rat retinal cells differentiated into RGC-like cells which stained positive for nestin, neurofilament, Map2, Thy1.1 and exhibited protein expression patterns similar to that of isolated RGCs [155]. Co-culturing of human BMSCs with adult pig RPE cells in a transwell system resulted in differentiation of MSCs into cellular retinaldehyde binding protein (CRALBP), retinal pigment epithelium 65 (RPE65) and zonula occludins-1 (ZO-1) positive cells, secreted BDNF, GDNF and showed the ability to phagocytose extracellular elements of the photoreceptor outer segments in vitro [156]. Also, RPE-like cells that expressed RPE65 with phagocytic activity was generated from BMSC derived neurospheres in an in vitro study reported by Kadkhodaeien et al [157].

ADSCs

Huang et al reported in vitro differentiation of human ADSCs into retinal progenitors, RGCs and photoreceptors cells expressing characteristic retinal cell markers when treated with noggin, dickkopf related protein-1, IGF-1 and exhibited glutamate-evoked calcium response [158]. Amirpour et al reported that culturing human ADSCs in the presence of small molecule inhibitors of WNT, NODAL and BMP4 signaling pathways, or ADSCs derived conditioned media or with both the inhibitors and the conditioned media resulted in the differentiation of ADSCs into eye-field neuroectoderm (EFN) cells expressing OTX2, or cells expressing high levels of PAX6, RAX and SIX3 or cells with high expression of β-tubulin III respectively [159]. However, hanging drop cultures of ADSCs with the above conditions resulted in higher expression of EFN markers compared to monolayer cultures [160]. Similar to that observed in BMSCs, human ADSCs cultured with conditioned medium from RPE, showed the ability to differentiate into cells expressing typical RPE markers RPE65, cytokeratin 8, bestrophin and acquired high proliferative and migratory ability in vitro [161]. Rezanejad et al noted that the ADSCs transduced with human transcription factor Paired box 6 protein (PAX6, 5a) and cultured in a media supplemented with fibronectin differentiated into retinal progenitors, photoreceptors and RPE cells expressing cone-rod homeobox protein (CRX), rhodopsin and RPE65 [162].

DPSCs and UMSCs

Roozafzoon and colleagues found that DPSCs successfully differentiated into RGCs-like cells when cultured in a media containing FGF2, sonic hedgehog (Shh) on a biocompatible fibrin hydrogel (3D culture). The differentiated cells expressed astrocyte marker GFAP, neuronal marker MAP2, RGCs specific marker Brn3b, Pax6 and atonal bHLH transcription factor 7 (Atoh7) [163]. Further, ex vivo expansion of DPSCs in conditioned media obtained from chemically damaged rat retina resulted in morphological changes and expressed rhodopsin and BDNF [164].

Choi et al reported that when UMSCs were cultured in retinal differentiation inducing media with anti-miR-203, the cells exhibited a significant increase in expression of retina development genes (CRX, NRL and DKK1), and differentiated into cone photoreceptor-like cells with expression of OPN1MW, rod photoreceptor-like cells and expressed NR2E3, NRL, and Rhodopsin. [165]. Similarly, inhibition of miR-410 in UMSCs induced differentiation into RPE-like cells that expressed bestrophin and EMMPRIN, and exhibited phagocytosis ability [166].

Genetically engineered MSCs

Several research groups have genetically modified MSCs and tested their efficiency in treatment of retinal diseases in animal models and in vitro studies. Intravitreally injected murine BMSCs engineered to secrete BDNF was found integrated into the outer retinal layers and rescued damaged retinal cells through activation of anti-apoptotic factor B-cell lymphoma-extra-large-protein (BCL-XL) expression in a retinal degenerative rd6 mutant mouse model [167]. Similarly, neurotrophin-4 (NT-4) engineered murine BMSCs could be detected 3 months post intravitreal transplantation in a preclinical model of acute retinal injury. Here, the transplanted cells migrated to the sites of injury, resulting in significant improvement in morphology and function of the damaged retinal cells [168]. The presence of BDNF and NT-4 in the damaged retinal microenvironment activated the TrkB expression in the RGCs, which in turn activated the signaling pathways involved in neural cell survival (P13/Akt pathway), differentiation, migration and development (ERK pathway). NT-4 expressing BMSCs also induced the expression of several proteins of the crystalline β-γ superfamily, known to be actively involved in neuroprotection [168]. When Guan et al injected genetically modified rat BMSCs that secrete EPO in a retinal degenerative rat model, retinal morphology, function

improved significantly and the transplanted MSCs adopted RPE morphology [169]. EPO possesses anti-apoptotic, anti-oxidative, anti-inflammatory, neuroprotective properties [170] and can also enhance regenerative potential of engineered MSCs in an autocrine manner. Conditioned media from EPO expressing WJMSCs ameliorated glutamate-induced cell death in human retinal neurons in vitro [171] and placenta derived MSCs (PMSCs) expressing PEDF caused regeneration of oxidative stress damaged RPE cells when co-cultured in vitro or injected intravitreally in vivo [172].

MSCs require a niche for survival, differentiation and integrating them with a 2D or 3D biomaterial derived scaffold can mimic endogenous ECM and might result in superior in vivo integration. Hyaluronic acid (HA), a substance physically and chemically similar to the vitreous body of the eye, when intravitreally injected along with MSCs in a rat model of glaucoma, it promoted integration of MSCs into the basement membrane of müller glial cells and enhanced survival of RGCs by inducing the expression of NGF and BDNF [173]. Moreover, 3D cultures of DPSCs on biocompatible fibrin hydrogel [163], culturing BMSCs on silk fibroin films functionalized with integrin-binding laminin peptide motifs (GYIGSR and YIGSR) [174], culturing MSCs on amniotic membrane scaffold and differentiation of human conjunctival MSCs (CMSCs) towards photoreceptor like cells on fibrin hydrogel [175] resulted in significant enhancement of MSCs differentiation into the desired retinal cell types.

Clinical Trials with MSCs for retinal diseases

The encouraging outcomes seen with injecting MSCs in animal models of retinal degeneration led to initiation of several clinical trials. Whilst most trials are ongoing (Table 1), outcomes of some of the phase I trials are discussed below.

In a case report of SCOTS (Stem cell ophthalmology treatment study) clinical trial (NCT01920867), a patient suffering from autoimmune optic neuropathy prone to relapse, underwent a vitrectomy and intraoptic injection of autologous BMSCs in the right eye along with retrobulbar, subtenon and intravitreal injection of the same cells in the left eye. Significant improvement in visual acuity and visual field was observed 3 months and 6 months after the treatment [176]. In another SCOTS trial, a patient suffering from idiopathic optic neuropathy resulting in significant loss of central vision for approximately 5 years received retrobulbar, subtenon and intravitreal injection of autologous BMSCs in the right eye. The left eye was treated with vitrectomy and intra-optic nerve injection of the same cells, followed by intravenous infusion. The enhancement of visual acuity in both eyes remained stable when examined 12 months post-operation [177]. Weiss and Levy conducted a SCOTS clinical trial in 17 patients suffering from bilateral vision loss due to progressive RP with autologous BMSCs transplantation. A 6 months followup found an improvement in visual acuity in 11 out of 17 patients (64.7%), 8 patients (35.3%) exhibited stability in their condition and none experienced vision loss. This study also found that the ability of the eyes to respond to cell therapy was irrespective of the duration of the disease [178]. However, Satarian et al reported that intravitreal injection of autologous BMSCs in three patients suffering from advanced RP, resulted in improvement in visual acuity in only two of the patients whereas the third patient developed severe and progressive adverse effects. The patient developed vitreal and pre-retinal fibrosis two weeks after transplantation which led to total tractional retinal detachment at the end of the three-month follow-up period [179]. A prospective, non-randomized clinical study (ChiCTRONC-16008055) by Gu et al analyzed the safety and effectiveness of intravenous administration of autologous BMSCs. The study included 10 patients with severe NPDR and 7 patients with non-high-risk PDR. During 6 months follow-up, the patients of the NPDR group exhibited significant gain in BCVA (best corrected visual acuity) (P=0.006 at 3 months and P=0.027 at 6 months) and macular thickness reductions. On the contrary, only a slight BCVA improvement and macular thickening was recorded in the PDR group suggesting that the treatment regime is suitable for patients at NPDR stage, rather than PDR stage [180].

In a clinical trial involving 12 AMD patients, Limoli et al administered autologous adipocytes along with ADSCs obtained from stromal vascular fraction (SVF) and platelet rich plasma (PRP) between choroid and sclera and found a significant improvement in retinal functionality as observed by increased electroretinogram (ERG) values [181]. In the next phase of the trial, ADSCs along with PRP was administered in suprachoroidal space of 36 eyes involving 25 AMD patients. Six months follow up indicated that 19 out of 36 (52.78%) eyes exhibited better vision, 14 eyes (38.89%) showed no change in functionality, and the condition of three eyes (8.33%) worsened. The eyes which possessed greater retinal thickness prior to the treatment were seen to show greater improvement in vision and thus, high number of residual cells can lead to more interaction with paracrine factors secreted by ADSCs and chorio-retinal cell membrane receptors, allowing enhancement in vision quality [182]. Oner et al tested the safety and efficacy of subretinal implantation of ADSCs in 11 patients suffering from end-stage RP and found neither improvement nor adverse effects in most of the patients. However, five patients in the study group experienced ocular complication and one patient suffered from CNV [183]. In another phase II study, Oner et al found an improvement in visual acuity, visual field and multifocal electroretinography (mf-ERG) readings after suprachoroidal ADSCs implantation in patients with dry AMD (4 patients) and Stargardt's macular dystrophy (SMD, 4 patients). During the 6 month follow up,

Table 1 Ongoing and completed clinical trials with MSCs for retinal diseases

Condition	Cell Type	Route of administration	Dosage	Number of patients enrolled	Recruitment Status	Phase of Study	Clinical Trial (clinicaltrials.gov)	Start Date	Actual/ Estimated Completion Date
Retinitis Pigmentosa	Allogeneic WJMSCs	Intravitreal	2-6x10^6 cells/1.5mL	32	Completed and published [185]	III	NCT04224207	April, 2019	January, 2020
Retinitis Pigmentosa	UMSCs	Peribulbar	1x10^6 cells/1.8mL	18	Completed and published [186]	I/II	NCT04315025	October, 2018	September, 2019
Retinitis Pigmentosa	Autologous BMSCs	Intravitreal	1x10^6 cells/0.1mL	10	Enrolling by invitation	I	NCT01531348	February, 2012	December, 2020
RP, AMD, DR, VO, HRD	Autologous BMSCs*	Intravitreal	3.4x10^6 cells/0.1mL	15	Enrolling by invitation [202]	I	NCT01736059	July, 2012	January, 2022
Retinitis Pigmentosa	Autologous BMSCs**	Intravitreal	-	50	Active, Not recruiting	I/II	NCT02709876	April, 2014	March, 2021
AMD	Autologous BMSCs	Intravitreal	-	1	Unknown	I/II	NCT02016508	March, 2013	June, 2015
AMD	Autologous ADSCs	Intravitreal	-	-	Withdrawn [203]	NA	NCT02024269	December, 2013	June, 2017
Glaucoma	Autologous BMSCs	Intravitreal	1x10^6 cells/0.1mL	2	Completed	I	NCT02330978	January, 2014	September, 2016
Glaucoma	Autologous ADSCs***	Subtenon	0.5mL	16	Unknown	I/II	NCT02144103	May, 2014	January, 2019
Diabetic Retinopathy	Autologous BMSCs	Intravenous	2x10^6 cells/kg	20	Recruitment complete	I/II	IRCT201111291414N29	June, 2012	June, 2013
Diabetic Retinopathy	Autologous BMSCs	Intravenous	3x10^6 cells/kg	17	Completed and published [180]	I/II	ChiCTRONC-16008055	April, 2013	December, 2016
RD, RP,AMD,SD	Autologous BMSCs$	Intravitreal	-	30	Enrolling by invitation	I	NCT03772938	December, 2018	March, 2020
AMD, RP, SD, ON, OA, OND, RA, VLP,VLN, Maculopathy, Glaucoma	Autologous BMSCs$$	Retrobulbar, Subtenon, Intravitreal, Subretinal, Intravenous	-	500	Recruiting	II	NCT03011541	January, 2016	January, 2023
RD, AMD, HRD, OND, Glaucoma	Autologous BMSCs$$	Retrobulbar, Subtenon, Intravitreal, Intraocular, Intravenous	-	300	Enrolling by invitation [176, 177]	NA	NCT01920867	August, 2012	July, 2020

VO - Vein occlusions, HRD - Hereditary retinal disease, SD - Stargardt's disease, ON - Optic Neuropathy, OND - Optic Nerve Disease, OA - Optic Atrophy, RA - Retina Atrophy, VLN - Vision Loss Night, VLP - Vision Loss Partia,; NA- Not Applicable.

* $CD34^+$ bone marrow derived stem cells, ** $CD34^+$ $CD133^+$ $CD271^+$ bone marrow derived cells, *** adipose derived stromal cells, $ bone marrow-derived stem cells, $$ SCOTS bone marrow-derived stem cells

no ocular or systemic complications were observed in these patients [184].

Özmert and Arslan recently reported the result of an open label, phase III clinical trial (NCT04224207) with WJMSCs. In this study, WJMSCs were implanted in the sub-tenon space in 32 patients diagnosed with RP. In the 6 month follow up period, a significant improvement in mean BCVA, outer retinal thickness values, mf-ERG results and decrease in the visual field mean deviation value was observed. The authors did not observe any severe ophthalmic or systemic complication, thus, assuring its safety [185]. Mangunsong et al tested the safety and efficacy of peribulbar infusion of UMSCs in a prospective, multi-center, randomized clinical study (NCT04315025) involving 18 individuals suffering from RP. An improvement in light perception and visus was observed one week after the treatment and no serious side effects was seen during that period [186].

Challenges and future prospects

Although MSCs are promising therapeutic candidates for retinal degenerative diseases due to their ability to secrete a repertoire of NTFs, modulate inflammation and angiogenesis, regenerate pericytes and donate mitochondria, the therapeutic outcome is limited by poor cell survivability and self-renewal of the cells post-transplantation [187, 188]. For example, although, Inoue et al identified a delay in retinal degeneration after injection of MSCs into RCS rats, they did not find integration of the injected cells into the retinal layer [189]. Several reasons for cell death at the transplanted site have been

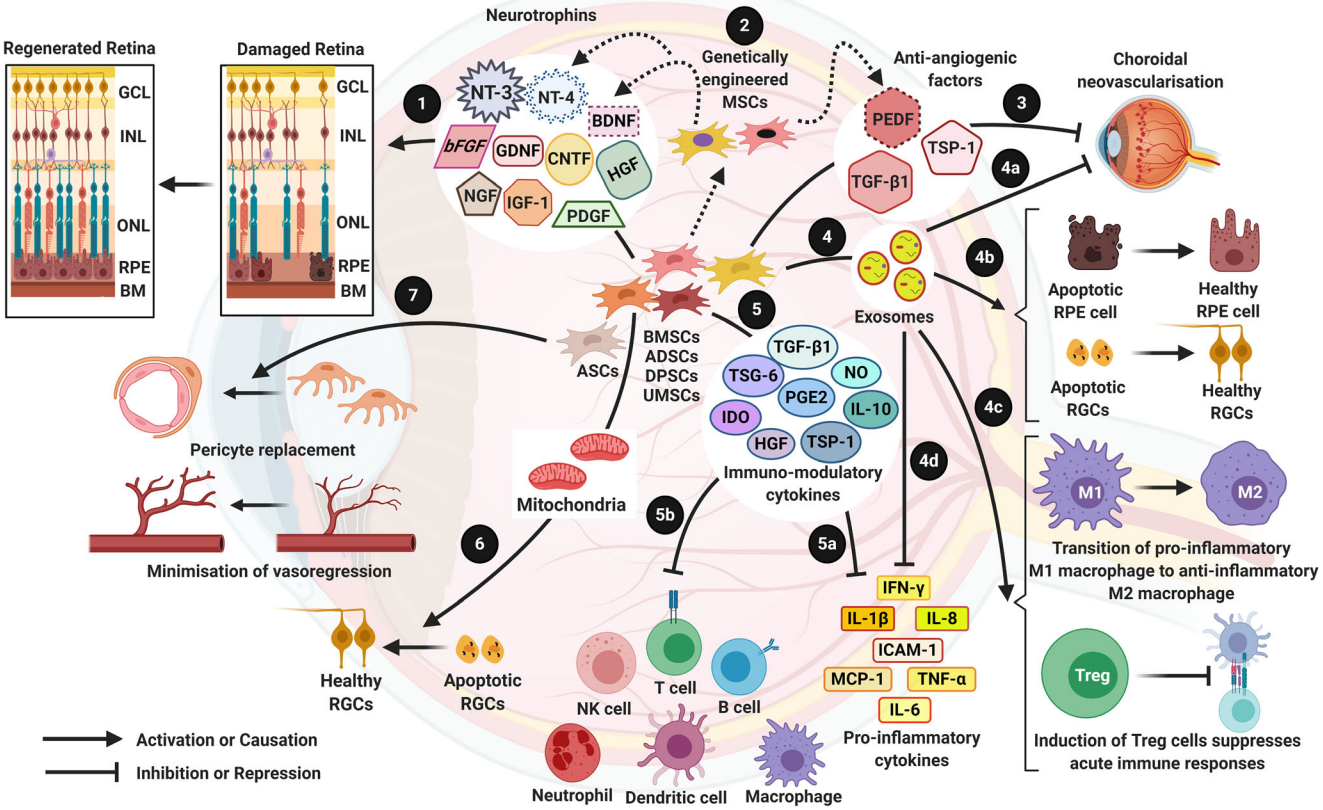

Fig. 1 Mesenchymal stem cells for treatment of retinal degenerative disorders 1) MSCs have the ability to secrete several neurotrophins which play a cytoprotective role in degenerated retina, found in multiple retinal diseases such as AMD, SD, DR, RP, and Glaucoma [63]. 2) MSCs can be genetically engineered to express neurotrophins such as NT-4 [168], BDNF [167] and anti-angiogenic factor PEDF [124] that can improve therapy outcome. 3) AMD and DR are associated with pathological angiogenesis which leads to abnormal growth of blood vessels (Choroidal neovascularisation) and haemorrhages within the ocular microenvironment [43, 198]. Anti-angiogenic factors released by MSCs can reverse abnormal pathological angiogenesis [77, 115]. 4) MSCs secrete exosomes, microvesicles which contain a cargo of biomolecules such as mRNA, lipids, several proteins with therapeutic advantages: (4a) Exosomes contain anti-angiogenic factors [87] that can inhibit pathological angiogenesis; (4b) mRNA molecules in the exosomes provide neuroprotection of essential retinal cells [88]; (4c) molecules within the exosomes prevent the activation of macrophages and induce Treg cells, hence downregulating disease causing immune responses within the ocular tissue [104]; and (4d) anti-inflammatory factors in the exosomes [86] aid in the recovery of retinal degeneration in AMD, DR and Glaucoma. 5) MSCs secrete immunomodulatory cytokines [102], which (5a) represses the action of pro-inflammatory cytokines and (5b) thwart acute immune responses, both of which are involved in the pathogenesis of AMD, DR and Glaucoma. 6) MSCs provide cytoprotection by donating healthy mitochondria to apoptotic retinal cells through formation of cell-cell contact via tunneling nanotubes or gap junctions [140]. 7) ADSCs can replace pericytes and stabilize vasculature in DR [151].

suggested such as exposure to harsh microenvironment featuring hypoxic conditions, oxidative stress or inflammation; lack of extracellular matrix for cell adhesion, thus leading to increased anoikis, mechanical stress during the transplantation procedure or lack of an optimized dosage and protocol for transplantation [187, 188]. Likewise, lack of integration of MSCs after intravitreal injection, might be due to the cells being drained out of the eye with the flow of aqueous humor [190]. Several preclinical studies utilized human MSCs in rat, mouse and rabbit disease models to test their potential use for retinal therapy, however, a major concern is that the diseased ocular environment in these animal models might not be identical to the human diseases [191]. Moreover, the secretome of MSCs in non-human ocular microenvironment might not resemble that of the human conditions and have the risk of overestimating or undervaluing the potential benefits.

Tassoni et al reported an adverse effect, induction of reactive gliosis in response to intravitreal transplantation of MSCs [192, 193]. This was due to the activation of müller glia cells via JAK/STAT3 and MAPK cascades, resulting in overexpression of intermediate filaments (vimentin, nestin, GFAP) and significant production of neurotoxic Lipocalin-2. Reactive gliosis is characterized by structural disorganization of the retina, infiltration of macrophages and inflammation [193]. Since glial reactivity can act as a deterrent to the retinal engraftment of transplanted MSCs, pharmacological inhibition of STAT3 could prevent the occurrence of reactive gliosis [193]. On the contrary, a subsequent study reported a reduction in gliosis and improvement in visual function within 3 weeks of infusion of MSCs in a STZ-induced diabetic retinopathy model [194]. Hence, the subject of occurrence of reactive gliosis after infusion of MSCs in the diseased ocular tissue needs further investigation and consideration before utilizing the cells for therapy. Further, some of the clinical trials discussed earlier reported adverse effects or worsening of the condition after administration of MSCs [179, 182, 183].

Additionally, the source of MSCs and the age of the donor tend to impact the differentiation and paracrine effects of MSCs, for example, ADSCs were found to secrete VEGF, unlike BMSCs [195]. Some studies have hypothesized that the pro- or anti-angiogenic effect of MSCs depend on the tissue microenvironment [196, 197, 121], and a detailed understanding of the pro or anti-angiogenic niche is also necessary. This is important in utilizing MSCs for ocular disorders where choroidal neovascularization plays a major role in pathogenesis [198]. Additionally, it is known that ASCs are able to replace pericytes and protect the vascular networks within the retina, however, serious considerations should be given before its therapeutic use since the pro-angiogenic ability of ASCs can promote disease progression in DR [199].

Although MSCs have been shown to differentiate into cell types of retinal lineages in several studies in vitro, it is still not clear whether the differentiated cells can exhibit the desired function in vivo. Specifically, the phagocytic ability of the RPE cells derived from MSCs [166, 156, 157] has to be critically analyzed before concluding the transdifferentiation of MSCs into functional RPE cells. There are some evidences that show that MSCs themselves can perform phagocytosis [200] and the phagocytic assays of RPE cells should include all the essential markers as reported by Mazzoni et al [201]. Nevertheless, secretion of NTFs and paracrine mediated therapy plays a more important role than the trans-differentiation of MSCs in repair of the damaged retinal tissue [63]. In this context, cell free therapy, consisting of conditioned media from cultured MSCs, that contains extracellular vesicles, mitochondria, NTFs and other paracrine factors might have greater clinical benefit as well as eliminate the safety issues associated with injecting the cells at the target site (Fig. 1). Thus, MSCs from different sources have potential benefits for the treatment of retinal disorders, as observed in several preclinical studies and human clinical trials, developing a standardized method for each disease type will help in utilizing these cells efficiently for the benefit of the patients.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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