

Mesenchymal Cells for RP Therapy

Subjects: [Cell Biology](#)

Contributor: Paolo Giuseppe Limoli , Enzo Maria Vingolo , Celeste Limoli , Marcella Nebbioso

Retinitis pigmentosa (RP) is a complex inherited retinal dystrophy currently lacking effective therapies: this represents one of the greatest challenges in the field of ophthalmological research. Stem cells, especially mesenchymal cells represents a feasible therapeutic option in RP, limiting both oxidative stress and apoptotic processes triggered by the disease and promoting cell survival.

[Retinitis Pigmentosa](#)[MSC](#)[Mesenchymal Cells](#)[Cell Therapy](#)[Oxidative Stress](#)

1. Introduction

Retinitis pigmentosa (RP) affects 1.5 million people around the world, representing the most widespread hereditary retinal dystrophy: globally, its prevalence is estimated at 1:4000.

The term 'RP' comprises a series of clinical conditions caused by a high number of genetic alterations that, either alone or in association, cause damage to the molecular processes necessary for the creation, conservation, use, or recovery of rhodopsin. The direct consequence is the progressive and total loss of rod cells [\[1\]\[2\]\[3\]](#).

The genetic etiology of RP underlies the damage and subsequent death of rod cells, while the central retina, which contains mainly cone cells, remains in relatively good condition until the advanced stage of the disease. This explains why RP patients are often diagnosed later on in life, after the second or third decade of life.

However, the clinical manifestations of RP are caused not only by rod cell loss but also by the cone cell injury, albeit in later phases.

The cone loss goes beyond genetics [\[4\]\[5\]\[6\]](#) and involves other biomolecular mechanisms, including alterations in hemodynamics [\[7\]](#), oxidative stress due to the higher availability of oxygen after rod loss [\[8\]\[9\]](#), and the impaired response to oxidative stress [\[2\]\[3\]\[10\]\[11\]\[12\]](#).

This sequence of events underlies the prevailing symptoms of RP: night blindness, tunnel vision, followed by progressive loss of central vision and complete or near complete blindness.

Rod cells account for about 95% of all photoreceptors, and the oxidative metabolism of fatty acids is their main source of energy [\[13\]](#).

More than 80 causative genes of RP responsible for rod damage have already been identified, although a significant number of them are still unknown [\[14\]](#).

Genetic mutations responsible for RP in some cases also involve genes expressed not only in rods but also in the retinal pigment epithelium (RPE), such as MERTK [\[15\]](#), RLBP1 [\[16\]](#), and RPE65 [\[17\]](#).

RPE plays many vital roles for photoreceptor cells, and the most fascinating is certainly its protective action against oxidative stress [\[18\]](#).

Recent studies have confirmed a high level of reactive oxygen species (ROS) in RPE, and fatty acids are one of their molecular targets. If oxidized, they can compromise transduction pathways and gene expression [\[19\]](#).

At this point, a cascade of molecular phenomena—such as para-inflammation, synaptic impairment, apoptosis, and cell death—which hugely impact visual function, is triggered.

Therefore, oxidative damage is considered the leading cause of cone apoptosis and progressive vision loss [\[6\]](#)[\[7\]](#)[\[20\]](#)[\[21\]](#).

However, this chain of events, which is triggered after the rod death and leads to the cone loss, highlights a number of key points that can potentially be leveraged therapeutically to slow down or stop the disease progression towards its terminal stages, modulating the rod damage and preventing or delaying cone death [\[22\]](#)[\[23\]](#)[\[24\]](#).

In order to stimulate neuronal survival, many research groups have worked on animal models of RP.

New therapeutic approaches for RP include the restoration of defective genes and stem cell transplantation to replace or repair impaired or dead cells [\[25\]](#)[\[26\]](#).

2. Oxidative Stress and Retinitis Pigmentosa

2.1. Animal Models of RP

There are a complex variety of animal models that have allowed the molecular study of RP.

The refinement of these genetic models offers a deeper comprehension of biological and etiopathogenetic mechanisms of the disease. Based on these studies, it is also possible to develop new treatments and prevention strategies.

Examples of those models are Rd1 mice [\[27\]](#), Rd10 mice [\[28\]](#), P23H and S334ter Rhodopsin Transgenic Rats [\[29\]](#), Rd mice [\[30\]](#), Rds mice [\[31\]](#), Royal College of Surgeons rats [\[32\]](#), and RPE65 dog [\[33\]](#).

Rd1/rd1 mouse has a mutation at the level of β subunit of phosphodiesterase cGMP gene that leads to cGMP toxic accumulation, higher level of intracellular Ca^{2+} , and finally rod death [27][34][35][36][37]. The rod loss leads to a greater amount of oxygen available, that injures the cones, causing their death. In view of this, antioxidative therapy could prevent cone death in this RP murine model [34][35][36][37].

A similar mutation has been found in a particular type of autosomal recessive RP, and therefore Rd1/rd1 mouse has become an ideal RP model [34].

Rd10 mouse has allowed the study of ceramide in retinal degeneration. Ceramide is a proapoptotic sphingolipid and its level increases during the rod cell death.

It has been shown that the photoreceptor loss can be blocked by hindering the ceramide proapoptotic pathway.

Intraocular injection or continuous eye drops administration of myriocin, inhibitor of serin palmitoyl-CoA transferase, can return ceramide to normal levels and stop the apoptotic death of photoreceptors. Therefore, this therapeutic approach can be applied to humans [28].

P23H rat model has established that the photoreceptor loss triggers major changes in the number and morphology of glial cells affecting the inner retina.

Both astrocytes and Müller cells promote retinal cell survival by releasing neurotrophic factors, providing anti-oxidative support, catabolizing neurotransmitters in the extraneural space, and supporting synapse formation. They also contribute to activating microglial cells and regulating vascular tone [38]. In addition to the photoreceptor loss in P23H rat model, the alteration of retinal vascular plexuses has been observed. The reduced capillary density may hinder the oxygen and nutrient supply to the retinal cells and foster the retinal degeneration. Thus, vascular injuries should be considered as an important therapeutic target in degenerative retinal diseases [39].

In Rd [30], Rds [31], in Royal College of Surgeons rat [32], and in RPE65 dog [33], the identification of a single mutation has allowed to develop targeted gene therapy and to partially limit the retinal degeneration. However, there are only few types of RP with specific mutations, restricting the application of gene therapy.

The use of trophic factors [40][41][42], calcium channel blockers [43], or MSCs [44] have been observed to slow down the disease progression in some RP animal models.

2.2. Synoptic Aspects of Oxidation and Antioxidation

Photoreceptors are particularly sensitive to oxidative damage exerted by the light, with which they constantly interact [45][46][47]. In fact, to phototransduce electromagnetic radiation into visual stimuli, retinal cells contain numerous photosensitive molecules, a considerable amount of polyunsaturated fatty acids (15% of photoreceptor's mass) and are characterized by an extremely high metabolism, from which unstable metabolic byproducts, called ROS, are continuously generated. ROS are represented by several unstable molecules, including superoxide anion

(O₂⁻), ozone (O₃), hydrogen peroxide (H₂O₂), hydroxyl radical (*OH) derived from the decomposition of peroxides, peroxide radical (LOO·) which removes an atom of hydrogen from another lipid molecule, and nitric oxide (NO·), a messenger in many cytosolic pathways.

Furthermore, under oxidative stress conditions, non-metabolizable advanced glycation end-products (AGEs), responsible for para-inflammation and permanent cell damage, are produced [48].

Over time, oxidative stress can alter transduction pathways and gene expression [49] and damage all the cellular components, including phospholipid membranes, proteins, and nuclear and mitochondrial DNA (mtDNA). Those injuries lead to the progressive loss of function of photoreceptor as well as RPE [50][51][52].

However, photoreceptors are able to protect themselves against these oxidative injuries through several mechanisms.

The first antioxidant defense is mediated by enzymes—such as catalase, glutathione peroxidase, and reductase—which promote the decomposition of hydrogen peroxide into water and oxygen molecules; superoxide dismutase (SOD), which is normally found in the mitochondria of cone's inner segments [53][54][55] or the glyoxalase system [56], which neutralizes ROS by acquiring electrons from oxidizing substances.

Another important defense is provided by the endoplasmic reticulum (ER) through the activation of a cellular stress response, called unfolded protein response (UPR). As a reaction to the accumulation of misfolded proteins in the ER lumen, UPR is initially set to restore normal cell function; if this process does not occur in the proper time and way, UPR activates apoptosis. The persistent activation of UPR has been implicated in the pathogenesis and progression of several diseases, such as RP [57][58].

Another protective mechanism against oxidative stress is the production of stress granules, proteins able to bind and protect specific mRNAs, preventing their degradation. Through the selective inhibition of such mRNAs, the transcription of constituent genes is selectively blocked while the translation of stress-induced transcripts is facilitated, allowing energy savings and cell survival [59].

Furthermore, retinal cells can resort to autophagy to catabolize damaged proteins and organelles, ensuring a homeostatic balance and promoting their survival following oxidative damage [11][60].

About 1–5% of ROS is generated in the mitochondria, organelles responsible for energy production in the cell. As a response to specific signals including oxidative stress, hunger, and mitochondrial protein modification, the selective autophagy of mitochondria can be activated [61].

Autophagy plays a protective role against oxidative stress and other cellular lesions, but the build-up of autophagosomes due to prolonged insults ends up becoming harmful to cells [62].

Finally, RPE cells have been shown to protect photoreceptors against ROS [63]. They are also known to provide many other vital functions for photoreceptors, such as light absorption, bi-directional epithelial transport, spatial ion buffering (in order to maintain the predisposition to depolarization), visual cycle regulation, phagocytosis of external photoreceptor segments (POS), secretion of trophic factors and signaling molecules, and support to the eye seen as an immunologically privileged site [64].

In conclusion, the balance between oxidative stress and antioxidant mechanisms is crucial for cell survival. If the cell is over-stressed or has an altered protection (e.g., due to pathologies), programmed death cell, i.e., apoptosis, is induced [65][66][67][68][69]. Therefore, it is necessary to preserve the homeostasis to avoid cell death by regulating the excess of ROS that the metabolism continuously produces.

It is especially true for RP in which the impairment of antioxidant responses has a key role in triggering the disease progression [12][47].

In fact, the photoreceptors—in particular the rods, responsible for scotopic vision, and the RPE—are the most vulnerable cell types to oxidative damage [3], especially because they are believed to reside in a terminal G0 phase.

2.3. Oxidative Stress and RP

The impairment of retinal vascularization, mainly mediated by oxidative stress, is considered to play a key role in the RP progression.

Many studies have shown a reduction both in choroidal [61][70] and macular [4][71] hemodynamics associated with a reduced visual sensitivity in RP patients.

The catabolic products released by photoreceptors not only lead progressively to rod loss but also have negative effects on microcirculation. In fact, the retinal vessels appear thin. It becomes a vicious circle in which the altered perfusion fosters photoreceptor injury and loss [72].

Several studies highlight the role of the impaired retinal circulation in RP and its correlation with residual function [73] and choroidal thickness [74]. In particular, the reduction in retinal blood flow both as a whole [20] and at the subfoveal level has been shown, with related alterations in electroretinographic recordings [75].

Several studies have shown that both endogenous ROS produced by retinal metabolism and the lipid peroxidation or DNA damage, produced by external agents, such as exposure to sunlight or cigarette smoke, can contribute to photoreceptor death.

The most pathognomonic aspect of RP is that the blood, passing through the choroid, maintains an arterial oxygen saturation until it enters the venous system. Moreover, unlike retinal capillaries, choroidal capillaries allow plasma protein diffusion in order to meet the metabolic photoreceptor needs [76].

The rods, which make up about 95% of all photoreceptors, are progressively lost in RP; consequently, the intracapillary oxygen level remains elevated, increasing ROS production and inducing an oxidative damage in the cones, surviving cells that are eventually impaired and lost [\[9\]\[45\]](#).

The following factors have been shown to exacerbate the oxidative damage and the rod death: foveal area's exposure to light, choroidal stasis, metabolic deterioration of cones and RPE cells, lack of antioxidant enzymes such as SOD, which is normally found in the mitochondria of the cone inner segments (but not in the outer ones), glutathione peroxidase, glyoxalase and catalase, and autophagy impairment [\[8\]\[10\]\[11\]\[77\]\[78\]\[79\]](#).

In recent years, it has been demonstrated that the oxidative damage can also interfere with particular RNA molecules called long non-coding RNAs [\[80\]\[81\]](#). These are involved in several critical biochemical pathways, such as chromosome conformation modeling, genomic imprinting modulation, allosteric control of enzymatic activity, as well as cell state coordination, differentiation, and development. Dysregulation or mutation of non-coding genes has been associated with various human diseases, including RP [\[80\]\[81\]](#).

The alteration of lipoproteins and DNA derived from hyperoxia can cause irreparable damage in the residual cells (mainly cones), and therefore in the foveal region [\[9\]\[45\]\[79\]\[82\]\[83\]\[84\]](#).

In RP, the cell apoptosis induced by oxidative stress determines the so-called retinal gliosis, i.e., a state of para-inflammation in which microglial and macroglial cells are activated [\[85\]](#).

The microglial cells, which are normally dormant resident retinal macrophages, provide neuroprotection against ROS damage under physiological conditions.

Debris from apoptotic or dead cells, damaged lipopolysaccharides and ROS [\[21\]\[86\]](#) can trigger the activation of apoptotic photoreceptors in RP, which generally occurs just before or at the peak of apoptotic photoreceptor death [\[87\]\[88\]\[89\]](#).

Their activation involves the expression of inflammatory regulatory proteins such as peroxiredoxin 2 (PRDX2), pro-inflammatory cytokines such as TNF- α , interleukin-1 β or interferon- γ in RPE cells [\[90\]\[91\]](#), chemokines and neurotoxic agents, including hydrogen peroxide, and superoxide anion with additional oxidative stress [\[92\]\[93\]](#).

The microglia chronic activation promotes the microglial phagocytosis against the altered components of neuronal cells, determining the evolution of RP [\[94\]](#).

Conversely, the suppression of their activation improves the survival of rods [\[95\]](#).

On the other hand, the macroglia represented by retinal Müller glia (RMG)—which form the columns of retinal tissue and have multiple connections with retinal neurons, microglia, astrocytes, and endothelial cells—modulate different responses depending on the severity of the stimulus. The activation of these macroglial cells leads to hypertrophy, which in turn induces the overexpression of vimentin (an intermediate filament) and glial fibrillary

acidic protein (GFAP), which is considered a hallmark of retinal stress [96]. As an immediate response to non-permanent acute stimuli, the RMG promotes the secretion of trophic and antioxidant factors, but as it becomes chronic, their secretory role can be clearly deleterious to neuronal cells [96].

Therefore, the abovementioned state of hyperoxia and the ensuing ROS formation are fundamental underlying causes of accelerated rod loss and cone injury in the retina affected by RP.

3. Mesenchymal Cells: Therapeutic Strategies in Retinitis Pigmentosa

Over the past few years, different therapeutic approaches aiming to delay the rod death and to prevent the cone injury in RP have been explored. In particular, much emphasis has been placed on cell therapy and gene therapy. The latter one, however, has achieved limited results in vivo and it may not modify the retinal damage once it has occurred. Consequently, scientific interest is particularly focused on cell therapy, a promising tool of regenerative medicine [97].

Some researchers have used embryonic stem cells [98] or induced pluripotent stem cells [99] to generate neurons that could replace lost cells. Although these cells effectively express neuronal markers, most of them show a poor retinal integration, remaining close to the injection site.

Other researchers have used mesenchymal stem cells (MSC) by exploiting their primary ability to paracrinally modulate the neuronal microenvironment by secreting growth factors (GF) in different retinal degeneration models [100][101][102][103][104][105].

Cell therapy can contribute to maintain both the neuronal density and the function of the retina by improving and preserving intra- and extra-cellular conditions [106].

Compared to ESCs and iPSCs, MSCs have a lower differentiation potential, but numerous advantages: they do not induce risks of uncontrolled growth and rejection reactions, not requiring immunosuppressant use; they do not have ethical problems; they are relatively inexpensive and easy to collect (especially those derived from adipose tissue); finally, they have a higher immunomodulatory capacity, meeting the prerequisites of regenerative medicine [107][108][109].

MSCs are characterized by the group of cell surface markers, both positive and negative, proposed by the International Society for Cellular Therapy in 2006 [110]. The MSC population is defined as >95% positive for CD105, CD73, CD34, and CD90, and >95%, negative for CD45, CD14 or CD11, CD79, CD19, and HLA-DR. MSCs also express other surface markers, such as CD44, CD166, Stro-1, CD106, and CD146 [111].

MSCs, spread ubiquitously throughout the body, play a key role in organogenesis, tissue remodeling, and repair [112].

They can migrate to injury sites, following the intravascular administration. This process is due to the distinctive molecules present on the surface of MSCs and endothelial cells, such as P-selectin and integrins [113]. For this reason, these cells have the ability to adhere to the endothelium and cross it by metalloprotease [114].

Among the different sources, the most interesting MSCs exploited for clinical therapeutic purposes in retinal diseases include:

- Adipose-derived stem cells (ADSCs)
- Adult adipocytes
- Platelets

Adipose tissue is one of the most interesting collection sites of MSC. Like bone marrow, adipose tissue contains a large population of stem cells, called ADSCs, within its stromal compartment. They can be obtained using simple procedures such as lipoaspiration performed under local anesthesia. ADSCs are more numerous, have a faster expansion, and a greater secretory and immunomodulatory capacity [109].

ADSCs produce basic fibroblast GF (bFGF) also known as FGF2, vascular endothelial GF (VEGF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), placental GF (PIGF), transforming GF beta (TGF- β), hepatocyte GF (HGF), insulin-like GF-1 (IGF-1), interleukin (IL), angiogenin, ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF) [108][115], and glial cell-derived neurotrophic factor (GDNF) [116].

Adult adipocytes are another type of mesenchymal cell that can be used for regenerative purposes. These can secrete specific hormones, called adipokines, which play a role in energy homeostasis. Adipose cells produce epidermal GF (EGF), bFGF, IGF-1, IL, TGF β , pigment epithelium-derived factor (PEDF), and adiponectin [117][118][119][120].

Finally, also the platelets, originating from the subdivision of megakaryocytes, originate from mesenchymal tissue.

They are well known for their hemostatic action, but they can also release substances that promote tissue repair and angiogenesis, and modulate inflammation [121]. In addition, they induce cell migration and adhesion at angiogenesis sites, as well as differentiation of endothelial progenitors into mature endothelial cells [122].

Platelets produce platelet-derived GF (PDGF), IGF-1, TGF β , VEGF, bFGF, EGF, platelet-derived angiogenesis factor (PDAF), and thrombospondin (TSP), and several authors have used them in eye diseases such as glaucoma, age-related macular degeneration (AMD), and RP [123][124][125][126].

They are used in regenerative therapy in the state of platelet rich plasma (PRP), obtained from plasma centrifugation, because it allows to achieve a greater production of cytokines, even 4–5 times greater than the

initial conditions.

Several cell grafting methods have been developed: intravitreal [\[104\]\[127\]](#), subretinal [\[128\]](#), epiretinal, subtenon [\[126\]](#), and suprachoroidal [\[129\]\[130\]\[131\]\[132\]](#) ([Table 1](#)). Each has its advantages and disadvantages.

Table 1. Main clinical studies exploiting MSC for therapeutic purposes in RP.

Disease	Cell Source	Delivery	WHO identifier	References
AMD (GA), RP and ischaemic retinopathy	Autologous BMHSC	Intravitreal injection	NCT01560715	
			NCT01518127	[103][104]
			NCT01518842	
AMD (GA), RP, RVO and DR	Autologous BMHSC	Intravitreal injection	NCT01736059	[105]
RP	Autologous ADMSC	Subretinal application	Not registered	[128]
AMD (GA), RP, OA	Autologous ADMSC And PRP	Suprachoroidal application	Not registered	[131][132][133][134]
RP	Autologous PRP	Subtenon injection	Not registered	[126]
RP	Eterologous UC-MSCs	Suprachoroidal application	Ministry of Health 56733164/203	[129]

RP: Retinitis Pigmentosa; AMD: Age related Macular Disease, GA: Geographic Atrophy, OA: Optic Atrophy; DR: Diabetic retinopathy; RVO Retinal Venous Occlusion; BMHSC: Bone Marrow Human Stem Cell; ADMSC: Adipose Derived Mesenchymal Stem Cell; PRP: Platelet Rich Plasma; UC-MSC: Umbilical Cord Mesenchymal Stem Cell.

In particular, the suprachoroidal implantation of MSCs according to Limoli Retinal Restoration Technique uses three types of autologous mesenchymal cells: ADSCs, adipocytes, and platelets concentrated in PRP. With this method, improvements have been observed in electroretinographic parameters and visual performance in AMD, opticopathies, and RP. Furthermore, it seems to be devoid of the potential complications reported for the intravitreal and subretinal methods [\[128\]](#)[\[131\]](#)[\[132\]](#)[\[133\]](#)[\[134\]](#).

The ocular administration of MSC promotes a significant restoration of the visual system in a variety of eye diseases, including RP [\[100\]](#)[\[135\]](#)[\[136\]](#)[\[137\]](#)[\[138\]](#), through several mechanisms, as follows:

- Cell differentiation and trans-differentiation for lost/damaged cell replacement
- Paracrine action for cell repair and functional stimulation
- Exosomes and microvesicle secretion
- Modulation of host immune responses in inflammation site

4. Cell-Mediated Biomolecular and Antioxidative Mechanisms in RP

The therapeutic effect of MSCs is mainly based on the paracrine secretion of cytokines, GFs, extracellular vesicles and exosomes. In recent years, the scientific literature has highlighted the several mechanisms through which the cell therapy can slow down the RP progression. The therapeutic mechanisms are summarized below:

- Hemorheological activity
- Antioxidant activity
- Anti-inflammatory activity
- Anti-apoptotic activity
- Cytoprotective activity

5. Conclusions

In view of the highlighted influence of MSC secretome on oxidative stress, the MSC graft in retina or adjacent tissues may slow down RP progression [\[100\]](#)[\[101\]](#)[\[104\]](#)[\[126\]](#)[\[128\]](#)[\[131\]](#)[\[132\]](#): the bioactive factors released by MSCs could exert a trophic effect on photoreceptors, RMG, and RPE cells, so that the rod and cone lifespan could be prolonged.

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