Review

Antioxidant and biological properties of mesenchymal cells used therapeutically in retinitis pigmentosa

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Abstract: Both tissue repair and regeneration are a priority in regenerative medicine. Retinitis pigmentosa (RP), a complex retinal disease characterized by the progressive loss of impaired photoreceptors, is currently lacking effective therapies: this represents one of the greatest challenges in the field of ophthalmological research. Although this inherited retinal dystrophy is still an incurable genetic disease, the oxidative damage is an important pathogenetic element that may represent a viable target of therapy. In this review, we summarize the current neuroscientific evidence regarding the effectiveness of cell therapies, especially those based on mesenchymal cells, in RP and focus on their therapeutic action: limitation of both oxidative stress and apoptotic processes triggered by the disease, while promoting cell survival. Cell therapy could therefore represent a feasible therapeutic option in RP.

Keywords: retinitis pigmentosa; MSC; 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 1:4,000.

The term 'retinitis pigmentosa' 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 the rod cells (Pagon, 1988; Hartong et al., 2006; Hamel, 2006).

The genetic etiology of RP underlies the damage and subsequent death of the 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 these patients are often diagnosed later on in life, when they become aware of the disease after the second or third decade of life.

However, the clinical manifestations of RP are not only caused by the disappearance of the rod cells but also by the involvement, albeit in later phases, of the cone system.

The loss of cones goes beyond genetics and involves other biomolecular mechanisms, resulting from alterations in hemodynamics, cytotoxic effects of high levels of oxygen in the retina after the loss of rods, and the impaired response to oxidative stress.

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 (Agbaga et al., 2018).

Their damage finds its logical explanation in the altered genetic processes involved, and more than 80 causative genes of RP have already been identified, although a significant number of them are still unknown (Birtel et al., 2019).

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 (Audo et al., 2018), RLBP1 (Scimone et al., 2017), and RPE65 (Miraldi et al., 2018).

RPE plays many vital roles for photoreceptor cells, and the most fascinating is certainly its protective action against oxidative stress (Sparrow et al., 2010).

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 (Nowak et al., 2013).

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 (Campochiaro and Mir, 2018; Yang et al., 2018; Beutelspacher et al., 2011; Punzo et al., 2011; Langmann et al. 2007).

However, this chain of events, which is triggered after the death of the rods and leads to the death of the cones, highlights a number of key points that can potentially be leveraged therapeutically to slow down or stop the progression of the disease towards its terminal stages, modulating the damage to the rods, and preventing or delaying the death of the cones (Otani et al., 2004; Liang et al., 2001; Guadagni et al., 2015).

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 defective or dead cells (He et al., 2014; Tucker et al., 2014).

2. Oxidative Stress and Retinitis Pigmentosa

2.1. Synoptic aspects of oxidation and antioxidation

The retina physiologically interacts with light, which naturally oxidizes lipids, proteins and DNA (Samardzija et al, 2019; Rohowetz et al., 2018; Domènech et Marfany, 2020)

This occurs because retinal cells, due to their particular function, are characterized by an extremely high metabolism, are constantly exposed to the action of light, contain numerous photosensitive molecules, are made up of a considerable amount of polyunsaturated fatty acids (15% of the mass of a photoreceptor), which are particularly sensitive to oxidation damage, and transfer membranous discs and therefore metabolic waste products to RPE cells.

Therefore, as a result of normal cell activity, both in photoreceptors and RPE, highly unstable metabolic by-products called reactive oxygen species (ROS) are generated continuously.

Therefore, in order for the retina to function, a condition of oxidative stress is created in the retina. However, retinal cells, especially photoreceptors and ganglion cells, have protective mechanisms designed to ensure survival, capable of neutralizing the negative consequences of ROS. If stress exceeds a certain threshold or the activation of protective mechanisms fails (e.g., due to pathological alterations) cell homeostasis is altered, and cells activate alternative signaling pathways that eventually lead to apoptosis and mortality (Fulda et al., 2010; Galluzzi et al., 2018; Tang et al., 2019; Sies et Jones, 2020; Sies, 2015).

In order for ROS not to become toxic for cell survival, it is essential to maintain a balance between oxygen, necessary for the appropriate metabolic reactions and antioxidant activities, necessary to counter the excess of reactive oxygen species (ROS) that the metabolism produces.

ROS are represented by several rather unstable molecules, such as, to cite the best known, 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.

In addition to ROS, non-metabolizable advanced glycation end-products (AGEs) responsible for para-inflammation and permanent cell damage build up in dysregulated redox balances and oxidative stress conditions (Nedic et al., 2013).

The balance between oxidative species and antioxidant defense mechanisms is mediated by enzymes responsible for the metabolism or neutralization of ROS, 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 the inner segments of the cone (Trachootham et al., 2008; Benhar, 2020; Saccà et al., 2013) or the glyoxalase system (Donato et al., 2020), which, by acquiring electrons from oxidizing substances, neutralize them.

One of the main cellular sensors against an oxidative damage is provided by the endoplasmic reticulum (ER), an organelle where the biosynthesis and folding of transmembrane proteins takes place. Alterations in the redox state lead to the activation of proteins capable of determining unfolded protein response (UPR) and control of the antioxidative response.

If the harmful stimulus persists, the excess unfolded protein response (UPR) triggers the activation of the genes expressing an inflammatory response by promoting the development and progression of possible pathological conditions such as, for example, RP (Sano et al., 2013; Li et al., 2009).

Another cellular mechanism capable of achieving balance in oxidative stress-induced processes is the initiation of a cascade of signals to form stress granules (SG), protein agglomerates that 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 (Anderson et Kedersha, 2009).

Furthermore, in order to promote their survival following oxidative damage, retinal cells can resort to autophagy mechanisms capable of catabolizing damaged proteins and organelles, ensuring a homeostatic balance capable of modulating cell viability (Moreno et al., 2018; Kunchithapautham et al., 2007).

About 1 to 5% of ROS is generated in the mitochondria, organelles responsible for energy production in the cell. Acute ROS release into mitochondria can be a crucial activator of mitochondria, which is a process of selective autophagy of mitochondria in response to specific signals, including oxidative stress, hunger, and mitochondrial protein modification (Lin et al., 2014).

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 (Mitter et al., 2014).

If under physiological conditions maintaining the balance between oxidative stress and antioxidant mechanisms appears to be crucial for cell survival, the impact that a given pathology has on this homeostasis can become devastating (Sies, 2015).

In fact, the impairment of antioxidant responses represents one of the main inducers in the presence of genetic diseases such as retinitis pigmentosa (RP), particularly sensitive to oxidative stress (Donato et al., 2019; Domenech et Marfany, 2019).

The cytological objectives of these disorders usually are the photoreceptors, in particular the rods responsible for scotopic vision and retinal pigmented epithelium (RPE), although other retinal cytotypes are not excluded (Hamel, 2006).

Oxidative damage is expressed through a variety of structural and functional changes to lipids, proteins, and nuclear and mitochondrial DNA, where alteration of the telomeres occurs. Their damage or shortening may induce an altered and senescent cell phenotype. The damage of mtDNA or telomeric DNA is particularly compromising for cells that are not divisible or have a longer replicative lifespan, such as those in the brain, skeletal muscles of the heart, photoreceptors, and

other cells of the retina, such as the RPE cells: over time oxidative stress promotes the accumulation of DNA damage (Honda et al., 2001; Cai et al., 2000; Kaarniranta et al., 2018).

The consequences of this damage are a progressive loss of photoreceptor functional capacity as well as RPE cells, which, in addition to having a trophic function, provide many 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 of the immune privilege of the inner eye (disconnected from the immune system of the bloodstream) (Fuhrmann et al., 2014) and, finally, protection against oxidative stress (Datta et al., 2014). 2017). Several studies have confirmed the presence of high levels of ROS and AGE in RPE, which are able to alter transduction pathways and gene expression (Kaarniranta et al., 2019).

2.2. Oxidative Stress and Retinitis Pigmentosa (RP)

In order to fully understand the extent of oxidative stress during RP, we need to stress the impact that retinal vascularization has on the progression of the disease. Many studies have shown a reduction in choroidal (Wangsa-Wirawan and Linsenmeier, 2003); (Langham and Kramer, 1990) and macular (Murakami et al., 2015; 2016) hemodynamics associated with reduced visual sensitivity in patients with RP.

Apoptosis and the progressive loss of rods that occurs in RP is related to the release of cellular waste products, which has negative effects on microcirculation. The retinal vessels appear thin. Through a vicious circle, altered perfusion can ultimately lead to the loss of the photoreceptor (Marc and Jones, 2003).

The alterations in retinal circulation during RP have been highlighted in several studies correlating residual function with circulatory stasis (Peng et al., 1990) and choroidal thickness (Ayton et al., 2013), showing a reduction in retinal blood flow both as a whole (Beutelspacher et al., 2011) and in particular at the subfoveal level, with consequent specific alterations in electroretinographic recordings (Falsini et al., 2011).

Several studies show that both endogenous OS produced during retinal metabolism, such as lipid peroxidation or DNA damage, and external agents, such as exposure to sunlight or cigarette smoke, contribute to the death of photoreceptor cells.

But the most pathognomonic aspect of RP is that the blood, passing through the choroid, maintains an arterial oxygen saturation that remains unaltered until it enters the venous system. Moreover, unlike retinal capillaries, choroidal capillaries also allow the diffusion of plasma proteins in order to meet the metabolic needs of the photoreceptors (Bill et al., 1983).

Physiologically, this is attributable to the high metabolic needs of the retina.

In RP, the loss of rods, which make up about 95% of the photoreceptors, makes the availability of oxygen too high, and causes higher levels of oxygen to penetrate the residual tissue, thus increasing ROS production, and inducing oxidative damage in the surviving cells (mainly cones), which will eventually result in the death of the cone [Samardzija et al., 2019; Campochiaro et al., 2015).

Oxidative stress combined with deterioration and death of the rods, exposure to light from the foveal area, choroidal stasis, metabolic deterioration of the cones and RPE cells, lack of antioxidant enzymes such as superoxide dismutase (SOD), which is normally found in the mitochondria of the inner segments of the cone (but not in the outer ones), glutathione peroxidase, glyoxalase and catalase, and impairment of autophagy mechanisms exacerbate oxidative damage (Lieberthal et al., 1998). (Punzo et al., 2011; Shen et al., 2005; Yu and al., 2004; 2005; Moreno et al., 2018).

In recent years, it has been demonstrated that oxidative damage also interferes with particular RNA molecules called long non-coding RNAs (lncRNAs). 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 (Jain et al., 2017; Donato et al., 2020).

The alteration of lipoproteins and DNA derived from hyperoxia will cause irreparable damage in the residual cells (mainly cones), and therefore in the foveal region (Yu et al., 2005; Fisher, 2004; Turksever et al., 2014: Samardzija et al., 2019; Campochiaro et al., 2015; Donato et al., 2018).

In RP, the cell apoptosis induced by oxidative stress determines a condition in the retina called retinal gliosis, i.e., a state of para-inflammation in which microglial and macroglial cells are activated.

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 or ROS (Langmann , 2007; Kreutzberg, 1996) trigger the activation of apoptotic photoreceptors in RP, which generally occurs just before or at the peak of apoptotic photoreceptor death (Zeiss et al., 2004; Gupta et al., 2003; Zeng et al., 2005).

Their activation involves the expression of inflammatory regulatory proteins such as peroxiredoxin 2 (PRDX2), pro-inflammatory cytokines such as TNF-α, interleukin-1β or interferon-γ in RPE cells (Detrick et Hooks, 2020; Rashid et al., 2019), chemokines and neurotoxic agents, including hydrogen peroxide, and superoxide anion with additional oxidative stress (Banati et al, 1993; Boje et Arora, 1992).

The chronic activation of the microglia promotes the phagocytic function of the microglia against the altered components of neuronal cells, determining the evolution of retinitis pigmentosa (Zhao et al., 2015).

Conversely, the suppression of their activation improves the survival of the rods (Peng et al., 2014).

On the other hand, the macroglia represented by Müller glia, 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. As an immediate response to non-permanent acute stimuli, the Müller glia promote the secretion of trophic and antioxidant protective factors, but after chronicization, their secretory role can be clearly deleterious to neuronal cells (Subirada et al., 2018).

Therefore, the ensuing hyperoxia in the retina affected by RP is one of the underlying causes of accelerated rod loss and cone deterioration because it predisposes to the formation of ROS and more intense oxidation processes.

3. Mesenchymal cells: therapeutic strategies in Retinitis Pigmentosa

All the molecular events during RP after the onset of apoptotic phenomena affecting the rods, however complex, offer potentially useful points for therapies that aim to delay the death of the rods and to prevent or modulate damage to the cones.

Gene therapy, however causal, is currently in an experimental phase, and has only achieved limited in-vivo therapeutic results. Moreover, it may not modify the retinal damage once it has occurred. Consequently, scientific interest is particularly focused on stem cell therapy (Klassen et al., 2015).

Some researchers have used embryonic stem cells (HSC) (Idelson et al., 2009) or induced pluripotent stem cells (iPSC) (Takahashi et Yamanaka, 2013) to generate neurons that could replace lost cells.

However, although the cells thus generated express neuronal markers, most transplanted cells remain close to the injection site, showing only modest integration capacity in the retina.

Another line of investigation has used mesenchymal stem cells (MSC) (Ding et al., 2017) to influence the neuronal environment by reducing its inhibitory characteristics in favor of more permissive ones.

Cell therapy based on MSCs, a promising tool of regenerative medicine, appears to have the potential to influence some of the mechanisms underlying the progression of RP, expressing itself in

various ways, including hemorheological, anti-oxidative, anti-inflammatory, antiapoptotic, neurotrophic, and cytoprotective.

Cell therapy, by improving intra- and extracellular conditions and preserving the residual retina, can help us to maintain the retinal neuronal density and its function (Jones et al., 2017).

MSCs, compared to ESCs and iPSCs, though having a lower differentiation potential, do not induce risks of uncontrolled growth, do not create rejection reactions and, therefore, do not require the use of immunosuppressants, do not present ethical problems, do not have significant costs, do not create collection difficulties, especially if derived from adipose tissue, and have a higher immunomodulatory capacity, meeting the prerequisite needs of regenerative medicine (Romanov et al., 2005; Lindroos et al., 2010; Oner et al., 2017).

MSCs are characterized by the group of cell surface markers, both positive and negative, proposed by the International Society for Cellular Therapy in 2006 (Dominici et al., 2006). 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 (Bara et al., 2014).

Physiologically, MSCs, spread ubiquitously throughout the body, and play a key role in organogenesis, tissue remodeling and repair (Baddour et al., 2012).

MSCs can migrate to injury sites as a result of their 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 (Rüster et al., 2006). For this reason, these cells have the ability to adhere to the endothelium, and cross it by metalloprotease (de Becker et al., 2007).

Experimental studies have described the ability of MSCs to differentiate mainly into adipocytes, chondrocytes, osteoblasts, vascular endothelial cells, cardiomyocytes, pancreatic beta cells, and hepatocytes, as well as into retinal progenitor cells, photoreceptors, and retinal neuron-like cells (Huo et al., 2010; Zarbin 2016).

In fact, it has been shown that in the presence of retinal cells, or a supernatant from retinal cell cultures, or in the presence of retinal cell extracts, MSCs differentiate into cells expressing genes and markers typical of retinal cells (Salehi et al., 2017).

In addition to having a certain potential related to their multipotent differentiation capacity, MSCs also have a strong capacity for paracrine secretion of active ingredients, such as cytokines, chemokines and, generally, growth factors (GF or Growth Factors) (Fig. 1) (Moraes et al., 2012; Kyurkchiev et al., 2014; Johnson et al., 2014; Mead et al., 2014; Çerman et al., 2016; Pittinger et al., 1999; Siniscalco et al., 2010; Rezeanejad et al., 2014; Emre et al., 2015; Hofer et Tuan, 2016).

The cytokines produced by mesenchymal cells after binding with the specific receptor on the target cell activate specific signaling pathways. After their activation by the necessary phosphorylation processes, the transcription factors enter the nucleus, and after interaction with nuclear DNA, regulate the cellular transition from G0 to G1, which is necessary to activate gene expression and the required cellular modifications, promoting a greater synthesis of proteins, including enzymes and cytokines. These end products play a key role in cell survival, including mitosis, migration and cell differentiation (Limoli et al., 2014; 2016; 2018; 2020; Oner et al., 2019; Garcia et al., 2016).

In addition, growing evidence has been reported on the therapeutic potential of another cytological characteristic of MSCs, namely the ability to release extracellular vesicles and exosomes into the environment (Lai et al., 2015; Burrello et al., 2016).

Exosomes and microvesicles are very different from each other but have common characteristics in terms of size and content: both carry RNA, proteins, enzymes, and lipids, as well as mitochondria and ribosomes, which implies their involvement in the regulation of various biological functions, including the repair of tissues affected by pathogenic noxa (Lai et al., 2015; Wyse et al., 2014).

These particles could explain the therapeutic action without the implanted cell directly passing into the pathological tissue, as is the case when using only the mesenchymal cell secretome for therapeutic purposes (Lai et al., 2015).

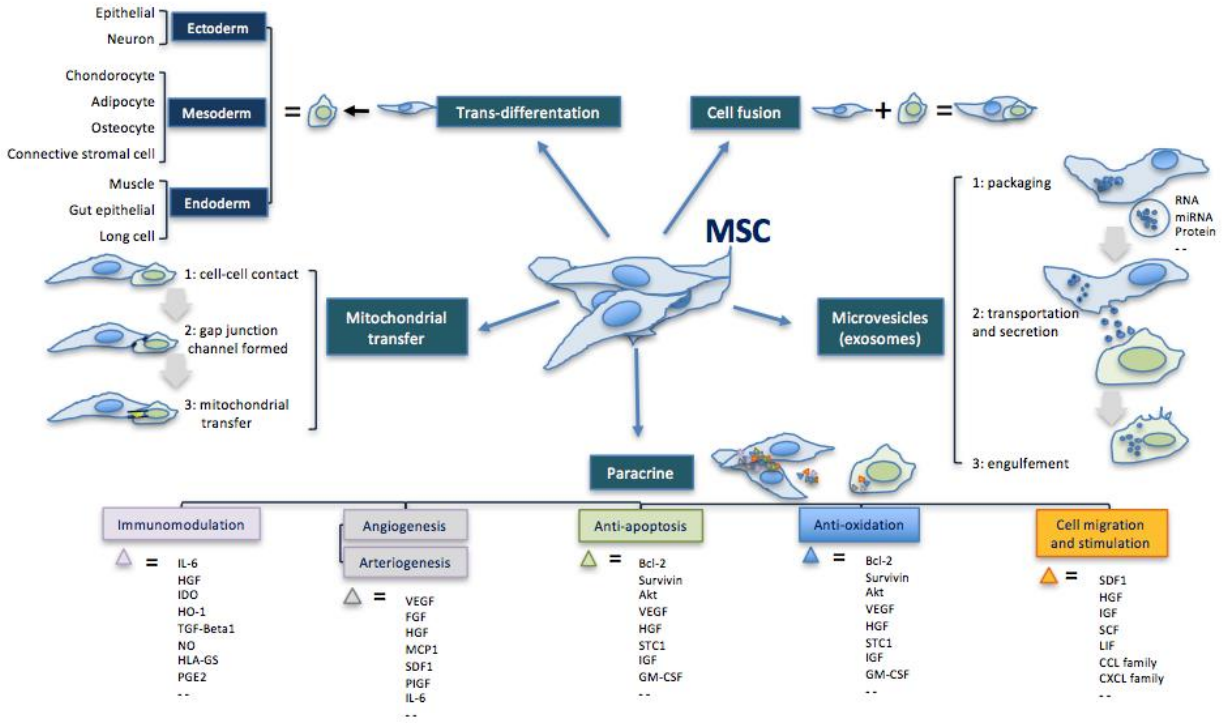

Figure 1. Schematic representation of the main mechanisms of the therapeutic effect of MSCs, modified by Liang (Liang et al., 2014).

Many studies have suggested that MSCs can maintain and regulate the microenvironment in different retinal degeneration models (Huo et al., 2010; Zarbin, 2016; Siqueira et al., 2011 and 2015; Park et al., 2014).

Intravitreal injection of MSC-derived exosomes has been shown to exert a repair and protective action in murine models of laser-induced retinal damage (Yu et al., 2016). The author noted that transplanted exosomes inhibit infiltration of inflammation-mediated cytokines, including stromal cell-derived factor 1 (SDF1), monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor (TNF-α), and intercellular adhesion molecule-1 (ICAM-1) and, generally, T-cell-mediated immune responses (Yu et al., 2016, Liang et al., 2014).

Adipose tissue is one of the most interesting collection sites of MSC. Like bone marrow, adipose tissue contains a large population of stem cells, usually called adipose-derived stem cells (ADSCs), within its stromal compartment. They can be obtained using simple procedures such as lipoaspiration performed under local anesthesia. MSCs derived from adipose tissue are more numerous, have a faster expansion, and have a greater secretory and immunomodulatory capacity (Oner and Sevim, 2017).

ADSCs produce basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), placental growth factor (PlGF), transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), interleukin (IL), angiogenin, ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF) (Lindroos et al., 2010; Luo et al., 2013), and glial cell-derived neurotrophic factor (GDNF) (Hu et al., 2017).

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 growth factor (EGF), bFGF, IGF-1, IL, TGFβ, pigment epithelium-derived factor (PEDF), and adiponectin (Wang et al., 2008; Tilg and Moschen et al., 2006; Nakagami et al., 2006; Schaffler and Buchler, 2007).

Finally, another type of cell of mesenchymal origin, originating from the subdivision of megakaryocytes, is represented by platelets.

Platelets are well known for their hemostatic action, but they can also release substances that promote tissue repair, angiogenesis, and inflammation modulation (Jurk and Kehrel, 2005). In addition, they induce cell migration and adhesion at angiogenesis sites, as well as differentiation of endothelial progenitors into mature endothelial cells (Mishra et al., 2011).

Platelets produce platelet-derived growth factor (PDGF), IGF-1, TGFβ, VEGF, bFGF, EGF, platelet-derived angiogenesis factor (PDAF) and thrombospondin (TSP), and several authors have used them in eye diseases such as glaucoma, AMD, and retinitis pigmentosa (Qureshi et al., 2009; Osborne et al. 2018; Lykov et al., 2018; Arslan et al., 2018).

The use of platelets in regenerative therapy generally occurs after their concentration by centrifugation in a state called platelet rich plasma (PRP), which makes the production of cytokines even 4-5 times greater than the initial conditions.

The characteristics of mesenchymal cells make their grafting for therapeutic purposes the most desirable and effective method, without having to resort to repeated intravitreal treatment of their secretome due to the short half-life of the factors it contains (Sluch and Zack, 2014; Mesentier-Louro et al., 2016). The variety of molecules produced improves the therapeutic efficiency of cellular implants through synergistic effects.

Several cell grafting methods have been developed: intravitreal (Siqueira et al., 2014; 2015), subretinal (Oner et al., 2016), epiretinal, subtenon (Arslan et al., 2018), and suprachoroidal (Oner 2019; Limoli, 2014; 2019; 2020). Each has its advantages and disadvantages.

In particular, the suprachoroidal implantation of mesenchymal cells, according to our technique (LRRT or Limoli Retinal Restoration Technique), uses three types of autologous mesenchymal cells: ADSCs, ASCs, 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 (Limoli et al., 2016; 2018; 2019; 2020; Oner et al., 2016).

The ocular administration of MSC promotes a significant restoration of the visual system in a variety of eye diseases, including RP (Oner, 2018; Ding et al., 2017; Mok et al., 2013; Kim et al., 2016; Zhao et al., 2016), through therapeutically mediated mechanisms such as:

-cell differentiation and trans-differentiation processes to replace cell loss or damage,
-paracrine action for the repair and functional stimulation of cells,
-modulation of host immune responses in the inflammation site,
-secretion of exosomes and microvesicles with biological functions.

Let us see specifically how this implant can counter the evolution of retinitis pigmentosa.

4. Cell-mediated biomolecular and antioxidative mechanisms in RP

Cell therapy is based on the stabilizing effect exerted by cytokines, growth factors, extracellular vesicles, and exosomes released paracrinically by grafted mesenchymal cells.

There are several ways in which cell therapy can positively interfere with the evolution of RP.

The therapeutic mechanisms are summarised below:

1. Hemorheological activity
2. Antioxidant activity
3. Anti-inflammatory activity
4. Anti-apoptotic activity
5. Cytoprotective activity

It is important to note that the boundaries between these mechanisms cannot be clearly distinguished.

4.1. Hemorheological activity

MSCs, through their paracrine secretion, help regulate retinal microhemodynamics.

In a study conducted on a murine model of induced diabetic retinopathy, the administration of bone marrow-derived MSCs determined, compared to healthy eyes, their integration into the retinal structure and their subsequent differentiation into Müller glia, likely by contact mechanisms, thus exerting selective protection against retinal gliosis, and restoring vascular integrity and function (Çerman, et al., 2016).

In another study conducted on a murine model of diabetes, intravitreal administration of adipose tissue-derived MSCs was not followed by any signs of diabetic angiopathy, such as neovascularization, ischemia, loss of RGC or increased pro-angiogenic factors compared to untreated cases (Ezquer et al., 2016).

The implanted MSCs secrete a wide range of growth factors and cytokines, as well as other proteolytic and angiogenic proteins, including VEGF, bFGF, angiogenin, PDAF, PlGF, PDGF, EGF, TGF-β1, SDF-1, cathepsins, MMP (or matrix metalloproteinases), and PAI-1 (plasminogen activator inhibitor 1) in response to tissue repair (Kim et al., 2016; Kinnaird et al., 2004).

This way they help to promote endothelial regeneration and can thus contribute to boosting microhemodynamics. However, the suppression of the inflammatory response, a prerogative of MSCs, tends to counterbalance the neovascular risk through the release by these cells of anti-angiogenic factors, such as TSP-1 and PEDF, which exert an inhibitory action on pathological neovascularization (Gao et al., 2016; Ezquer et al., 2016; Sheibani et al., 2000; Carron et al., 2000).

In 2013, Chu et al. also observed similar suppression in VEGF activity, which was attributed to indirect inhibition of TSP-1 on the VEGF receptor through the binding to CD36 and subsequent recruitment of SHP-1 (Src Homology 2 domain-containing Protein tyrosine phosphatase 1), a negative regulator of cell activation and proliferation (Chu et al., 2013).

Platelets can also release factors such as PDGF, bFGF, EGF, VEGF, IGF-1, TGF-β, PDAF, and TSP that promote tissue repair and regeneration, and angiogenesis. In addition, they can modulate inflammation and apoptosis, stimulate cell migration and adhesion at angiogenesis sites, and improve the differentiation process of endothelial progenitor cells into mature cells (Yang et al., 2016; Jurk et Kehrel, 2005).

Inserted in a concentrated way through PRP, the platelets act as a trigger for the early development of a new capillary plexus, facilitating the supply of nutrients to the grafted cells (Bhanot et Alex, 2002).

Subretinal injection of PRP in a neonatal mouse model has been shown to promote the formation of denser vascular networks (Mammoto et al., 2013).

Even adipose-derived stromal cells grafted at an early stage in the subretinal space can prevent the progression of diabetic retinopathy (Rajashekhar et al., 2014).

4.2. Antioxidant activity

As seen above, OS has been shown to play a significant role in the pathogenesis of PR and disease progression. Based on the causative gene of RP, antioxidant treatments could preserve the function of the cones and prolong the survival of the rods (Yu et Cringle, 2005; Shen et al., 2005).

Among the various treatments that can limit oxidative damage, MSCs seem to play an interesting therapeutic role (Cui et al. 2016; Ding et al., 2017; 2019).

The operational molecules secreted by MSCs vary in different experimental contexts, probably due to non-uniform ROS inductors with different levels of production. However, there is evidence that MSC therapy can have a broad influence on the redox context due to these antioxidant factors (Whone et al., 2012), as it can positively influence the evolution of RP (Fig. 2) (Limoli et al., 2019; 2020).

Indeed, the concentration of bFGF, one of the most effective molecules in promoting photoreceptor survival in a dose-dependent manner, increases within the external retina in response to oxidative stress (Yamada et al., 2001).

BFGF is produced physiologically by the Müller glia stimulated by the glial cell-derived neurotrophic factor (GDNF), which is responsible, *inter alia*, for the nuclear transcription of bFGF.

MSCs are capable of producing GDNF. This trophic factor stimulates the Müller glia homeostatically and these, through the production of factors such as bFGF and VEGF, act by promoting ischemic containment, metabolic recovery, and neuroprotection (Hauck et al., 2006).

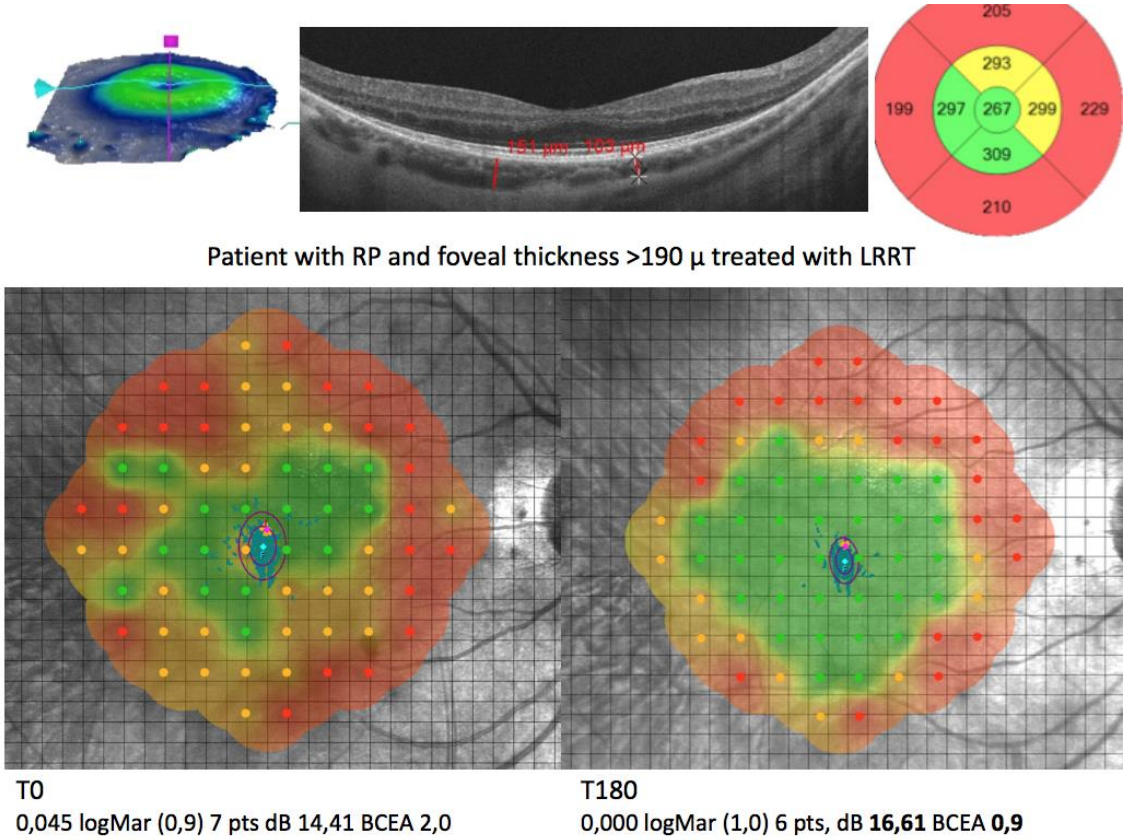

Figure 2. The image shows the effect of a suprachoroidal implantation of autologous mesenchymal cells in a patient with retinitis pigmentosa. The wealth of cells in the foveal area, documented by OCT, and therefore the high number of interactions between growth factors produced and specific membrane receptors, has allowed (T180) an increase in visual performance (BCVA, dB, pts). Image courtesy of P. Limoli-Low Vision research Centre of Milan.

MSCs are capable of producing bFGF also independently. Even in the presence of functional alterations of the Müller glia, as in RP, the bFGF produced alternatively by MSCs can modulate the anti-oxidative activity.

Adipose tissue-derived MSCs release other neurotrophic factors, such as NGF, bFGF, and GDNF, in order to preserve retinal cell survival and reduce oxidative stress damage in the retina (Ezquer et al., 2016).

Moreover, in a mouse model of diabetic retinopathy, after MSC transplantation, some of these cells were integrated into the retinal structure by differentiating into retinal astrocytes, RGC, pericytes, and Müller glia, exerting selective protection against retinal gliosis (Çerman et al., 2016).

The therapeutic effect of MSCs has also been identified by the neurotrophic action of ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) secreted by MSCs in an RGC culture, after inducing an oxidative state (Ding et al., 2017).

The containment of oxidative stress delays the death of the rods, and also indirectly influences the vitality of the cones, since the paracrine secretion of rod cone viability (RdCVF) by the rods is crucial for the development of cone survival (Yang et al., 2009; Aït-Ali et al., 2'15). 93, 94). It has been found that, through an antioxidant effect, RdCVF prevents cone death in transgenic rat models rd10 and P23H (Yu et al., 2004; Byrne et al., 2015).

4.3. Anti-inflammatory activity

To counter the activation of the numerous proinflammatory factors expressed in the retina as a result of oxidative stress induced by RP mutations, the Müller glia and RPE produce a single set of anti-inflammatory factors such as IL-10, IL-11, and TGF-β. These factors are essential for homeostasis and retinal function. However, their action becomes highly insufficient as RP progresses.

Several studies have suggested that MSCs can express many factors with anti-inflammatory, immunomodulatory and chemotactic action through crosstalk between the MSCs and the microenvironment of the damaged area (Madeira et al., 2015; Lull and Block, 2010; Holan et al., 2019; Katsuda et al., 2013).

It follows that the extent of inflammation and damage can also be modulated therapeutically by creating a balance in the production of pro- and anti-inflammatory molecules.

The intravitreal administration of MSCs can have a significant impact on the immune response of the host through secretion of CNTF and BDNF, neurotrophic factors that can promote the down-regulation of pro-inflammatory cytokines such as TNF-α, interferon-γ and interleukin-1β (IL-1β) (Cui et al., 2016; Mathew et al., 2017; Tilg and Moschen, 2006).

In addition, they have been proven to exert a protective action against retinal cells through the paracrine release of anti-inflammatory growth factors such as IL-6, PDGF, NGF, interferon beta (IFN-ß) (Hooks et al., 2008), and activation of the prostaglandin E2 receptor (PGE2R) (Mead et al., 2014).

Cytokines, such as bFGF, M-CSF, GM-CSF, and IL, which are normally released by the MSCs, have an anti-inflammatory function, and recruit macrophages by chemotaxis that help to eliminate intraretinal cell debris (Nemunaitis, 1993; Schneider et al., 2005; La Vail et al., 1992).

The release of TGF-β1 by the MSCs appears to contribute to creating a retinal environment favorable to the survival of the cones through an immunomodulatory strategy focused on microglia attenuation (Nagineni et al., 2003; 2005; Wang, et al., 2020;).

A study conducted by Guadagni et al. (Guadagni et al., 2015) assessed that an integrated microenvironment with growth factors can slow down the genetically determined death of photoreceptors while reducing retinal inflammation, and thus create better conditions for the viability of the overall cell population.

4.4. Antiapoptotic activity

In RP, excessive generation of reactive oxygen species (ROS) causes damage to membrane lipoproteins and cellular DNA, leading to apoptosis and photoreceptor death (Valentijn et al., 2004; Lieberthal et al., 1998).

But the administration of mesenchymal cells can hinder apoptosis involved in retinal degeneration.

Apoptosis, or programmed cell death, is an active and evolutionary process that, starting from stimuli of different nature (toxic substances, drugs, oxidative stress, ionizing radiations that cause DNA damage, severe stress on the endoplasmic reticulum or mitochondria, as in ischemic conditions), leads to cellular self-digestion.

On a morphological level, a cell that has activated the apoptotic pathway undergoes a progressive reduction in volume and loss of contact with adjacent cells, following a fragmentation of its nuclear DNA. Subsequently, the cell disintegrates into cellular fragments, which, through the activation of phagocytosis mechanisms, are self-digested, completing the apoptotic process.

Apoptosis in the developing nervous system is mainly related to the lack of growth factors such as NGF, BDNF, and NT-3 and NT-4, which are normally available at the target structure level,

i.e., those neuronal populations to which candidate neurons for suicide send their axon. The unavailability of these factors would trigger the process of self-destruction of the cell, indicating at the same time their effectiveness in an anti-apoptotic sense.

This mechanism is what makes it possible to eliminate, during embryonic development, excess cells that have not established the right connections (Valentijn et al., 2004).

MSCs, through their neurotrophic paracrine secretions, can represent a support for the neutralization in RP of the aforementioned apoptotic behaviors (Calkins, 2017).

To prevent programmed cell death, MSCs synthesize and secrete proteins such as Bcl-2, survivin and Akt, which have apoptosis-inhibiting characteristics (Okazaki et al., 2008).

B-cell lymphoma 2 (Bcl-2) is a protein encoded in humans by the Bcl-2 gene, progenitor of the family of Bcl-2 regulatory proteins that regulate apoptosis, through the expression of caspases (by cysteine aspartase), a family of essential enzymes in the cell to implement apoptosis, i.e., programmed cell death.

Bcl-2 has an anti-apoptotic action. The association with the protein Bax transforms Bcl-2 into proapoptotic Bcl-2 (Bax).

The relationship between Bcl-2 and its Bax form determines the sensitivity of cells to a pathological stimulus (Oltvai et al., 1993). The prevalence of Bcl-2 expression over Bcl-2 (Bax) prevents the release of caspase activators; therefore, cells are less likely to respond to apoptotic signaling and vice versa (Green and Reed, 1998).

Survivin is a member of the IAP (inhibitor of apoptosis protein) family, which groups together apoptosis-inhibiting proteins. The protein survivin has the function of inhibiting caspase activation, thus resulting in a negative regulation of apoptosis, or programmed cell death.

Akt also called protein-kinase B or Pkb is a cytosolic protein that plays a key role in the PI3K\Akt pathway. One effective result of the activation of Akt is the activation of biochemical pathways that lead to cell growth and resistance to apoptosis.

Tang et al. detected the down-regulation of Bax expression in the ischemic myocardium after autologous MSC transplantation (Tang, et al., 2005).

By releasing VEGF, MSCs could prevent apoptosis by overregulating the expression of Bcl-2 in the vascular endothelial cells (Gerber et al., 1998).

VEGF also exerts an antiapoptotic action by phosphorylation of FAK (focal adhesion kinase), a critical signal for cell survival that acts by suppressing p53-mediated apoptosis, a protein that physiologically participates in eliminating cells with DNA damage (Ilic et al., 1998; Liu et al., 1997; Lobo and Zachary, 2000).

Through the paracrine release of exosomes and microvesicles in paracrine mode, MSCs can transfer different molecular types or organelles for antiapoptotic purposes.

These transfers are particularly evident when potential target cells are damaged or under stress. For example, MSCs have recently been shown to prevent apoptosis in endothelial cells by transferring mitochondria during ischemic stress (Liu et al., 2014).

Furthermore, it is known that RPE cells (Sternfeld et al., 1989; Tanihara et al., 1993; Adamis et al., 1993), and the Müller glia (Wahlin et al., 2000; Frasson et al., 1999; Bringmann et Reichenbach, 2001) release growth factors in the retinal cytosol, and their progressive loss as a result of damage triggered by the changing vital conditions of the retina in RP hinders the growth of these bioactive agents, whose anti-apoptotic action is therefore prevented.

These factors can be released alternatively by the implanted MSCs by stimulating survival in photoreceptors and ganglion cells (Ding et al., 2017), but also on Müller glia and RPE cells by supporting their functions.

4.5. Cytoprotective activity

Growth factors produced by MSCs have been shown to contribute to neuroprotection by regulating photoreceptor metabolic activity, which is physiologically intense but largely compromised in RP (Mesentier-Louro et al., 2016, Kolomeyer and Zarbin, 2014).

In rat models with hereditary retinal dystrophy, it has been reported that MCS can improve visual function: the paracrine release of trophic cytokines by MSCs can promote the clearance of dysmetabolic photoreceptor products by RPE phagocytes (Ortín-Martínez et al., 2014).

In addition, their cytoprotective action is expressed through the release of numerous different neurotrophic factors.

Among the numerous factors with neuroprotective properties of mesenchymal origin, suffice it to mention PDGF (platelet-derived growth factor) regulator of cell growth and division. In particular, PDGF plays a significant role in the formation of blood vessels, starting with other vascular structures, in mythogenesis and chemotaxis, inducing photoreceptor survival.

The neuroprotective effects of PDGF are comparable to those of the brain-derived neurotrophic factor (BDGF) (Othberg et al., 1995; Kim et al., 2003).

This result is based on the ability of PDGF and other molecules produced by MSC to activate the PI3K/Akt/mTOR pathway, and thus to upregulate mTOR signaling, which appears to have decreased in the course of several eye diseases (Tsang et al., 2007).

It was also discovered that MSC transplantation reduces damage to the outer segment layer of the retinal photoreceptor by promoting cell regeneration through the paracrine release of hypoxia-inducible factor-1 (HIF-1) and axonal regeneration through growth-associated protein-43 (GAP-43) (Chung et al., 2016).

Data from another similar study assessed that neurotrophic factors, such as NGF, bFGF, and GDNF, released by adipose tissue-derived MSCs, are involved both in maintaining retinal ganglion cell survival, and in reducing stress-related oxidative retinal damage (Frasson et al., 1999).

Another factor produced by MSCs is EGF, which exerts a neuroprotective action on Müller glia, stimulating their intracellular transcription and bFGF expression (Hauck et al., 2006; Zack, 2000).

The IGF factor, released by MSCs, promotes the synthesis of DNA and RNA, as well as the increase of the cells in both number and size. IGF can also regulate neuronal growth and development through a variety of processes, such as neurogenesis, myelination, synaptogenesis, dendritic branching, and neuroprotection following neuronal damage. IGF not only facilitates neuronal connections but also inhibits neuronal death (Slomiany et al., 2004; Gasperi et Castellano, 2010).

In a murine model of hypertonic ischemia followed by retinal reperfusion, Li and colleagues (2009) injected BM-MSC into the vitreous body: 4 weeks later, the treated eyes had a much increased number of RGC compared to the untreated eyes. The treated retinas also showed increased expression of bFGF, BDNF, and CTNF (Li et al., 2009).

During cell therapy with MSC, the Trk receptor blockade in its three variants - A, B or C - significantly reduced the neuroprotective effect, suggesting a possible key role of neurotrophic factors, in particular NGF, BDNF, and neurotropin-3, which bind to this family of receptors, whose activation has significant effects on the functional properties of neurons through survival pathways and cyto-functional regulation (Mead et al., 2016).

Another support mechanism by mesenchymal cells is the release of exosomes and microvesicles, which take this name from their size, which allows them to be transported from one cell to another. Their load consists of proteins, mRNA and microRNA, or organelles such as ribosomes and mitochondria, in order to increase the AMPc levels, and therefore the energy levels of the receiving structures (Katsuda et al., 2013).

This way, MSCs can transfer mitochondria to host cells, as demonstrated by the most recent work by Islam et al. (2012), which provided in-vivo evidence of the transfer (Islam et al., 2012).

Proteins present in the extracellular BM-MSC vesicles also include signaling molecules such as mitogen-activated protein kinase (MAPK1), an enzyme expressed by the MAPK1 gene, cell adhesion mediators such as fibronectin, and surface receptors such as the PDGF receptor. MSC-derived extracellular vesicles also express regulatory molecules such as transforming growth factor beta (TGF-β), galectin-1 and programmed death-ligand1 (PD-L1), mediators involved in the processes of differentiation, proliferation, and cell apoptosis (Drago et al., 2013).

5. Conclusions

In the light of the influence of the MSC secretome on oxidative stress and its consequences after the expression of genetic mutations during retinitis pigmentosa, it is possible to hypothesize that their grafting at the level of the retina or neighbouring tissues has a therapeutic action capable of modifying the evolution of this pathology (Huo et al., 2010; Limoli et al., 2019; 2020; Oner et al., 2016; 2018; Siqueira et al., 2015; Ding et al., 2017; Arslan et al., 2018).

The increase in the bioactive factors produced by mesenchymal cells could promote increased trophism of photoreceptors, as well as Müller glia and RPE cells in patients with RP through cytokine-membrane receptor interactions. The life of the rods could be prolonged, and that of the cones preserved longer.

Abbreviations

ADSCs: Adipose Derived Stem Cells
AMD: Age Macular Disease
ASCs: Adipose Stromal Cells
BCEA: Bivariate Contour Ellipse Area
BCVA: Best Corrected Visual Acuity
BDNF: Brain-Derived Neurotrophic Factor
bFGF: basic Fibroblast Growth Factor
BM-MSCs: Bone Marrow Mesenchymal Stem Cells
CASPasis: Cysteine Aspartate-specific Proteinases
cERG: cone ERG or Photopic ERG
CNS: Central Nervous System
CNTF: Ciliary Neurotrophic Factor
EGF: Epidermal Growth Factor
ERG: ElectroRetinoGram
ESCs: Embrionic Stem Cells
GAP-43: Growth-Associated Protein-43
GDNF: Glial Derived Neurotrophic Factor
GF: Growth Factor
GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor
HGF: Hepatocyte Growth Factor
HIF-1alpha: Hypoxia-Inducible Factor-1alfa
IFN-β: interferon-β
IGF-1: Insulin-like Growth Factor-1
IL-1RA: IL-1 Receptor Antagonist
IL: Interleukin
iPSCs: Induced Pluripotent Stem Cells
IRD: Inherited Retinal Disease
LRRT: Limoli Retinal Restoration Technique
M-CSF: Macrophage Colony-Stimulating Factor
MAPK1 (Mitogen-Activated Protein Kinase)
MCP-1: monocyte chemoattractant protein-1
MSCs: Mesenchymal Stem Cells
OS: Oxidative Stress
PDGF: Platelet-Derived Growth Factor
PDAF: Platelet-Derived Angiogenesis Factor
PEDF: Pigment-Epithelium-Derived Factor
PGE2R: Prostaglandin E2 Receptor
Ph: photoreceptor
PI3-K: Phosphatidylinositol-3-Kinase
PlGF: Placental Growth Factor
PLTs: Platelets
PRP: Platelet-Rich Plasma
PRDX2: Peroxiredoxin 2
RdCVF: Rod Cone Viability Factor
RGC: Retinal Ganglion Cell
RMG: Retinal Müller Glia
ROS: Reactive Oxygen Species
RP: Retinitis Pigmentosa
RPE: Retinal Pigment Epithelium
SOD: superoxide dismutase
SVF: Stromal Vascular Fraction
TGF-: Transforming Growth Factor-
TNF-alpha: Tumoral Necrosis Factor – alpha
TSP: Thrombospondin

VEGF: Vascular Endothelial Growth Factor

PRDX2: Peroxiredoxin 2

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