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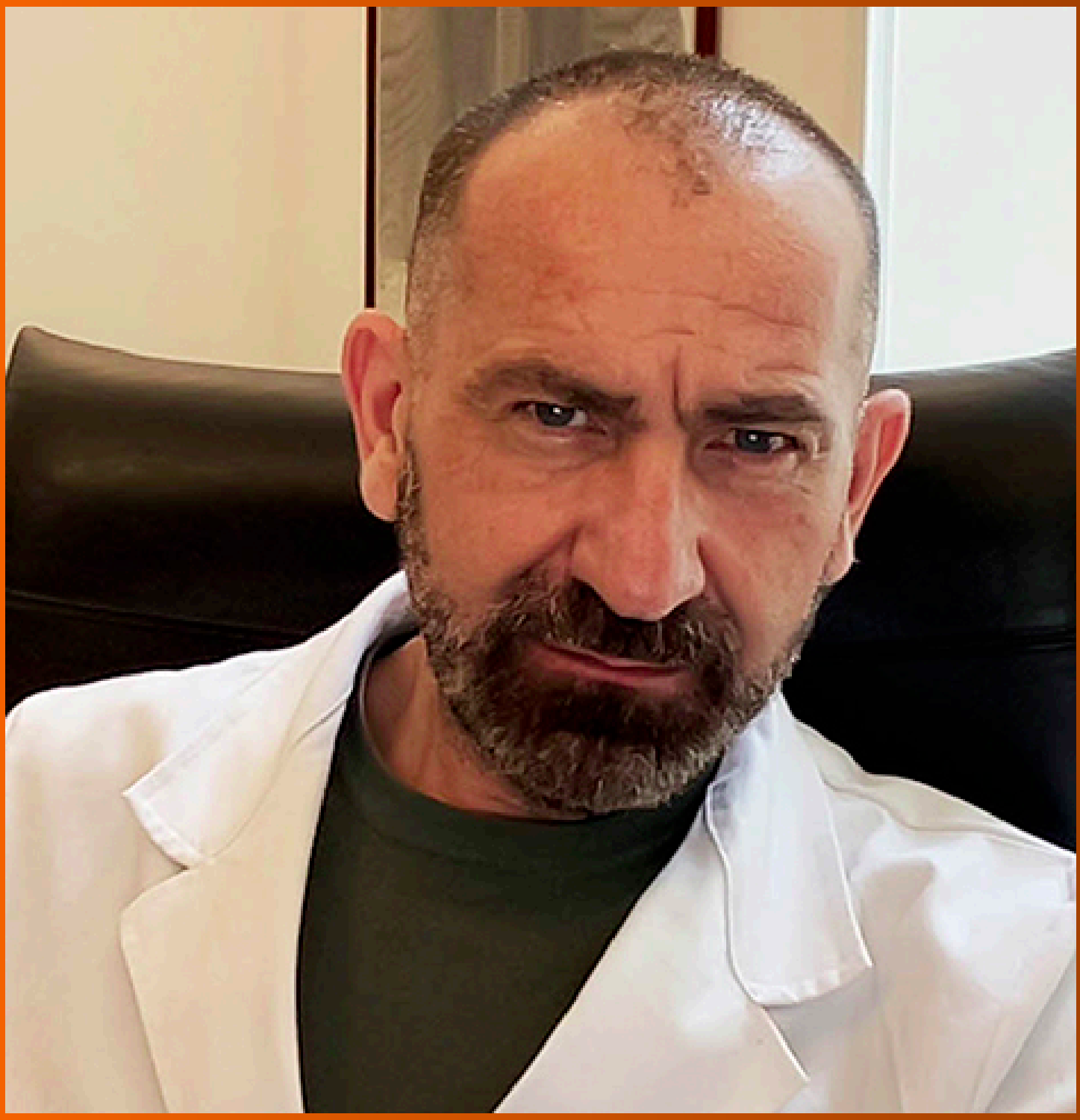

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REVIEW

Human retinal secretome: A cross-link between mesenchymal and retinal cells

Luigi Donato, Concetta Scimone, Simona Alibrandi, Sergio Zaccaria Scalinci, Domenico Mordà, Carmela Rinaldi, Rosalia D'Angelo, Antonina Sidoti

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Abstract

In recent years, mesenchymal stem cells (MSC) have been considered the most effective source for regenerative medicine, especially due to released soluble paracrine bioactive components and extracellular vesicles. These factors, collectively called the secretome, play crucial roles in immunomodulation and in improving survival and regeneration capabilities of injured tissue. Recently, there has been a growing interest in the secretome released by retinal cytotypes, especially retinal pigment epithelium and Müller glia cells. The latter trophic factors represent the key to preserving morphofunctional integrity of the retina, regulating biological pathways involved in survival, function and responding to injury. Furthermore, these factors can play a pivotal role in onset and progression of retinal diseases after damage of cell secretory function. In this review, we delineated the importance of cross-talk between MSCs and retinal cells, focusing on common/induced secreted factors, during experimental therapy for retinal diseases. The cross-link between the MSC and retinal cell secretomes suggests that the MSC secretome can modulate the retinal cell secretome and vice versa. For example, the MSC secretome can protect retinal cells from degeneration by reducing oxidative stress, autophagy and programmed cell death. Conversely, the retinal cell secretome can influence the MSC secretome by inducing changes in

MSC gene expression and phenotype.

Key Words: Secretome; Mesenchymal stem cells; Retinal cells; Extracellular vesicles; Retinal diseases

Core Tip: Recently, the mesenchymal stem cell secretome, a solution rich with paracrine bioactive factors and extracellular vesicles, acquired a significant role in immunomodulation and survival induction of damaged tissues. A secretome is also released by retinal cells, physiologically or following pathological stimuli. One of the most promising therapeutic frontiers is represented by a possible "cross-talk" between mesenchymal stem cells and retinal cells through the secretomes in order to improve the knowledge on released factors mechanisms of action during their potentially beneficial role.

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INTRODUCTION

In recent years, mesenchymal stem cells (MSCs) have been indicated as the most effective source for cell-based therapy, particularly in regenerative medicine. In particular, MSCs produce major therapeutic effects releasing soluble paracrine bioactive components and extracellular vesicles (EVs) constituting the so called secretome. These secreted factors play crucial roles in modulating immunity and improving survival and regeneration capabilities of injured tissue[1].

Secreted trophic factors are also key to preserving the morphofunctional integrity of the retina, regulating biological pathways involved in survival, function and response to injury[2]. Additionally, these factors can play a fundamental role in onset and progression of retinal diseases after damage of cell secretory functions[3]. In this review, we discussed the link between the secretome of MSCs to the retinal cell secretome, in order to highlight the current knowledge of secreted factor involvement in retinal diseases.

Main features of MSCS

One of the most recent fields of therapy research concerns MSCs, multipotent non-hematopoietic stem cells that originate from the mesoderm. They can reach a pathological site following the release of different biologically active immunomodulatory and regenerative factors related to different diseases[4]. There are multiple sources of MSCs, including umbilical cord blood, placenta, adipose tissue, skin and bone marrow tissue, with the latter representing the most widely used source[5]. Isolation of different types of MSCs, such as adipose tissue-derived mesenchymal stromal/stem cells (ASCs), is a non-invasive process, and this represents a fundamental advantage from an ethical and/or legal point of view[6]. The key point for MSC use is their low immunogenicity, permitting allogeneic trans-plantation in the medical setting[7].

Moreover, recent studies have shown that MSCs can produce an immune response, mediated by T cells regulated by IFN-γ[8]. When activated, MSCs can reach the correct pathological site to exert reparative functions, triggered by a huge number of secreted factors from the injured cells, such as cytokines, chemokines and growth factors[9]. Among the latter, placental growth factor plays a pivotal role, along with VEGF, EPO, SDF-1, ANG2, G-CSF, stem cell factor, PDGF, EGF, HGF and IGF-1[10]. Regarding cytokines and chemokines, the former include TNF-α and interleukins such as IL-1b, IL-2, IL-3, IL-6 and IL-8, and the latter includes, among others, CCL5 and CCL22[11].

Various studies have confirmed that human MSCs evade allorecognition, affect T lymphocytes and dendritic cell activities and produce a local immunosuppressant microenvironment by releasing the already cited cytokines[12]. Moreover, MSCs can be easily genetically manipulated, with elevated metabolic activity and low mutation rate, and can efficiently secrete a wide number of proteins[13]. Today, preclinical and clinical trials using MSCs, especially human bone marrow-derived MSCs (hBMMSCs) and human adipose mesenchymal stem cells (hADSCs), have been performed in different kinds of pathologies with promising results, such as autoimmune disease, joint reconstruction, vascular disease, nerve injury, organ transplantation, degenerative disease and severe infection[14].

In particular, one of the fields with the highest number of ongoing clinical trials is represented by eye diseases (Table 1). The protective activity of MSCs was initially linked to their direct differentiation and replacement of injured tissues, as evidenced by human MSCs becoming hepatocyte-like cells or rat MSCs turning into neuron-like cells[15]. However, today the protective action of MSCs is well known to be primarily mediated through paracrine properties, exerted by what is defined as the MSC secretome.

MSC secretome

The secretome released by MSCs consists of a conditioned medium (CM) made up of soluble elements (cytokines and growth factors) and a vesicular part made up of exosomes and microvesicles, which are fundamental for protein and genetic material transfer towards other cells[16]. The most recent *in vitro* and *in vivo* studies on the features of the MSC

Table 1 Ongoing clinical trials on eye diseases based on the use of mesenchymal stem cells

Title	Sponsor/collaborators	URL
Safety and Efficacy of Pluripotent Stem Cell-derived Mesenchymal Stem Cell Exosome (PSC-MSC-Exo) Eye Drops Treatment for Dry Eye Diseases Post Refractive Surgery and Associated With Blepharospasm	Second Affiliated Hospital, School of Medicine, Zhejiang University | Zhejiang University | Hangzhou yuansheng biotechnology Co., Ltd	https://ClinicalTrials.gov/show/NCT05738629
Therapeutic Effect of Stem Cell Eye Drops on Dry Eye Disease	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School	https://ClinicalTrials.gov/show/NCT05784519
Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cells for Eye Diseases	The Foundation for Orthopaedics and Regenerative Medicine	https://ClinicalTrials.gov/show/NCT05147701
The Role of Transscleral Cyclophotocoagulation in Patients Undergoing a Boston Keratoprosthesis	Centre hospitalier de l'Université de Montreal (CHUM) | Fonds de recherche en ophtalmologie de l'Université de Montreal	https://ClinicalTrials.gov/show/NCT04232982
Characterization of Potential Biomarkers of Eye Disease and Vision	Association for Innovation and Biomedical Research on Light and Image	https://ClinicalTrials.gov/show/NCT02500862
Long-term Safety of UC-MSC Transplantation in Patients With Retinitis Pigmentosa	PT. Prodia Stem Cell Indonesia	https://ClinicalTrials.gov/show/NCT05786287
Clinical Evaluation of Two Daily Disposable Lenses in Sphere Design	Coopervision, Inc.	https://ClinicalTrials.gov/show/NCT05516082
Efficacy of Locally Delivered Allogeneic Mesenchymal Stromal Cells	University of Illinois at Chicago | United States Department of Defense	https://ClinicalTrials.gov/show/NCT05705024
Diquafosol *vs* Hyaluronic Acid for Diabetic Dry Eye	He Eye Hospital	https://ClinicalTrials.gov/show/NCT05682547
Eye Length Signal With Myopia Control	Brien Holden Vision Institute	https://ClinicalTrials.gov/show/NCT04813640
Patient Acceptability of Autonomous Telemedicine	Ufonia | Buckinghamshire Healthcare NHS Trust | Innovate UK	https://ClinicalTrials.gov/show/NCT04885868
Phase 2b Pivotal Study of Izokibep in Non-infectious, Intermediate-, Posterior- or Pan-uveitis	ACELYRIN Inc.	https://ClinicalTrials.gov/show/NCT05384249
Dose Optimization for Safe and Efficient Fluorescein Angiography (DOSE Study)	Seoul National University Bundang Hospital	https://ClinicalTrials.gov/show/NCT05664555
Analysis of the Results of Intense Pulsed Light Treatment Previously to Laser Refractive Surgery	Vissum, Instituto Oftalmologico de Alicante	https://ClinicalTrials.gov/show/NCT05139511
Study of the Association Between Digital Eye Syndrome With Binocular Vision and the Ocular Surface in Higher Education Students in the Area of Health Technologies	Universidade Nova de Lisboa | NOVA Medical School Faculdade de Cinecias Medicas, Universidade Nova de Lisboa | Escola Superior de Tecnologia da Salude de Lisboa (ESTeSL) | University of lâvora | CINTESIS@RISE, NOVA Medical School Faculdade de Ciencias Medicas, Universidade Nova de Lisboa | Comprehensive Health Research Center (CHRC), Universidade Nova de Lisboa	https://ClinicalTrials.gov/show/NCT05675475
Caffeine Consumption and Cataract Prevention	Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT05194696
Rotational Stability of the TECNIS Eyhance Toric	Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT05126368
Reading Performance in Patients With Acrysof IQ Vivity Versus Acrysof IQ	Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT05194657
Performance of Two Intraocular Lenses With Extended Depth of Vision	Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT05194150
Assessment of Retinal Vascular Changes With and Without ILM Peeling in Diabetic Vitrectomy Using OCT-A	Kasr El Aini Hospital	https://ClinicalTrials.gov/show/NCT05739539
Primary Vitrectomy With Silicone Oil or SF6 for Rhegmatogenous Retinal	Cairo University	https://ClinicalTrials.gov/show/NCT05377606

Detachment		
Intravitreal Sirolimus as Therapeutic Approach to Uveitis	Stanford University | Santen Inc.	https://ClinicalTrials.gov/show/NCT01280669
Clinical Trial With Artiflex Presbyopic	Ophtec BV	https://ClinicalTrials.gov/show/NCT04632784
Post-Market Evaluation of the EVO ICL	Staar Surgical Company	https://ClinicalTrials.gov/show/NCT05538754
Clinical Evaluation of Two Multifocal Contact Lenses	Coopervision, Inc.	https://ClinicalTrials.gov/show/NCT05457608
Ologen Collagen Matrix Versus Mitomycin-C in Patients With Juvenile-onset Open Angle Glaucoma	L.V. Prasad Eye Institute	https://ClinicalTrials.gov/show/NCT03548805
A Comparative Study of Visual Outcome of Two Extended Depth of Focus Intraocular Lenses After Cataract Surgery	Cairo University	https://ClinicalTrials.gov/show/NCT05647421
Keratometric Change After XEN, Trabeculectomy and Tube Shunts	Centre hospitalier de l'Universitè de Montreal (CHUM) | Allergan	https://ClinicalTrials.gov/show/NCT04602923
Post-market Follow Up Study on Paragon CRT 100 (Paflufocon D)	Coopervision, Inc. | TigerMed	https://ClinicalTrials.gov/show/NCT04187599
Evaluating Two Multifocal Daily Disposable Contact Lenses	Coopervision, Inc.	https://ClinicalTrials.gov/show/NCT05579886
A Clinical Comparison of Two Soft Multifocal Contact Lenses	Coopervision, Inc.	https://ClinicalTrials.gov/show/NCT05794126
Ocular Surface Disease and IOP Monitoring With Travoprost Without Conservatives	Democritus University of Thrace	https://ClinicalTrials.gov/show/NCT05319470
Performance of Two Hydrophobic IOLs	Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT05639049
RayOne EMV Mini-monovision - Efficiency and Safety of 3 Grades of Mini-monovision	Somich, s.r.o.	https://ClinicalTrials.gov/show/NCT05417633
A Clinical Study to Evaluate the Potential Role of ACTH Gel in Patients With Scleritis	Metropolitan Eye Research & Surgery Institute | Mallinckrodt | Stanford University | Ocular Imaging Research and Reading Center | Foresight Studies, LLC	https://ClinicalTrials.gov/show/NCT03465111
Zimbabwe Eyecare And Learning (ZEAL): Formative Research on Hyperopia and Educational Outcomes in Primary School Children	Queen's University, Belfast | L.V. Prasad Eye Institute | University of Zimbabwe | University of Ulster | New England College of Optometry | Peek Vision | Zimbabwe Optometric Association | Clearly | Christian Blind Mission	https://ClinicalTrials.gov/show/NCT05538182
Vision and Balance Changes After Bilateral Implantation of Toric IOLs	University of Plymouth | Carl Zeiss Meditec AG | Glasgow Caledonian University | University of St Mark and St John Plymouth | University Hospital Plymouth NHS Trust	https://ClinicalTrials.gov/show/NCT05629078
Multicenter Study on the Efficacy and Safety of OCS-01 in Subjects With Uveitis Related and Post Surgical Macular Edema	Quan Dong Nguyen | Global Ophthalmic Research Center (GORC) | Oculis | Stanford University	https://ClinicalTrials.gov/show/NCT05608837
Inflammatory Biomarkers in Ocular Surface in Primary Open Angle Glaucoma or Ocular Hypertension Under Topical Prostaglandins	Instituto Universitario de Oftalmobiologia Aplicada (Institute of Applied Ophthalmobiology) - IOBA | Hospital Clvinico Universitario de Valladolid	https://ClinicalTrials.gov/show/NCT05039684
Ranibizumab *vs* Bevacizumab for Type 1 Retinopathy of Prematurity	Zagazig University | Cairo University	https://ClinicalTrials.gov/show/NCT05033106
Dresden Corneal Disease and Treatment Study	Technische Universitut Dresden	https://ClinicalTrials.gov/show/NCT04251143
Reliability, Validity of the Turkish Version of the Primary Sjogren Syndrome Quality of Life (PSS-QoL) Questionnaire	Gazi University	https://ClinicalTrials.gov/show/NCT04858464
Mean Visual Acuity Changes Following Five Injections of Aflibercept	McMaster University	https://ClinicalTrials.gov/show/NCT02645266

Targeted Fluorescence Imaging in AMD	University Medical Center Groningen	https://ClinicalTrials.gov/show/NCT05262244
Treatment of Ligneous Conjunctivitis in Children With Plasminogen Deficiency	University of Saskatchewan | Canadian Blood Services	https://ClinicalTrials.gov/show/NCT05404932
Can the Risk for AMD be Modulated?	Association for Innovation and Biomedical Research on Light and Image	https://ClinicalTrials.gov/show/NCT05735730
Study to Evaluate the Response to Supplementation With Postbiotics in Patients With Macular Degeneration	Institut de la Macula y la Retina | Igen BioLab SLU	https://ClinicalTrials.gov/show/NCT05056025
Development of a Tele-Physiotherapy Tool for the Early Management of Muskuloskeletal Pain in People With Visual Impairement (TeleEDxPhysio)	Escuela Universitaria de Fisioterapia de la Once | Universidad de Zaragoza	https://ClinicalTrials.gov/show/NCT05478200
Clinical Trial to Evaluate Safety and Efficacy of Cell Therapy in Patients With Cicatricial Conjuntivitis	Instituto de Investigacion Sanitaria de la Fundacion Jimenez Diaz | Effice Servicios Para la Investigacion S.L	https://ClinicalTrials.gov/show/NCT05520086
Advanced Glaucoma Progression Study	University of California, Los Angeles | National Eye Institute (NEI)	https://ClinicalTrials.gov/show/NCT01742819
Retrobulbar Methylprednisolone as Adjunctive Treatment in Optic Neuritis Trial	Asociacion para Evitar la Ceguera en Mexico	https://ClinicalTrials.gov/show/NCT04942002
Nystagmus Assessment for Patients Consulting in the Emergency Department for Acute Vertigo	CHU de Quebec-Universite Laval	https://ClinicalTrials.gov/show/NCT05176015
Effectiveness of Periocular Drug Injection in CATaract Surgery	Luigi Rondas | European Society of Cataract and Refractive Surgeons | Academisch Ziekenhuis Maastricht	https://ClinicalTrials.gov/show/NCT05158699
Clinical Trial Comparing Two Non-Surgical Treatments for Severe Blepharoptosis	Massachusetts Eye and Ear Infirmary | National Eye Institute (NEI)	https://ClinicalTrials.gov/show/NCT04678115
Stem Cell Ophthalmology Treatment Study II	MD Stem Cells	https://ClinicalTrials.gov/show/NCT03011541
Effect of Intravenous Methylprednisolone and Intravenous Erythropoietin in Toxic Optic Neuropathies: Randomized Clinical Trial	Asociacion para Evitar la Ceguera en Mexico	https://ClinicalTrials.gov/show/NCT05748561
SPT Screening in Irradiated Hereditary Retinoblastoma Survivors	Amsterdam UMC, location VUmc | ODAS	https://ClinicalTrials.gov/show/NCT02329002
Community Access Through Remote Eyesight (CARE) Study	New England College of Optometry | National Institute on Disability, Independent Living, and Rehabilitation Research | University of California, Los Angeles	https://ClinicalTrials.gov/show/NCT04926974
Electro-acupuncture and Transcorneal Electrical Stimulation (TES) for Retinitis Pigmentosa	Nova Southeastern University | National Eye Institute (NEI)	https://ClinicalTrials.gov/show/NCT02086890
Evaluation of NeoRetina Artificial Intelligence Algorithm for the Screening of Diabetic Retinopathy at the CHUM	Centre hospitalier de l'Universitè de Montreal (CHUM) | DIAGNOS Inc.	https://ClinicalTrials.gov/show/NCT04699864
Clemastine Fumarate as Remyelinating Treatment in Internuclear Ophthalmoparesis and Multiple Sclerosis	Amsterdam UMC, location VUmc	https://ClinicalTrials.gov/show/NCT05338450
The K-Map Study, Global Prevalence of KC	University Hospital, Geneva | ELZA Institute	https://ClinicalTrials.gov/show/NCT03115710
Methotrexate For The Prevention and Treatment of Proliferative Vitreoretinopathy in Pediatric Patients	Stanford University	https://ClinicalTrials.gov/show/NCT04830878
A Collaborative Resource of Heidelberg Multimodal Imaging of Intermediate and Early Atrophic AMD Cases to Study Prediction of Disease Progression	Association for Innovation and Biomedical Research on Light and Image | European Vision Institute Clinical Research Network	https://ClinicalTrials.gov/show/NCT05698316

Clinical Trial of Multi-Periscopic Prism Glasses for Hemianopia	Massachusetts Eye and Ear Infirmary | National Eye Institute (NEI)	https://ClinicalTrials.gov/show/NCT04827147
Feasibility Tests for Various Prism Configurations for Visual Field Loss	Massachusetts Eye and Ear Infirmary | National Eye Institute (NEI)	https://ClinicalTrials.gov/show/NCT04424979
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0.01% Hypochlorous Acid in the Treatment of Blepharitis	Eye & ENT Hospital of Fudan University | ShuGuang Hospital	https://ClinicalTrials.gov/show/NCT05608980
Birdshot Chorioretinopathy: Prospective Follow-up and Immuno-genetic Studies(CO-BIRD)	Assistance Publique - Hopitaux de Paris	https://ClinicalTrials.gov/show/NCT05153057
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Swiss Pediatric Inflammatory Brain Disease Registry (Swiss-Ped-IBrainD)	University of Bern | Schweizerische Multiple Sklerose Gesell-schaft | University Hospital Inselspital, Berne | Roche Pharma (Switzerland) Ltd | Novartis	https://ClinicalTrials.gov/show/NCT05017142
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Comparison of Phacoemulsification and Corneal Damage Between FLACS and Standard Phaco With Two Handpieces	Centre hospitalier de l'Universitè de Montreal (CHUM)	https://ClinicalTrials.gov/show/NCT05119270
Computer-based Tutorial and Automated Speech Recognition for Intravitreal Drug Injections	Prim. Prof. Dr. Oliver Findl, MBA | Vienna Institute for Research in Ocular Surgery	https://ClinicalTrials.gov/show/NCT04142164
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PROgressive Supranuclear Palsy CorTico-Basal Syndrome Multiple System Atrophy Longitudinal Study UK	University College, London | University of Cambridge | University of Oxford | University of Manchester | Newcastle University | University of Sussex | Royal Gwent Hospital	https://ClinicalTrials.gov/show/NCT02778607
Therapeutic Recommendations For The Treatment Of Children With A Retinoblastoma	French Africa Pediatric Oncology Group	https://ClinicalTrials.gov/show/NCT04425434
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A Patch Free Treatment for Young Children With Amblyopia	University of Waterloo | Retina Foundation of the Southwest | McGill University | Queensland University of Technology	https://ClinicalTrials.gov/show/NCT04086524
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A Computerized, Adaptive Therapeutic Gaming Approach Training Visual Perceptual Skills in Children With CVI	Universitaire Ziekenhuizen KU Leuven | Vrije Universiteit Brussel | Fund for Scientific Research, Flanders, Belgium	https://ClinicalTrials.gov/show/NCT05014503
Re-Orchestration of Interregional Oscillatory Activity to Promote Visual Recovery	Ecole Polytechnique Federale de Lausanne	https://ClinicalTrials.gov/show/NCT05220449
Effect of Type of Head Positioning on Retinal Displacement in Vitrectomy for Retinal Detachment	Unity Health Toronto	https://ClinicalTrials.gov/show/NCT04035343
Macular Perfusion Changes After Anti-VEGF Versus Targeted Retinal Photocoagulation in Proliferative Diabetic Retinopathy	Cairo University	https://ClinicalTrials.gov/show/NCT04674254
Metabo-lipidomics of the Ocular Surface for Cataract Surgery	University Hospital, Tours	https://ClinicalTrials.gov/show/NCT05802550
Macular Involvement in Diabetic Retinopathy Evaluated With Swept-Source OCT	University of British Columbia	https://ClinicalTrials.gov/show/NCT03765112
EyeConic: Qualification for Cone-Optogenetics	University Hospital, Basel, Switzerland | Institute of Molecular and Clinical Ophthalmology Basel	https://ClinicalTrials.gov/show/NCT05294978
Suprachoroidal Visco-buckling for the Treatment of Rhegmatogenous Retinal Detachment	King's College Hospital NHS Trust | Norfolk and Norwich University Trust Foundation | St Thomas' Hospital, London | University of Sunderland | Moorfields Eye Hospital NHS Foundation Trust | Mid and South Essex NHS Foundation Trust | Sheffield Teaching Hospitals NHS Foundation Trust	https://ClinicalTrials.gov/show/NCT04557527
S.T.O.P. Technology Contact Lenses Versus Dual-focus Contact Lenses for Slowing Down Myopia Progression in Children	nthalmic Pty Ltd | Brighten Optix Corporation	https://ClinicalTrials.gov/show/NCT05243836
PMCF Study on EDOF (Isopure) *vs* Monofocal (Micropure) IOL	Beaver-Visitec International, Inc. | targomedGmbH	https://ClinicalTrials.gov/show/NCT04249492
ARTFL LEFFTDS Longitudinal Fronto-temporal Lobar Degeneration (ALLFTD)	Mayo Clinic | University of California, San Francisco | National Institute on Aging (NIA) | National Institute of Neurological Disorders and Stroke (NINDS)	https://ClinicalTrials.gov/show/NCT04363684
Systematic Assessment of Laryngo-	Kliniken Beelitz GmbH | University Hospital	https://ClinicalTrials.gov/show/NCT04706234

pharyngeal Function in Patients With MSA, PD, and 4 repeat Tauopathies	Muenster | Medical University of Warsaw | University Hospital Carl Gustav Carus | University of Ulm | Medical University Innsbruck | Hannover Medical School | University of Barcelona

secretome have highlighted its role in facilitating cell survival, proliferation, differentiation and physiological processes [17]. A huge number of secreted growth factors are well known today, including VEGF, SDF-1, TGF-β, IGF-1, fibroblast growth factor (FGF), nerve growth factor-beta (NGF-β), HGF, G-CSF and EGF[18]. With regard to MSC secreted cytokines and chemokines, the most investigated are CCL2, CCL5 and CXCL12 (SDF-1)[19].

One of the most useful aspects of the MSC secretome is the possibility to tailor or modify its composition depending on the desired cell-specific therapeutic effects. This promising possibility depends on MSC tissue sources or on the number of passages, allowing the creation of distinct secretory profiles and exosomal compositions[20]. However, several controversial studies have already been published. It was shown, for example, that the impact of MSCs extracted from adipose tissue was more noticeable on axonal growth than MSCs coming from bone marrow, while cell passaging did not influence the secretome content/activities supporting postnatal neuronal survival and axonal growth[21]. During the last few years, it has been revealed that MSCs are able to modify the microenvironment by releasing EVs, primarily distinct into apoptotic bodies, microvesicles and exosomes[22] (Table 2). The latter subtype consists of a bilayered lipid film of 30-120 nm, originating from convex membranes in late endosomes, determining the production of multi-alveolar bodies[23].

Different and various proteins are typical markers of exosomes, such as tetraspanin (CD9, CD63, CD81), annexin, heat shock proteins, caveolin and clarins as well as protein characteristics of source cells[24]. Furthermore, exosomes present specific lipids, comprising lipid raft portions, ceramides, sphingomyelin, cholesterol, GM1 ganglioside and phosphatidylserine. Additionally, they can contain nucleic acids, mRNA and ncRNA[25]. MSC-derived exosome biosynthesis and secretion are complex pathways that differ in microenvironmental stimuli, like inflammation or hypoxia[26]. The mTOR and Wnt pathways seem to play a pivotal role in exosome release[27]. Interestingly, recent studies have shown that MSC-derived exosomes may be involved in antigen presentation and immunologic response, coagulation, angiogenesis and apoptosis, as confirmed by the expression of antigens such as CD9, CD44 and CD89 on their surface [28]. Thus, the secretome obtained from the culture of MSCs would appear to promote tissue repair and modulate immune response *in vitro* and *in vivo*, showing a translational impact on regenerative medicine[29]. The use of CM could present diverse advantages if compared to the original MSC implantation, such as: (1) Removal of the inherent risks of cell transplantation; (2) Simpler storage, transport and conservation requirements; and (3) Possible application as a ready-to-go biologic product[30].

Secretome preconditioning modulated by the MSC cultural microenvironment

In recent years, it has been shown how preconditioning approaches for improving paracrine secretion, such as hypoxia, biochemical stimuli and 3D microenvironment, can increase the viability, proliferation and paracrine features of MSCs, thus expanding the therapeutic potential of these cells and their derived products[31]. In detail, dynamic culture conditions, such as 3D aggregate culture and fluid flow, could noticeably impact cellular behavior[32]. Boosted levels of growth factors and cytokines were detected in 3D MSC cultures grown on rotatory orbital or shaking platforms, in stirred systems, such as stirred tank reactors or spinner flasks, and in microgravity bioreactors[33]. Nevertheless, little is still known about the dynamic culture conditions and procedures for 3D aggregate MSC cultures as a scalable and reproducible plan for secretome production. However, the possibility of culturing cells under 3D conditions in a way to better mimic the *in vivo* environment has emerged[34].

A dynamic cross-talk between the cells could permit them to constantly modify their secretome following received stimuli, generating a microenvironment able to promote secretome enrichment for specific applications. Additionally, enhancing the manufacturing process allows MSC cell populations to be obtained that can be cryopreserved for clinical applications to expand clinical efficacy[35]. Recently, the use of matrix-conjugated hydrogel cell culture materials normalized a culture of induced pluripotent stem cell-derived MSCs (iPSC-MSCs), leading to a well-defined secretory profile able to promote enhanced neovascularization both *in vitro* and *in vivo*[36]. Using such innovative biomaterials, it was possible to stimulate reproducible secretion of proangiogenic and immunomodulatory cytokines from iPSC-MSCs that improved tubulogenesis of endothelial cells in Geltrex and neovascularization in chick chorioallantoic membranes [37].

Treatment with both IFN-γ and TNF-α permitted optimization of the MSC secretome. Recently, a unique supernatant of MSCs from human umbilical cord-derived MSCs, pretreated with TNF-α, was discovered to be more powerful in promoting macrophage migration, M2 polarization and pha-gocytosis, due to the induced high levels of CCL2 and IL-6 [38]. Another way to overcome the expansion limitation of MSCs is to work with MSCs derived from human-induced pluripotent MSCs, serving as a reproducible and sustainable cell source. In a way similar to hBMMSCs, human-induced pluripotent MSCs can release EVs with *in vitro* immunomodulatory properties, with an increased expression of well-known immunomodulatory genes, such as *HLA-DRA*, *IDO1* and *CXCL8/IL8* and at least another 100 regulated by NFKB signaling, known to play a pivotal role in immune response[39].

Interestingly, it has recently been shown that hypoxic preconditioning appears to induce the ASC secretome to release a secretome with enhanced anti-apoptotic effects by promoting the autophagic process of ASCs[40]. Furthermore, the specific content of EVs can be modulated by hypoxia, with their source cell responding by triggering HIF at low oxygen levels. The pleiotropic effects of HIF regulate the expression of many genes involved in pathways such as inflammation, angiogenesis, migration, differentiation, metabolism, proliferation and apoptosis. Expression of these genes is reflected in the interior of secreted EVs, which showed a greater regenerative ability than those achieved under normal oxygen conditions[41]. Moreover, the preconditioning of MSCs in an oxidative stress (OS) environment provides the release of

Table 2 Secretome and extracellular vesicle features

Type	Dimension	Origin	Collection	Content
Medium-size EVs (microvesicles)	200-1000 nm	Plasma membrane shedding	Filtration, ultracentrifugation, chromatography, precipitation, immunoaffinity	Similar to exosomes + cytosolic/plasma membrane/post-translational modified proteins
Small-size EVs (exosomes)	Up to 200 nm	Multivesicular bodies pathway	Filtration, ultracentrifugation, chromatography, precipitation, immunoaffinity	Receptors, transcription factors, enzymes, proteins, lipids, nucleic acids (DNA, mRNA and miRNA)
Soluble factors	Up to 5 nm	Protein synthesis	Protein extraction methods	Proteins, growth factors, chemokines, cytokines, enzymes
Secretome	From protein size to 1000 nm	Cell secretion/shedding	Cell culture media (concentration is possible)	The combination of the other components

EV: Extracellular vesicle; miRNA: MicroRNA.

many proteins, growth factors, cytokines and exosomes that could increase the antioxidant ability of MSCs against OS, enforcing the secretome as an encouraging, novel, cell-free tissue regeneration approach[42].

Characterization of MSC secretome EVs

A detailed analysis of the secretome structure might contribute to the improvement of secretome application for regenerative purposes and allow the discovery of novel biomarkers circulating in patient blood, improving pathology diagnosis and discovering new therapeutics targets[43]. As already anticipated, secretome fractions consist of lipids, proteins and non-coding RNAs able to impact the physiology of target cells. MSC-EVs were shown to contain a significant number of microRNAs (miRNAs), such as miR-210, miR-200b-3p and miR-4732-3p, involved in improving myocardial function[44]. BM-MSC-EVs, PD-L1-MSC-EVs and human umbilical cord-derived MSC-EVs also exhibited a healing role in autoimmune conditions[45]. miR-146a and miR-27a/b, upregulated in ASC-derived EVs, were able to induce neoangiogenesis pathways, while miR-122-5p, miR-27a, miR-206 and lncRNA MALAT1 played a relevant role in osteogenic regenerative processes[46].

Other studies identified specific factors from the secretome released by tumor cells that might be actively involved in cancer progression, thus representing optimal biomarkers[47]. Additionally, a customized secretome could be rich in proapoptotic factors that are helpful against cancer or higher levels of proangiogenic and pro-osteogenic factors suitable for regenerative applications. An interesting case is represented by human fetal MSCs, producing a secretome rich in anti-apoptotic factors as well as proangiogenic and antiangiogenic and osteogenic differentiative proteins[48]. On the contrary, the multipotent fetal dermal cell secretome is enriched in upregulated proteins involved in wound healing processes, angiogenesis and cellular metabolism[49]. Such data underlined that the fetal MSC secretome could be more beneficial for regenerative purposes if compared to the adult MSC secretome. In agreement with reports on the secretome derived from 3D cultured cells, fetal cells cultured under 3D conditions might further improve the therapeutic abilities of their secretome[50].

Unique immunomodulatory properties emerged for amniotic MSCs. Their secretome was able to reduce the polarization of T cells toward inflammatory helper T cell subgroups, inducing regulatory T cells, to decrease the proliferation of activated peripheral blood mononuclear cells, to affect monocyte polarization to antigen-presenting cells stimulating the synthesis of anti-inflammatory macrophage (M2) markers and to reduce the activation of B lymphocytes into plasma cells[51]. The most intriguing aspect of secretome EV fractions is the functional mitochondria release from human mesenchymal stromal cells[52]. Recent studies in non-orthopedic tissues proposed that MSCs can rescue damaged cells by donating mitochondria, repairing mitochondrial activity in target cells, preserving cell viability and stimulating tissue repair. To obtain this goal, MSCs might be able to package mitochondria for export into EVs, and these "mitoEVs" could provide a delivery approach for cell-free mitochondria-targeted therapy[53].

Therapeutic role of the secretome in central nervous system pathologies

The MSC secretome is a significant element of the paracrine and autocrine cell signaling mechanism, playing a crucial role in the regulation of many physiological and pathological processes. In particular, its effects on immunomodulation, neuronal survival and regeneration, due to the action of soluble and vesicular factors, are pivotal in reducing or even arresting neuronal disease evolution and in promoting repair[54]. Thus, the various MSC secreted factors and vesicles seem to be an effective tool for the protection and survival of neuronal and glial cells[55]. Traumatic brain injury (TBI) is determined by external mechanical forces able to cause physical, cognitive and emotional impairments[56]. In this case, the MSC-derived secretome may be used to control the secondary injury mechanisms of TBI, modulate the abnormal inflammatory cascade, reduce proinflammatory cytokines and stimulate neural stem cell proliferation and differentiation [57]. Moreover, EVs released by MSCs reduced neuroinflammation and supported neurogenesis and angiogenesis, rescuing spatial learning and motor damage in TBI animal models[58].

Spinal cord injury is characterized by long-term functional deficits following the loss of neurons and glial cells, inflammation and demyelination[59]. The paracrine factors secreted into the lesion site by MSCs, such as HGF, BDNF and NGF could promote immunomodulation, glial scar reduction, axonal regeneration and neurite outgrowth. Additionally, the

ASC-derived secretome reduced the production of TNF-α by M1 macrophages while it improved TGF-β1 and IL-10 production by M2 macrophages[60]. MSC exosomes could stimulate anti-inflammatory and proangiogenic effects and axonal regeneration and suppress glial scar formation and cell apoptosis, reducing lesion size and improving functional recovery after traumatic spinal cord injury[61].

Ischemic stroke is a cerebrovascular pathology induced by blood vessel occlusion or injury, leading to a blood supply defect, determining focal tissue loss and endothelial and neuronal cell death[62]. The use of MSC secreted factors such as IGF-1 and BDNF could induce neuroprotection by impeding neuronal damage and tissue loss and reduce astrocyte injury by GFAP downregulation[63].

Parkinson's disease (PD) is a neurodegenerative pathology characterized by the progressive degeneration of dopaminergic neurons. In PD, it has already been seen that the addition of the MSC secretome can promote a partial reversion of PD histological impairments and gains in animal motor ability by the secretion of immunomodulatory, anti-inflammatory, neurogenic, neurodevelopmental, neurorescuing or antiapoptotic factors[64]. Recent evidence highlighted the particular ability of the MSC secretome to reduce one of the hallmarks of the disease, the alpha-synuclein aggregates, through an MMP-2-based mechanism[65].

MAIN FEATURES OF RETINAL CELLS

Even if peripherally localized, the retina represents an important part of the central nervous system. Though it presents the same types of functional elements and neurotransmitters sited in other portions of the central nervous system, the retina includes five classes of neurons: photoreceptors (rods and cones); bipolar cells; amacrine cells; horizontal cells; and ganglion cells. Light absorption by the photopigment in the outer segment of rods and cones, the two photoreceptors, starts a cascade of events that changes the receptor membrane potential and the quantity of neurotransmitter released by the rod and cone synapses onto the adjacent bipolar cells, in the outer plexiform layer. Then, in the inner plexiform layer, the short axonal processes of bipolar cells realize a synapse with the dendritic processes of ganglion cells whose axons form the optic nerve. Horizontal and amacrine cells, instead, present their cell bodies within the inner nuclear layer and are mainly involved in lateral interactions between already described retinal cells, impacting the sensitivity of the visual system to light contrast over a wide range of intensities. The amacrine cell processes, which ramify laterally in the inner plexiform layer, are postsynaptic to bipolar cells and presynaptic to ganglion cells, while the processes of horizontal cells instead extend in the outer plexiform layer. The existence of different subgroups of amacrine cells that play a distinct role within visual pathways is relevant. Furthermore, the neural retina and the choroid are connected by a monolayer of cells constituting the retinal pigmented epithelium (RPE). Light absorption, epithelial transport, spatial buffering of ions, visual cycle regulation and phagocytosis of rod and cone outer segment membranes represent the main functions exerted by the RPE[66].

RPE cell secretome and retinal diseases

The RPE is characterized by a polarized nature, with molecules expressed by these cells either secreted to the apical or basolateral membrane by the Na^+/K^+-ATPase associated channel or by the anion channel, respectively. These products, mainly growth, anti/proangiogenic and neurotrophic factors, are critical for the correct functioning of the neuroretina and choroid. Among them, the most characterized are VEGF[67,68], TGF-β[67,69], PEDF[70], MMPs[71], NGF[72], FGF-1, FGF-2, and FGF-5[73], IGF-1[74], BDNF[75], PDGF[76], CTGF[77], LEDGF[78], interleukins[79], tissue inhibitor of matrix metalloproteases[80], PIGF[81], angiogenin[82], EPO[83], somatostatin[84] and apolipoprotein A1[85]. These factors could also play a fundamental role in the etiology of several retinal diseases such as diabetic retinopathy (DR), age-related macular degeneration (AMD) and retinopathy of prematurity[86].

Deep proteomic analyses of RPE cells cultivated in these pathological condition microenvironments suggested that previously described molecules could be involved in membrane and cytoskeleton dynamics, mitochondrial trafficking, protection/induction of cellular stress, apoptosis, differential modulation of multidrug resistance-associated proteins and in other metabolic events already during the first stages of the diseases[87]. In physiological conditions, RPE cells release EVs characterized by proteins associated with biological pathways involved in AMD etiology, including drusen composition. Recently, it was shown that drusen-associated proteins are secreted as cargo of EVs produced by RPE cells in a polarized apical to basal way. Remarkably, drusen-associated proteins revealed differential regulation of polarized secretion in homeostatic conditions and in response to AMD stressors[88]. Findings suggested that a finely-tuned mechanism is pivotal to regulate directional sorting and secretion of drusen-associated proteins *via* RPE secretome EVs, supporting the influential role of vesicles as a strategic source of drusen proteins and critical elements to drusen development[89].

OS changed the release of several factors implicated in neovascularization and AMD, stimulating a proangiogenic microenvironment by increasing the secretion of VEGF, PTN and CRYAB and reducing the production of anti-PEDF and CFH. Apical secretion was influenced more than basolateral for PEDF, CRYAB and CFH, while directional secretion was impacted more for VEGF, which may have implications for choroidal neovascularization[90]. VEGF-A is an important proangiogenic factor released by different retinal cytotypes (endothelial cells, Müller cells, ganglion cells and pericytes) but primarily by the basolateral side of RPE in homeostatic conditions, shifting to apical during pathological conditions [91].

In particular, VEGF overexpression was highlighted in hypoxic and hyperglycemic conditions, by both *in vitro* and *in vivo* studies, demonstrating that in pathological conditions VEGF causes alteration of tight junction proteins and transepithelial resistance[92]. It has been confirmed that VEGF R2, placed in the apical side of RPE cells, can induce

disruption of the RPE barrier by promoting VEGF signaling[93]. Considered together, such findings led to the development of anti-VEGF therapies to treat retinal neovascularization in patients with DR and other related diseases. However, many associated complications are still present, such as repeated injection requirements, increased ocular pressure, macular edema, subconjunctival hemorrhage, pain, uveitis and the compromised viability of RPE, photoreceptors, choriocapillaris and Müller glia[94].

One of the most interesting relates to splice variants of VEGF, such as VEGF165b, expressed by RPE cells. It can appear to act as a powerful antiangiogenic isoform of VEGF with significant results in treating induced choroidal neovascularization and was decreased in DR[95]. Nevertheless, while inner retinal barrier and Müller cell association with VEGF is well known, the outer retinal barrier properties of RPE in relation to VEGF in diabetes and other ocular neovascularization-related diseases should be better investigated. One of the most significant glycoproteins of the RPE secretome is PEDF, a serine protease inhibitor with neuroprotective, antiangiogenic and anti-inflammatory features. In homeostatic conditions, PEDF is apically released from the RPE and preserves retinal and choriocapillaris integrity by preventing endothelial cell proliferation[96]. It was seen that PEDF was downregulated in human hyperglycemic RPE cells as well as in patients affected by proliferative DR (PDR), diabetic macular edema (DME), retinopathy of prematurity, retinitis pigmentosa and leber congenital amaurosis[97]. Thus, PEDF is primarily considered for its therapeutic potential, showing positive effects in photoreceptor survival, morphology and function while reducing vascular permeability in correlation with reduced levels of angiogenic factors (VEGF, VEGFR-2), cytokines and chemokines[98]. Additionally, recent animal studies have proven that in an oxygen-induced retinopathy model and in a rat model of choroidal neovascularization, PEDF upregulation blocked retinal neovascularization and inflammation[99].

Another prosurvival cytokine able to stimulate fibroblast chemotaxis/proliferation and preserve pericyte viability and physiological vascularization of the retina is PDGF. Similar to VEGF, it can promote pathologic neovascularization in PDR and DR and in a hypoxia-regulated microenvironment[100]. PDGF receptor activation suggests an autocrine mechanism in epiretinal membrane development and retinal wound repair[101]. Today, one of the most promising research fields is understanding the cross-talk of PDGF with other signaling pathways in order to identify the best molecular targets for combinatorial therapies. This idea arose from several animal studies that established that antagonism to PDGF-BB (a homodimeric form of the PDGF family), together with anti-VEGF, enhanced the arrest of retinal neovascularization[102].

An important cofactor of VEGF is PlGF. It can alter retinal fibrovascular integrity and RPE permeability by interaction with VEGF and activation of Akt and HIF-1 pathways[103]. Thus, it was found at high levels in AMD and PDR patients [104]. The use of anti-PlGF monoclonal antibody in different animal models revealed reduced inflammation and vascular leakage with no adverse effects in retinal ganglion cell (RGC) viability[105]. However, novel strategies that avoid the weaknesses observed in repeated intraocular injections should consider PlGF as a valid therapeutic target. RPE cells cultured in high glucose medium also showed an elevated expression of CTGF, one of the main fibrogenic factors involved in fibroblast proliferation and extracellular matrix synthesis, which could control the microenvironment around the distal retinal/RPE/Bruch's membrane complex and protect against neurodegenerative diseases[106]. Increased retinal CTGF levels might play an essential role in DR, probably by reducing VEGF levels[107]. Thus, the combined use of anti-CTGF and anti-VEGF in treating complications of DR could exert more beneficial effects than a monotherapy drug[108].

CTGF is corroborated in its activity by the more well-known FGF, which plays a crucial role in stimulating vascularization, angiogenesis and cell survival and acting as autocrine factors. FGF1, FGF2 and FGF5 are principally released in the RPE, reaching their highest levels in non-proliferative retinopathy, PDR with active proliferative retinopathy and diabetic conditions, respectively[109]. Recently, targeting of retinal FGFs exhibited worthy results in improving visual acuity of DME and exudative AMD patients, even if further studies are mandatory to determine long-term effects[110]. The secretome produced by human RPE cells also contained IGF-1 and IGF-2, natural proteins promoting growth and insulin-like metabolic effects, together with their receptor (IGF-R) and binding protein (IGFBP-2)[111]. Both growth factors seem to play a pivotal role for RPE autocrine/paracrine-mediated modulation of proliferation[112]. Recent evidence showed that another IGFBP family member, IGFBP-3, was able to reduce DR by considerably decreasing TNF-α levels and proapoptotic markers[113].

Among secreted factors, TGF-β represents one of the main elements that can modulate main cellular physiological processes, like growth, differentiation, proliferation and apoptosis[114]. However, there is scant information on its efficacy and potential mechanisms in relation to retinal homeostasis or pathology. In detail, comparable secretion levels of TGF-β from polarized RPE, differentiated from human embryonic stem cells and human RPE, promoting retinal homeostasis and sustaining the potential of human embryonic stem cell-RPE in replacement therapies, have recently been highlighted[115]. Human stem cell-derived RPE treated with reactive oxygen species for 1 wk or 3 wk released more than 1000 proteins, many of which showed relevant changes due to induced stress.

In particular, secreted APOE and TGF-β were decreased 4-fold, and urotensin-II, one of the most effective vasoconstrictors, doubled, similar to BMP1[116]. The glycoprotein EPO represents one of the most promising molecules found in the RPE secretome. It acts as an erythropoiesis regulator with different additive features such as vessel integrity, recruitment of endothelial progenitor cells, neuroprotection and antioxidative properties[117]. High levels of EPO were recently found in DR, PDR and DME patients[118]. Especially in hyperglycemic conditions, EPO seems to protect the RPE barrier, reducing retinal vasculogenesis, downregulating VEGF and VEGFR expression and protecting tight junctions by increasing the flow of Ca^{2+} ions in blood-brain barrier animal models[119]. However, the administration of EPO in the late stage of a hypoxia-induced murine retinopathy model worsened retinal neovascularization, suggesting that EPO might play a protective role in early DR and a pathologic one in late DR[120]. This dual nature of EPO could be related to its action mechanism, whose first step is its hypoxia-modulated binding to cell surface receptor EPOR. Thus, it can be predicted that in the first stages of DR, EPO exerts neuroprotective functions, while in the advanced stage of DR EPO acts as a neovasculogenesis inducing molecule that is regulated by hypoxia[121].

MMPs, apically secreted by RPE, are calcium-dependent endopeptidases involved in angiogenesis and are fundamental for ocular extracellular matrix and photoreceptor outer segment homeostasis[122]. Recently, it has been seen that basolateral secretion of MMP is related to AMD, and increased levels of MMP-2 and MMP-9 were also observed in the Bruch's membrane of AMD and DR patient eyes[123]. Thus, inhibitors of both cited MMPs might also exert an advantageous role by blocking capillary cell apoptosis, growth of vessels and reduce inflammatory-mediated permeability[124].

In addition to angiogenic and antiangiogenic factors, numerous inflammatory chemokines and cytokines were elevated in retinal diseases, such as PD and PDR. Among them, the most investigated were MCP-1, IL-6 and IL-8. It was seen that MCP-1 and IL-8 secretion levels are directly correlated to blood glucose levels, suggesting a crucial role in altered blood retinal barrier (BRB) activities of DR affected patients[125]. MCP-1 carries out chemoattractant activity for monocytes and lymphocytes to promote endothelial proliferation and may limit the impairment of neurosensory retina[126]. IL-6 and IL-8, were overexpressed in cultured RPE cells stimulated with IL-1b or TNF-β, suggesting that polarized release of growth factors/cytokines is favored in retinal diseases[127].

Additionally, it is interesting to cite the recently discussed role of somatostatin as a neuromodulator of retinal homeostasis, as hypothesized by its downregulation in the RPE of diabetic eyes[128]. Finally, several substrates of the serine protease HTRA1 were found in the RPE secretome, proposing a link between it and complement modulation and amyloid deposition in AMD etiopathogenesis. In detail, a cleavage of fibromodulin (90%), CLU (50%) and vitronectin (54%) involved in regulation of the complement pathway was seen, along with a cleavage of 2-macroglobulin (55%) and ADAM9 (54%) related to amyloid deposition as well as some cell surface protein cleavages including talin-1 (21%), fascin (40%) and chloride intracellular channel protein 1 (51%)[129].

Müller glia cell secretome and retinal diseases

Regarding the RPE, Müller cells can modulate trophic secretion depending on the healthy or pathological status of the retina[130]. The Müller cell physiological secretome mainly contains molecules that are crucial to increase BRB tightness, like thrombospondin-1 and PEDF[131]. In pathological circumstances, factor synthesis and secretion both shift towards an inflammatory environment. Under hyperglycemic conditions, IL-1b release by Müller cells is increased, leading to vascular impairment and cell death *via* a paracrine mechanism. Thus, by inhibiting IL-1b or knocking down its receptor, it was possible to decrease inflammation and photoreceptor/retinal vessel disruption in murine models, exerting a possible therapeutic role for ocular dystrophies related to chemokine expression and/or diabetes[132]. Furthermore, the proinflammatory IL-6 and TNF-α can be secreted by Müller cells, determining a possible promotion of both vascular dysfunction and angiogenesis, even if IL-6 may exert protective effects toward photoreceptor cells[133].

Stimulation of porcine and human Müller cells with IL-4, IL-6, IL-10, VEGF, INF-γ, TGF-β1, TGF-β2, TGF-β3 and TNF-α resulted in a primarily proinflammatory phenotype with release of cytokines and factors of the complement system[134]. Additionally, Müller cells expressed proteins linked to biosynthesis and maturation of phagosomes. These findings underline the relevance of Müller cell signaling in chronic retinal inflammation[135]. Additionally, under hyperglycemia and hypoxic conditions, Müller cells shift PEDF secretion to VEGF, contributing to ocular vascular diseases[136]. Therefore, inhibition or knockdown of Müller cell-derived VEGF could reduce ischemia-induced impairment of the BRB, prevent ischemia-induced retinal neovascularization and decrease vascular leakage[137].

Recent evidence highlighted that in the diabetic retina expression of VEGF could be regulated by increasing the activity of the receptor for retinoic acid alpha, which also stimulates the expression of glial cell line-derived neurotrophic factor, with a final significant decrease of vascular leakage[138]. Nevertheless, in recent years, the neuroprotective effects of VEGFR-2 in Müller glia have also been described, suggesting its significance for cell survival and consequential viability of neuronal cells in the diabetic retina[139]. Interestingly, the secretome of Müller cells also contains increased levels of MMP-2 and MMP-9 in patients with PDR and AMD, respectively[140]. It was proposed that the stabilization of HIF-1a could raise the level of VEGF, inducing MMP-2 expression in neighboring endothelial cells, with consequent retinal neovascularization[141]. As MMPs regulate crucial cellular pathways through angiogenesis and apoptosis, their targeting could represent an important therapeutic strategy for ocular diseases. Moreover, new evidence has proven that Müller glia release neurotrophic factors, such as CLU, osteopontin and basigin, that support RGC survival. The latter two significantly enhance RGC survival *in vitro*, suggesting that the survival-promoting activity of the Müller cell secretome is multifactorial[142].

Recently, it was shown that human iPSC-derived multinucleated giant cells (hiMGCs) could represent an alternative to primary MGCs in understanding glial cell involvement in retinal disorders, including DR. Under culture with palmitate, a major free fatty acid with elevated plasma levels in diabetic patients, hiMGCs and primary MGCs expressed low transcript levels of *AQP4*, *RLPB1*, *SLC1A3*, *KCNJ1* and *KCJN10*. Furthermore, the analysis of the palmitate-treated hiMGC secretome evidenced an upregulation of proangiogenic factors powerfully related to DR, including ANG2, endoglin, IL-1b, CXCL8, MMP-9, PDGF-AA and VEGF[143]. One of the most interesting pieces of evidence regarding the Müller cell secretome was linked to the production of different EVs from endfeet and microvilli of retinal Müller cells in adult mice. In particular, VAMP5 was identified as a Müller cell-specific snap receptor member that is part of EVs and responsive to ischemia, with relevant changes between the secretomes of Müller cells and neurons *in vitro*[144].

Other glial cell secretome and retinal diseases

Undifferentiated rat RGC line RGC-5 can secrete numerous protein markers of RGCs, even if they are unable to react to glutamate or N-methyl-D aspartate. Furthermore, it has recently been highlighted that human nonpigmented ciliary epithelial (HNPE) cells could release several neuroproteins located in the aqueous humor, many of which can influence the activity of neuronal cells. Recent works identified about 130 unique proteins from the HNPE cell-conditioned SF-medium, most of which are involved in cell differentiation. These results led to the hypothesis that a differentiation

system of HNPE cell-conditioned SF-medium with RGC-5 cells can promote a differentiated phenotype in RGC-5 cells, functionally close to primary cultures of rat RGCs[145].

The secretome of retinoblastoma, the solid malignancy of the developing retina, is immunosuppressive and induces a protumoral phenotype. This conclusion was the result of complex analyses that identified the cytokine extracellular matrix metalloproteinase inducer and macrophage migration inhibitory factor, both characterized by detected immunosuppressive activity and secreted at high levels in retinoblastoma primary cell cultures. In addition, macrophages derived from peripheral blood mononuclear cells increased the expression of M2-like polarization markers following exposure to retinoblastoma-conditioned medium or recombinant migration inhibitory factor[146].

CROSS-LINK BETWEEN RETINAL AND MESENCHYMAL SECRETOMES: DIFFERENT MSC-DERIVED SECRETOMES AS INNOVATIVE APPROACHES FOR RETINAL DISEASES

The MSC secretome is currently studied extensively for the treatment of several retinal diseases. Its therapeutic potential lies in its richness of immunomodulatory, antiangiogenic and neurotrophic factors, preventing retinal degeneration and improving retinal morphology and function. Additionally, exosomes secreted by MSCs showed anti-inflammatory and antiapoptotic effects (Figure 1 and Table 3). Based on MSC origins and their particular secreted factors, several promising preclinical and clinical studies were initiated to explore the potential advantages of MSC secretome for the treatment of retinal diseases.

Novel evidence on the role of MSC secreted factors in retinal disease etiopathogenetic pathways

Novel evidence showed that MSC conditioned media inhibits abnormal neovascularization and decreases vaso-obliteration (promoting revascularization) in retinopathies by restoring neuronal Sema3E levels, which reduce pathological concentrations of IL-17A (and associated proinflammatory factors, such as IL-1b) in myeloid cells[147]. Among MSC released factors, PDGF secretion may play a crucial role in MSC-mediated RGC neuroprotection. These results were obtained from the arrest of PDGF signaling by small molecule PDGF inhibitors, neutralizing antibody or downstream phosphatidylinositol 3 kinase, which blocked RGC neuroprotection conferred by MSC co-culture. Furthermore, intravitreal injection of PDGF led to relevant optic nerve neuroprotection *in vivo* after experimental induction of high intraocular pressure[148]. Application of conditioned media obtained from MSCs protected against Aβ 1-42 oligomer-induced retinal pathology in RGCs of both rat and ARPE-19 cells, due to proteins associated with SIRT1/pAKT/pGSK3β/β-catenin, tight junction proteins and the apoptosis pathway[149]. Furthermore, in recent years, the administration of EVs in models of neurological disorders has highlighted a relevant improvement of neurological dysfunction. In particular, miRNAs from MSC-EVs, as one of the central mediators that control various genes and decrease neuropathological change, have been identified in various neurological pathologies[150].

Bone marrow MSC-derived secretome regulates retinal cell neuroprotection

The BMMSC secretome protects retinal morphology, regulates autophagy-, proapoptotic– and pronecroptotic–related gene and protein expression and promotes the activation of antioxidant machinery, exerting a neuroprotective ability during retinal degeneration[151]. A recent expression analysis of about 1000 proteins exhibited high levels of paracrine factors secreted by hBMMSCs that might be fundamental in the neuroprotective effect of the stem cell secretome over *in vitro* retinal degeneration. These results support the hypothesis that the paracrine effect of hBMMSCs may slow photoreceptor death and be a therapeutic possibility in retinal photoreceptor degenerative diseases[152]. Additionally, rat BMMSCs cultured with the secretome from neonatal rat retinal cells were able to differentiate into RGC-like cells, exhibiting protein expression patterns similar to those of isolated RGCs such as Map2, nestin and Thy1.1[153].

Adipose MSC-derived secretome regulates retinal cell regeneration

Recent evidence showed an important therapeutic effect of hADSCs and its secretome on an *in vivo* model of sodium iodate retinal neurodegeneration. The studies highlighted that the hADSC secretome effects were particularly striking, especially in terms of photoreceptor regeneration and retinal function, as underlined by increased expression of retinal regeneration markers such as Pax6, Chx10, S-Opsin (Opn1sw), Nrl, Crx and GFAP[154]. Oxidatively stressed ARPE-19 cells treated with adipose MSC conditioned media and/or combined with nicotinamide, vasoactive intestinal peptide or both factors showed an improved recovery from the damaged status. Additionally, the same treatment could determine better protection of the neuroretinal architecture, mainly rods and cones, and a lower degree of glial cell activation[155].

The preclinical efficacy of adipose-derived stem cell concentrated conditioned medium (ASC-CCM) was recently tested in repetitive ocular blast injury mice, highlighting a significant rescue from retinal injury and a significant restoration of visual function, also associated with a significant reduction of neuroinflammation markers, retinal GFAP and OS. Furthermore, *in vitro*, oxidatively stressed Müller cells pre-incubated with ASC-CCM exhibited normalized levels of GFAP, viability and catalase activity[156]. Intravitreal injection of ASC-CCM was safe and efficient against the visual impairments of mild TBI. Blast mice treated with ASC-CCM exhibited improved vision at 5 mo but minimal effects at 10 mo, associated with alterations of GFAP and proinflammatory gene expression in retina. Thus, the unchanged glial response and the risk of retinal injury with live cells suggested that ASC-CCM might have better safety and efficacy than live cells for visual dysfunction therapy[157].

Table 3 Key molecules of the mesenchymal secretome derived from different cell types in the treatment and regeneration of retinal cells

MSC	MSC secretome	Müller glia cell secretome	RPE cell secretome	Other retinal cell secretome
IFN-γ[8]	IFN-γ[8]	TSP-1[131]	VEGF[68]	TSP-1[131]
VEGF[10]	VEGF[10]	PEDF[70]	TGF-β[69]	PEDF[70]
PIGF[81]	PIGF[81]	IL-1b[11]	PEDF[70]	IL-1b[11]
SDF-1[10]	SDF-1[10]	IL-1R[143]	MMPs[71]	IL-1R[143]
ANG2[10]	ANG2[10]	TNF-α[11]	NGF[72]	IL-6[11]
G-CSF[10]	G-CSF[10]	IL-4[134]	FGF-1[73]	TNF-α[11]
SCF[10]	SCF[10]	IL-6[134]	FGF-2[73]	IL-4[134]
PDGF[10]	PDGF[10]	IL-10[134]	FGF-5[73]	IL-10[134]
EGF[10]	EGF[10]	VEGF[10]	IGF-1[74]	VEGF[10]
HGF[10]	HGF[10]	IFN-γ[8]	BDNF[75]	IFN-γ[8]
IGF-1[10]	IGF-1[10]	TGF-β1[34]	PDGF[76]	TGF-β1[34]
TNF-α[11]	TNF-α[11]	TGF-β2[34]	CTGF[77]	TGF-β2[34]
IL-1b[11]	IL-1b[11]	TGF-β3[34]	LEDGF[78]	TGF-β3[34]
IL-2[11]	IL-2[11]	MMPs[71]	IL-1b[79]	MMPs[71]
IL-3[11]	IL-3[11]	CLU[121]	IL-2[79]	CLU[121]
IL-6[11]	IL-6[11]	SPP1[142]	IL-3[79]	SPP1[142]
IL-8[11]	IL-8[11]	BSG[142]	IL-6[79]	BSG[142]
CCL5[11]	CCL5[11]	AQP4[143]	IL-8[79]	AQP4[143]
CCL2[11]	CCL2[11]	RLBP1[143]	TIMP[80]	RLBP1[143]
	TGF-β[18]	SLC1A3[143]	PIGF[81]	SLC1A3[143]
	FGF[18]	KCNJ1[143]	ANGIOGENIN[82]	KCNJ1[143]
	NGF-β[18]	KCNJ10[143]	EPO[83]	KCNJ10[143]
	CXCL12[19]	ANG2[143]	SOMATOSTATIN[84]	ANG2[143]
	miR-210[44]	ENDOGLIN[143]	APOA1[85]	ENDOGLIN[143]
	miR-200b-3p[44]	CXCL8[39]	APOE[116]	CXCL8[143]
	miR146a[46]	PDGF[10]	TGF-β[69]	PDGF[76]
	miR27a/b[46]	VAMP5[144]	BMP1[116]	VAMP5[144]
	miR-122-5p[46]		HTRA1[129]	TGF-β[69]
	miR-206[46]			NGF[72]
	MALAT[46] (lncRNA)			FGF-1[73]
				FGF-2[73]
				FGF-5[73]
				IGF-1[74]
				BDNF[75]
				PDGF[76]
				CTGF[77]
				LEDGF[78]
				IL-2[79]
				IL-3[79]
				IL-8[79]

	TIMP[80]
	PIGF[81]
	ANGIOGENIN[82]
	EPO[83]
	SOMATOSTATIN[84]
	APOA1[85]
	APOE[116]
	BMP1[116]
	HTRA1[129]

MSC: Mesenchymal stem cell; RPE: Retinal pigment epithelium; FGF: Fibroblast growth factor; NGF: Nerve growth factor.

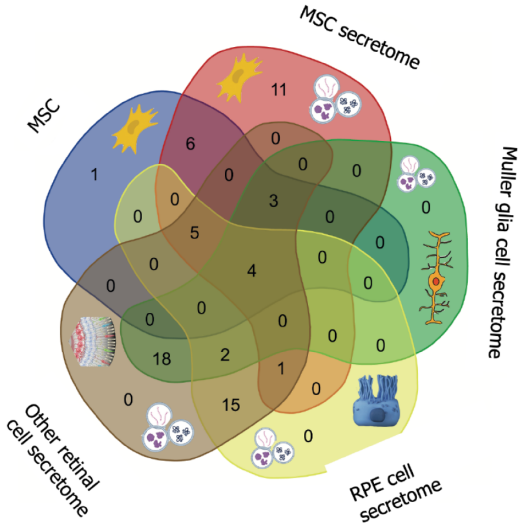

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Figure 1 Common factors released by retinal and mesenchymal cell secretomes. Both groups of cells can release different clusters of factors that are able to influence the microenvironment by paracrine mechanisms. The most common factors are highlighted in the cytotypes. More details are available in Table 3. MSC: Mesenchymal stem cell; RPE: Retinal pigment epithelium.

Human uterine cervical and Wharton's jelly MSC-derived secretomes regulate retinal cell immunomodulation

The treatment of oxidatively stressed ARPE-19 cells with human uterine cervical stem cells-conditioned medium evidenced a significant increase of *VEGFA*, *HO-1*, *HSPB1*, *GCLC*, *PDGFA* and *PDGFB* mRNA expression, highlighting a potential stimulation of detoxifying genes, protection from damage by OS and better vascularization[158]. Recent studies demonstrated that RPE cell viability and the expression of anti-apoptotic Bcl2 were reduced significantly in conditioned media secreted by human Wharton's jelly MSC (WJMSCs)-treated RPE cells, while expression of proapoptotic biomarkers Bax and IL-1b was not significantly changed. WJMSCs are a subgroup of MSCs isolated from the Wharton jelly of the umbilical cord characterized by a high potential of proliferation and a secretome rich in trophic factors and immunomodulatory cytokines. Moreover, previously described experiments showed that the WJMSC secretome could induce apoptosis in RPE cells through activating apoptosis pathways, being a potential therapeutic target for pathologies like proliferative vitreoretinopathy[159].

CONCLUSION

The crosslink between mesenchymal cell and retinal cell secretomes is a topic of interest for regenerative medicine, as both types of cells secrete trophic factors that can modulate cellular pathways involved in survival, function and response to injury. The mesenchymal cell secretome is a collection of molecules secreted by MSCs and have a positive effect on re-establishing the intra-articular homeostasis and stimulating regeneration by different growth factors, cytokines and miRNA that are contained within the EVs of the secretome. The retinal cell secretome is mainly composed of the secreted factors from the RPE and Müller cells, which are key to maintain the structural and functional integrity of the retina. The crosslink between these two types of secretomes could potentially enhance the neuroprotective effect of the MSC

secretome on retinal degeneration, by modulating OS, autophagy and programmed cell death. This scenario could be of particular interest especially for MSC secretome-only factors, such as FGF, CXCL12, CCL511, NGF-, described miRNAs and the lncRNA MALAT, whose complementary action might play a functional compensation role towards retinal cell alterations.

However, many challenges still exist, including the specific characterization of secretome released factors to further target therapy to the pathology profile, better manipulation of the retinal secretome or from other cell sources for noteworthy therapeutic effect, improving methods for intraocular administration of secretome factors and developing personalized combinations of trophic factors involved in different pathological pathways (inflammation, reactive oxygen species, angiogenesis, proliferation) to evaluate the collective therapeutic potential. Nevertheless, the possible improvement of new efficient pharmaceutical formulations related to the secretome of MSCs and retinal cells, with the addition of exogenous factors or drugs without the necessity to deliver cells into the eye may represent a novel milestone towards a personalized approach to retinal disease.

FOOTNOTES

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