Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2025, 17(3), 26-34
https://ijbc.ir

Review

Chemokine-guided Stem Cell Migration for Retinal Regeneration: A Systematic Review

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Citation Chander A, Kumar Singh V, Sharma S, Singh Matreja P. Chemokine-guided Stem Cell Migration For Retinal Regeneration: A Systematic Review. Iran J Blood Cancer. 2025 Sep 30;17(3): 26-34.

doi 0

Article info:

Received: 24 July 2025
Accepted: 11 Sep 2025
Published: 30 Sep 2025

Abstract

Background: Retinal degeneration remains one of the predominant causes of blindness, with extremely low regenerative capacity in the mammalian retina. Stem cell-based therapy is a highly promising approach for retinal regeneration, but efficient stem cell migration and integration are significant challenges. This systematic review aimed to discuss chemokine-directed stem cell migration in retinal regeneration, summarising important chemokines, signalling pathways, and therapeutic opportunities.

Methods: A systematic literature search was done in PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, and PsycINFO between January 2010 and January 2025. Preclinical and clinical studies that explored chemokine-stimulated stem cell migration during retinal repair were included based on the inclusion criteria. The data extracted included chemokine-receptor interaction, signalling pathways, type of stem cells, route of delivery, and outcomes of retinal repair. The ROBINS-I tool was used to evaluate the risk of bias.

Results: In 384 studies, 12 were included. The SDF-1/CXCL12-CXCR4 pathway was explored in the most detail, augmenting stem cell homing and integration. Other pathways, such as ERK/MAPK, PI3K/Akt, and JAK-STAT, also played a role in migration and survival. Chemokine-modulated therapies enhanced retinal function and repair, but immune responses and delivery issues remain. New approaches such as biodegradable scaffolds, magnetic targeting, and chemically engineered chemokines were discovered to optimise stem cell localisation and efficacy.

Conclusion: Chemokine-directed stem cell migration is an exciting field for retinal regeneration, which has the potential to improve targeted cell delivery and integration. While SDF-1/CXCL12 remains the gold standard, other pathways and new delivery pathways are also extremely capable. Augmenting chemokine-based therapies, overcoming immunological barriers, and translating them into the clinic in the future will be paramount to optimising stem cell-mediated retinal repair.

Keywords:

Chemokines
SDF-1/CXCL12
PI3K/Akt pathway
JAK-STAT pathway

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[DOI: 10.61882/ijbc.17.3.26]

1. INTRODUCTION

Regeneration of the retina is confronted with a challenging set of biological, immunological, and technical problems. One of the key impediments is the relatively poor capacity of mammalian retinas to regenerate after damage, particularly since adult mammals do not possess a pool of retinal stem or progenitor cells. This deficiency is supplemented by retinal ganglion cell (RGC) and axonal atrophy, and this is a significant factor in vision loss in conditions such as glaucoma and other optic neuropathies [1,2]. Current efforts at RGC replacement therapy are troubled with many challenges, including the generation of viable donor cell sources, integration of regenerative materials, and minimising transplant rejection risks [3].

The immune reaction against transplanted tissues is of particular interest. The retinal pigment epithelium (RPE) of the retina health can cause immune rejection after transplantation and complicate therapeutic measures [4,5]. This is particularly true in age-related macular degeneration (AMD) and hereditary retinal disease, in which RPE dysfunction leads to chronic vision loss [4]. Techniques to reverse these immune responses, such as the use of induced pluripotent stem cells (iPSCs) or mesenchymal stem cells, have been explored but carry risks, e.g., tumorigenicity and potential for poor integration into existing retinal structure [3,6].

The regenerative mechanisms seen in model organisms such as zebrafish indicate the possibility of Müller glia functioning as progenitor cells after retinal damage. Yet, the mechanisms for this ability to regenerate in non-mammals remain to be fully realised. They cannot readily be replicated in mammals, where, instead, Müller glia undergo reactive gliosis and not reprogramming to entirely functional neurons [7,8]. Regulated gene networks and pathway activity, such as TGF-β and Notch, play a role in determining the fate of these glial cells during regeneration [9,10]. Knowledge of these pathways may elucidate how to boost regenerative abilities in mammalian retinas.

Aside from biological barriers, technical challenges also hinder retinal regeneration. Delivering regenerative therapy must deal with the complicated architecture of the retina, for example, the blood-retinal barrier, to potentially inhibit efficient drug delivery [11]. Also, ensuring that the regenerated neurons properly connect with others in the existing circuitry through synapses for the restoration of function is still one of the grand challenges in ongoing research [3].

Chemokines are important in the modulation of stem cell migration in the retinal compartment, and their role is to a large extent due to the fact that they can form gradients that direct cellular movement. Of the most potent chemokines involved in stem cell migration is SDF-1α, which targets C-X-C chemokine receptor type 4 (CXCR4) that is found on the majority of stem and precursor cells. Such interaction is critical in order to recruit stem cells to the site of injury or degeneration in Such interaction is critical for recruiting stem cells to the site of injury or degeneration, enabling their subsequent migration and differentiation [12,13]. The presence of CXCR4 on stem cells renders them sensitive to the gradient of SDF-1α, which incidentally becomes upregulated in case of pathologies and thus renders their homing ability to injured retina tissue [13].

Other than SDF-1α, CXCL12 and its receptor CXCR4 also play a central role in the migration of neural stem cells (NSCs) during retinal repair. CXCL12 binding to CXCR4 not only induces NSC migration but also initiates the process of repair within the cells to render them more effective at repairing retinal damage [13]. In addition, research has demonstrated that chemokines can modulate the expression of a number of receptors on stem cells and, thus, their migratory patterns. For example, CCR2 expression has been found to improve homing and engraftment of ADSCs in dystrophic models, and manipulation of chemokine receptor expression has been found to facilitate the promotion of stem cell migration to certain retinal lesions [14].

It has been discovered that the retinal microenvironment itself contains a number of growth factors and chemokines that can draw in glial and stem cells. Müller cell migration in retinal healing processes has been observed to be induced by HGF [15]. Additionally, chemokine gradient expression has been found to direct transplanted and regenerated retinal neurons to their original positions in the retina, illustrating the role of chemokines in making stem cells properly integrate into established retinal circuitry [16]. Further, the receptor-chemokine interaction is vital not only for migration but also for the general activity of stem cells within the retina. Chemokines can modulate stem cells and influence proliferation, differentiation, and survival, which are critical causes of tissue regeneration success [17]. The ability of chemokines to coordinate these events renders them even more prospective targets for therapy in regenerative medicine, particularly in retinal diseases with cell death and degeneration.

One of the most often examined signal pathways with which chemokine-induced cell migration is concerned is the SDF-1/CXCR4 pathway. SDF-1 interacts with its receptor, CXCR4, to stimulate many cascades, including the PI3K/Akt pathway. The PI3K/Akt pathway is involved in cell survival and growth and also in cell migration [18]. PI3K/Akt activation enhances stem cell migratory activity to correctly migrate

[DOI: 10.61882/ijbc.17.3.26]

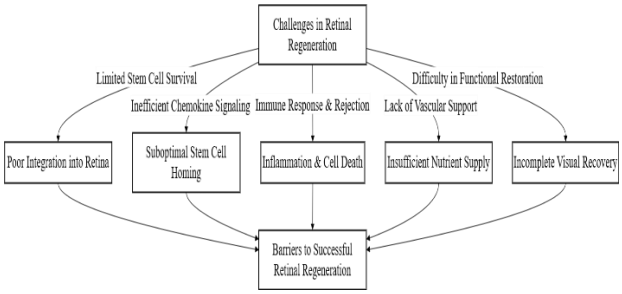

Figure 1. Challenges in retinal regeneration.

into the damaged tissue [18]. Further, the interaction between CXCL12 and CXCR4 has also been proven to be essential in the upkeep of the bone marrow niche of hematopoietic stem cells, once more reinforcing its critical role in the biology of stem cells [19].

The other very essential pathway, the ERK/MAPK signalling pathway, is activated following interaction with chemokine receptors. The pathway is involved in several cellular processes, including cell migration, differentiation, and cell growth. Chemokines are capable of stimulating ERK activation, which reorganises the cytoskeletal movement behind the movement of cells [20]. Cross-talk between the ERK pathway and other signalling molecules, such as Rho GTPases (Rac, Rho, and Cdc42), is necessary for coordinating stem cell migratory response [20,17].

In addition to this, the JAK-STAT pathway also plays a part in chemokine-induced stem cell migration. For example, some chemokines and their respective receptors have been shown to interact and activate JAK2, which has the ability to phosphorylate and activate STAT3 in return. Such a signalling cascade has been shown to increase migratory and invasive stem cell characteristics, particularly when coupled with cancer [21]. The JAK-STAT pathway is also important in the tumour microenvironment, where it can be involved in the regulation of stem-like cancer cell behaviour [21].

In addition to these mechanisms, endosomal signalling is a new mechanism by which to regulate chemokine receptor function. Internalised chemokine receptors continue to signal from endosomes and thereby preserve migratory responses even when the original ligand-receptor interaction is terminated. Signalling that is prolonged in nature can influence several aspects of cell physiology, among them migration [22].

This systematic review critically evaluates the chemokine-guided process of stem cell migration in retinal regeneration, mechanisms, therapeutic potential, and limitations. Chemokines play a crucial role in directing stem cells to injured retinal tissue for repair and functional restoration. This review seeks to identify the prominent chemokines and receptors that are involved in stem cell homing, establish the pathways that trigger their migration, and analyse the efficiency of chemokine-based treatments for retinal regeneration. It will also identify issues related to immune responses, methods of delivery, and long-term incorporation of transplanted stem cells. By the integration of preclinical and clinical research results, the present review has endeavoured to help achieve feasibility and potential in chemokine-directed stem cell therapy as a hopeful therapy for retinal degenerative disease.

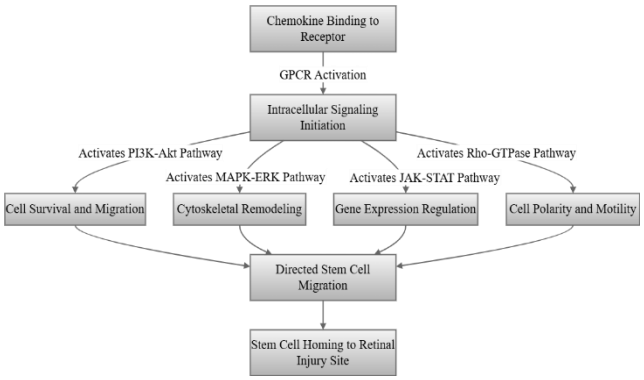

Figure 2. Key signaling pathways in chemokine-mediated stem cell migration.

2. MATERIALS AND METHODS

2.1. Review design

The PECOS protocol of this systematic review (Population, Exposure, Comparison, Outcomes, Study design) adopted the reporting framework of PRISMA so that it can be made transparent and reproducible.

Table 1. Inclusion and exclusion criteria devised for this review.

Criteria	Inclusion	Exclusion
Population	Studies involving animal models or human subjects with retinal degeneration/damage	Studies unrelated to retinal regeneration or not involving stem cells
Exposure	Research investigating chemokine-guided stem cell migration	Studies focusing solely on non-chemokine signaling pathways
Comparator	Studies comparing chemokine-guided stem cell migration to other regenerative approaches	Studies without a control or comparison group
Outcomes	Functional and structural retinal repair, improved visual function, stem cell integration, and migration efficiency.	Studies without measurable outcomes related to retinal regeneration
Study design	Randomised controlled trials (RCTs), cohort studies, case-control studies, preclinical animal studies, in vitro studies	Review articles, expert opinions, and non-systematic case reports.
Publication language	English only.	Non-English publications.
Publication year	Studies published from Jan 2010 to Jan 2025.	Studies published more than 15 years.

[DOI: 10.61882/ijbc.17.3.26]

2.2. Database search protocol

To ensure an all-inclusive capture of literature, a database search strategy was conceptualised. The databases searched include PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, and PsycINFO. The precision of the search was maximised using Boolean operators and MeSH keywords. It included combinations such as:
("Chemokines" OR "Chemokine signalling" OR "CXCL12" OR "SDF-1" OR "CCL2" OR "CCR2" OR "CXCR4") AND ("Stem Cells" OR "Mesenchymal Stem Cells" OR "Induced Pluripotent Stem Cells" OR "Neural Stem Cells") AND ("Retinal Regeneration" OR "Retinal Repair" OR "Retinal Diseases" OR "Retinal Degeneration") AND ("Migration" OR "Homing" OR "Directed Movement").

2.2. Data extraction protocol and data items

The data were extracted using a pre-formatted data extraction form in order to achieve a systematic compilation of study details. Independent reviewers performed data extraction to avoid errors and minimise bias. Data extracted consisted of study descriptors like the author, year, site, study type, sample, and demographics; chemokine data, such as chemokine type, receptor use, signalling pathways, and stem cell type; intervention details, including method of delivery, dose, duration, and controls; and results, including the efficacy of retinal repair, the efficacy of stem cell migration, adverse events, and functional gains in vision. Besides, major findings were recorded along with statistical outputs like odds ratios, beta coefficients, and confidence intervals. Environmental determinants influencing stem cell migration, including inflammatory disease, oxidative stress, and hypoxia, were also extracted. A third reviewer cross-checked the extracted information and resolved any discrepancies by consensus.

3. RESULTS

The database search initially retrieved 384 records from four databases: Google Scholar (n = 52), PubMed (n = 24), Web of Science (n = 116), and other databases (n = 192). After removing 89 duplicate records, 103 unique records were screened, with no exclusions at this stage. Full-text retrieval was attempted for all 103 records, but 44 reports could not be obtained. The remaining 59 reports were assessed for eligibility. Among these, 46 were excluded due to non-chemokine-based stem cell migration studies (n = 16), irrelevant scope (n = 23), or duplicates/incomplete reports (n = 8). Ultimately, 12 studies were included in the final review.

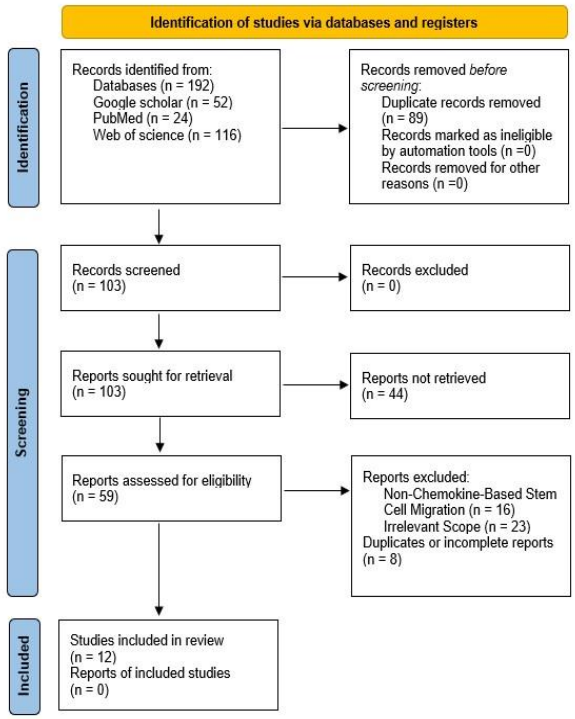

Figure 3. PRISMA flowchart.

Several studies highlight the chemokine stromal cell-derived factor-1 (SDF-1/CXCL12) and its receptor CXCR4 as central regulators of stem cell migration. Demonstrated that CXCL12-mediated signalling enhances the homing of bone marrow-derived and mesenchymal stem cells (MSCs), leading to improved retinal function and reduced inflammation [26,27]. Similarly, found that SDF-1 gradients facilitated the migration of retinal ganglion cells (RGCs) and photoreceptor precursor cells (PPCs), emphasising the importance of chemotactic guidance for targeted cell delivery [24,25].

Beyond CXCL12/CXCR4 signalling, other molecular pathways have been explored. Investigated netrin-1/DCC signalling in RGC axon guidance, demonstrating enhanced axon growth and functional regeneration in human embryonic stem cell-derived RGCs [31]. A chemically modified CXCR4 agonist was evaluated, showing improved neural stem cell (NSC) homing while mitigating inflammation [34]. In ischemic retinopathy, semaphorin 3E (Sema3E) and PlexinD1 signalling were identified as regulators of angiogenesis, suppressing pathological vascular growth in the retina [33].

highlighted in a well-organized study the neuroprotective potential and safety of the treatment of retinal degeneration with bone marrow-derived stem cells (BMSC) [23]. Researchers examined new delivery platforms like magnetic

[DOI: 10.61882/ijbc.17.3.26]

Table 2. Chemokines' Function in Retinal Regeneration and Stem Cell Migration.

Author(s) & Year	Study Design	Intervention	Chemokines & Receptors	Stem Cell Type	Delivery Method	Outcome Measures	Key Findings
Daher et al., 2022 [23]	Systematic Review	Bone marrow stem cell therapy for retinal degeneration	Not specified	Bone Marrow-Derived Stem Cells (BMSCs)	Intravitreal Injection	Retinal repair, neuroprotection	BMSCs preserved vasculature showed feasibility & safety
Soucy et al., 2022 [24]	Preclinical (In Vivo & In Vitro)	Chemokine-guided neuron migration	SDF-1 (CXCL12) - CXCR4	Retinal Ganglion Cells (RGCs)	Chemokine gradient-based guidance	Increased RGC migration & integration	SDF-1 improved RGC migration into the ganglion cell layer
Unachukwu et al., 2016 [25]	Bioinformatics & In Vitro	Chemotactic guidance of transplanted photoreceptor cells	SDF-1α - CXCR4	Photoreceptor Precursor Cells (PPCs), Retinal Progenitor Cells (RPCs)	Microfluidic ligand gradients	Enhanced PPC & RPC migration	Chemokine signaling plays a role in guiding transplanted cells
Enzmann et al., 2017 [26]	Preclinical (In Vivo)	Chemokine-mediated stem cell migration	CXCL12/SDF-1	Bone Marrow-Derived Stem Cells (BMSCs)	Intravitreal Injection	Retinal function improvement, cell homing	SDF-1 injection increased BMSC homing & visual function
Wang et al., 2018 [27]	Preclinical (In Vivo & In Vitro)	CXCR4-overexpressing MSCs for retinal repair	CXCR4 upregulation	Mesenchymal Stem Cells (MSCs)	Intravitreal Injection	Retinal protection, reduced inflammation	CXCR4 overexpression enhanced MSC homing & reduced retinal damage
Sharma et al., 2019 [28]	Preclinical (Rodent & Pig Models)	Stem cell-derived RPE patches	Not specified	Induced Pluripotent Stem Cells (iPSC)	Biodegradable scaffolds	RPE cell integration & visual function recovery	iPSC-RPE patches improved retinal structure & function
Yanai et al., 2012 [29]	Preclinical (Rodent Model)	Magnetic stem cell targeting	Not specified	Mesenchymal Stem Cells (MSCs)	Intravitreal & Intravenous Injection	Improved cell homing, retinal localization	Magnetic MSCs showed better homing efficiency in the retina
Xu et al., 2010 [30]	Preclinical (In Vitro)	Chemokine-mediated MSC migration	MCP-1, SDF-1	Mesenchymal Stem Cells (MSCs)	Chemotaxis assays	MSC migration towards glioma cells	SDF-1 and MCP-1 enhance MSC chemotaxis
Subramani et al., 2023 [31]	Preclinical (Human & Rodent Model)	Retinal ganglion cell (RGC) axon guidance	Netrin-1/DCC signaling	Human Embryonic Stem Cell-Derived RGCs	In Vivo & In Vitro	Axon growth, regeneration	Netrin-1/DCC interaction promotes axon growth and functional connectivity
Pena et al., 2018 [32]	Preclinical (In Vitro)	Chemokine effects on Müller glial cells	EGF, VEGF, FGF2	Müller Glial Cells (MGCs)	Microfluidic Assay	Chemotactic response, migration patterns	EGF gradient enhanced directional migration of MGCs
Fukushima et al., 2011 [33]	Preclinical	Angiogenesis regulation in ischemic retinopathy	Sema3E - PlexinD1	Endothelial Cells	Intravitreal Injection	Suppressed abnormal angiogenesis	Sema3E-PlexinD1 signaling guided vascular growth towards the ischemic retina.
Lee et al., 2020 [34]	Preclinical	Chemically modified CXCR4 agonist	CXCL12 - CXCR4	Human iPSC-Derived Neural Stem Cells	Intracerebral Injection	Enhanced NSC migration, reduced inflammation	Modified CXCR4 agonist promoted NSC homing without inflammatory effects

targeting and biodegradable scaffolds that enhanced stem cell integration and homing efficacy [28, 29]. In Muller glial cells' (MGCs) chemotaxis along growth factor gradients, EGF was also found to be a strong directional migration promoter [32].

Collectively, these results indicate the importance of chemokine signaling in retinal stem cell therapy. While

[DOI: 10.61882/ijbc.17.3.26]

SDF-1/CXCR4 is still the most characterized axis, novel pathways and new delivery systems hold significant promise for stimulating retinal regeneration. To utilize these findings in the clinic, however, further studies must be done to obtain precise and efficient stem cell migration for restoring vision.

4. ASSESSMENT OF BIAS

Risk of bias assessment, performed with the ROBINS-I tool, assessed seven principal domains in various studies. Bias is categorized into critical, serious, moderate, and low risk by the assessment.

The majority of the studies were at a moderate to severe risk of bias due to confounding (D1), and [30] and [22] were graded as critical under this category. Selection of participants (D2) was graded as low risk in most of the studies, but classification of the intervention (D3) showed a range from moderate to severe risk, and [28] and [32] had severe problems.

Bias caused by deviations from planned interventions (D4) was overall mostly moderate between studies, yet there were some cases of high risk, e.g., [22]. Incomplete data (D5) was also an issue because there were studies such as [30] and [32], which were indicated by a critical risk here. Measurement bias (D6) varied, with many studies indicating moderate risk, while others, e.g., [22], had serious concerns. Bias in selection of reported outcomes (D7) was mainly low to moderate, although some studies indicated serious risks.

In general, most of the studies were at moderate risk of bias, with some studies, like [30] and [32], having serious concerns in more than one domain. The results point to improved outcome measurement techniques, more sophisticated data processing, and higher methodological quality to reduce bias and increase research validity.

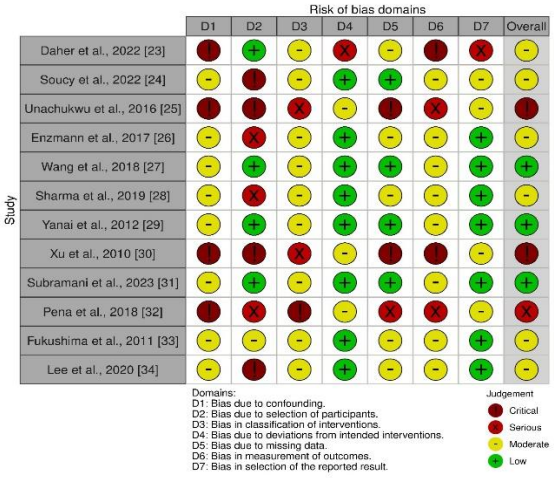

Figure 4. Bias assessment using the ROBINS-I tool.

5. DISCUSSION

As the studies summarized in the table reveal, stem cell therapies for retinal degeneration utilize a range of chemokines, receptors, and delivery routes to increase cell motility, integration, and therapeutic potency. The thread running through the reviewed publications is the application of chemokine-guided direction to promote stem cell homing and migration and thus initiate retinal repair and neuroprotection.

The ability of bone marrow stem cells (BMSCs) to treat retinal degeneration has been the subject of numerous investigations demonstrated the safety and effectiveness of BMSC treatment, vascular, and neuroprotection in retinal animal models of degeneration [23]. Similarly, investigated chemokine-induced MSC and BMSC induction and migration. Significantly improved homing and reduced retinal inflammation were made possible by increased CXCR4 expression in MSC, suggesting that chemokine-specific targeting could improve stem cell therapy [26,27].

The healing of the retina further relies on chemokine-directed neuronal migration. RGCs and PPCs are channelled by SDF-1 (CXCL12), as stated by in the context of RGCs and for PPCs [24,25]. This is in accordance with the assumption that chemokine gradients are purposefully being used to aid the process of stem cell integration into the retina. According to [31], Netrin-1/DCC signalling also significantly increased RGC axon development and functional connectivity, which is another feature of neurodegenerative methods.

Furthermore, biodegradable scaffolds and novel delivery techniques enhanced cell survival and engraftment. iPSC-derived RPE patches were demonstrated by to be able to restore retinal structure and function, and preclinical model results were encouraging [28]. In order to maximize stem cell localization in retinal therapy, proposed magnetic targeting as a way to improve MSC homing efficiency [29].

In addition to stem cells, the role of chemokines and their receptors in regulating retinal microenvironments has been studied. EGF gradients have been shown by to be a significant factor in Müller glial cell (MGC) migration and may play a key role in endogenous retinal healing [32]. examined the regulation of angiogenesis in ischemic retinopathy and discovered that pathologic neovascularization was inhibited by Sema3E-PlexinD1 signalling. Consequently, chemokine modulation's therapeutic value in vascular-related retinal disease was confirmed [33].

The impact of chemically modified CXCR4 agonists on NSC homing was examined by Lee et al. [34]. The findings suggest that disruption of the chemokine signalling system

[DOI: 10.61882/ijbc.17.3.26]

increases the therapeutic efficiency of chemokine-induced therapy by enhancing NSC homing with decreased inflammatory effect. In the area of future retinal regeneration treatments, chemokine-chemokine receptor interaction is a great area to study [34].

The importance of chemokine signalling for making stem cell therapy for retinal degeneration possible is demonstrated in these findings. Further work must be conducted even when these advances have recently been made to hone in on an effective delivery method, a proper gradient for chemokines, and clinical use of such findings. The use of bioengineering techniques, such as chemically made agonists and microfluidic ligand gradients (as illustrated by 2020), will gradually enhance stem cell guiding paradigms and therapeutic usefulness in retinal disease. Long-term safety and effectiveness will also depend on a better understanding of the immune response to stem cell transplantation and how chemokines affect it [34].

The combinatorial action of most chemokines and their interaction with the retinal microenvironment need to be explored. With the use of tailored techniques, it is now possible to further personalize patient-specific stem cells and chemokine profiles for the therapy of the retina. In addition, chemokine signalling cascades can be further fine-tuned by novel gene editing technologies such as CRISPR to deliver the best possible therapeutic outcomes. Through the use of personalized techniques, it is also possible to further personalize patient-specific stem cells and chemokine profiles to therapy in the retina. In addition, chemokine signalling cascades can also be further fine-tuned by emerging gene editing technologies such as CRISPR to deliver the best possible therapeutic outcomes. Second, the integration of machine learning algorithms and artificial intelligence can potentially identify the optimal stem cell migration patterns and attain the maximum therapeutic specificity.

Another possibility is a nanotechnology-based application for site-specific delivery of extremely specific chemokines. Nanocarriers can provide chemokine delivery with highly controlled spatiotemporal release, resulting in maximal therapeutic benefit with minimum systemic side effects. Interdisciplinarity between bioengineers, neuroscientists, and clinical scientists will also be important in translating such discoveries to clinic translational levels, taking stem cell-derived regenerative therapy into the clinic. Successful implementation of these strategies would realise the potential of new, patient-specific therapeutic therapies, eventually changing the model for treating retinal degenerative disease.

6. LIMITATIONS

Despite encouraging outcomes, stem cell treatments for retinal degeneration are not without several challenges. Variability in stem cell survival, integration, and migration affects the reliability of treatment, necessitating improved targeting approaches. Immune rejection and inflammation, particularly with allogeneic cells, pose threats, while long-term cell stability following transplantation is yet to be understood. Lack of standard differentiation and delivery protocols also results in variability of outcomes. Additionally, tumorigenicity potential, especially with pluripotent stem cells, requires serious evaluation. As valuable as chemokine-guidance potential is, the complexity of retinal signalling pathways requires ongoing research for successful therapy.

7. FUTURE DIRECTIONS

Follow-up research will have to shed light on the combined functions of two or more chemokines and interaction with the retina microenvironment in order to focus on targeted personalised stem cell therapies and genome editing methods such as CRISPR for increased precision. AI and machine learning would be capable of optimising stem cell migration patterns, and nanotechnology offers a promising technique for the targeted delivery of chemokines, offering precise, localised action with fewer side effects. There would be synergy between bioengineers, neuroscientists, and clinicians in taking these advances to clinical application. Extensive clinical trials must be conducted to confirm the safety and efficacy of chemokine-mediated stem cell therapy, and information regarding long-term effects on retinal function and integration of pharmacologic or gene therapy could further optimise therapeutic interventions, progressing with multimodal retinal regeneration strategies.

8. CONCLUSION

Chemokine-mediated stem cell migration provides a hopeful strategy for retinal regeneration by guiding stem cells to sites of injury, and the SDF-1/CXCL12-CXCR4 pathway is the most extensively investigated pathway for promoting homing and integration. Other signalling pathways, including ERK/MAPK, PI3K/Akt, and JAK-STAT, aid in stem cell survival and migration. Although encouraging preclinical results have been obtained, issues such as immune responses, restricted long-term integration, and delivery optimisation remain. New technologies, including biodegradable scaffolds, magnetic targeting, and chemically modified chemokines, are promising, but clinical

[DOI: 10.61882/ijbc.17.3.26]

application is in the future. Further work is needed for clinical translation. Optimisation of chemokine-based treatments, application of gene editing and bioengineering to allow controlled delivery and large-scale trials to verify safety and efficacy will eventually bring retinal regenerative therapies.

Acknowledgment

The authors would like to thank all the people who contributed to the writing of this article.

Conflict of interest

The authors declared no conflict of interest.

Funding

No fund was received.

Ethical statement

Not Applicable.

References

1. X. Wei, Z. Zhang, H. Zeng, X. Wang, W. Zhan, N. Qiaoet al., "Regeneration of functional retinal ganglion cells by neuronal identity reprogramming", 2020. https://doi.org/10.1101/2020.07.16.203497

2. P. Williams, L. Benowitz, J. Goldberg, & Z. He, "Axon regeneration in the mammalian optic nerve", Annual Review of Vision Science, vol. 6, no. 1, p. 195-213, 2020. https://doi.org/10.1146/annurev-vision-022720-094953

3. S. Behtaj, A. Öchsner, Y. Anissimov, & M. Rybachuk, "Retinal tissue bioengineering, materials and methods for the treatment of glaucoma", Tissue Engineering and Regenerative Medicine, vol. 17, no. 3, p. 253-269, 2020. https://doi.org/10.1007/s13770-020-00254-8

4. C. Petrash, A. Palestine, & M. Soler, "Immunologic rejection of transplanted retinal pigmented epithelium: mechanisms and strategies for prevention", Frontiers in Immunology, vol. 12, 2021. https://doi.org/10.3389/fimmu.2021.621007

5. A. Khan, T. Utheim, & J. Eidet, "Retinal pigment epithelium transplantation: past, present, and future", Journal of Ophthalmic and Vision Research, vol. 17, no. 4, 2022. https://doi.org/10.18502/jovr.v17i4.12325

6. L. Finocchio, M. Zeppieri, A. Gabai, L. Spadea, & C. Salati, "Recent advances of adipose-tissue-derived mesenchymal stem cell-based therapy for retinal diseases", Journal of Clinical Medicine, vol. 12, no. 22, p. 7015, 2023. https://doi.org/10.3390/jcm12227015

7. P. Sharma, S. Gupta, M. Chaudhary, S. Mitra, B. Chawla, M. Khursheedet al., "Biphasic role of tgf-β signaling during müller glia reprogramming and retinal regeneration in zebrafish", Iscience, vol. 23, no. 2, p. 100817, 2020. https://doi.org/10.1016/j.isci.2019.100817

8. M. Lahne, M. Nagashima, D. Hyde, & P. Hitchcock, "Reprogramming müller glia to regenerate retinal neurons", Annual Review of Vision Science, vol. 6, no. 1, p. 171-193, 2020. https://doi.org/10.1146/annurev-vision-121219-081808

9. M. Lee, J. Wan, & D. Goldman, "Tgfb3 collaborates with pp2a and notch signalling pathways to inhibit retina regeneration", Elife, vol. 9, 2020. https://doi.org/10.7554/elife.55137

10. T. Hoang, J. Wang, P. Boyd, F. Wang, C. Santiago, L. Jianget al., "Gene regulatory networks controlling vertebrate retinal regeneration", Science, vol. 370, no. 6519, 2020. https://doi.org/10.1126/science.abb8598

11. C. Yu, D. Li, Y. Lv, X. Shi, R. Zhang, W. [#], "Nanotherapy for neural retinal regeneration", Advanced Science, 2025. https://doi.org/10.1002/advs.202409854

12. L. Li, X. Liu, B. Gaihre, S. Park, Y. Li, A. Terzicet al., "Sdf-1α/op/bp composites enhance the migrating and osteogenic abilities of mesenchymal stem cells", Stem Cells International, vol. 2021, p. 1-12, 2021. https://doi.org/10.1155/2021/1938819

13. J. Lee, R. Zhang, M. Yan, S. Duggineni, D. Wakeman, W. Nileset al., "Chemical mutagenesis of a gpcr ligand: detoxifying “inflame-attraction” to direct therapeutic stem cell migration", Proceedings of the National Academy of Sciences, vol. 117, no. 49, p. 31177-31188, 2020. https://doi.org/10.1073/pnas.1911444117

14. L. Wang, H. Li, J. Lin, R. He, M. Chen, Y. [#], "Ccr2 improves homing and engraftment of adipose-derived stem cells in dystrophic mice", Stem Cell Research & Therapy, vol. 12, no. 1, 2021. https://doi.org/10.1186/s13287-020-02065-z

15. C. Hu, H. La, X. Wei, Y. Zhou, Q. Ou, Z. Chenet al., "Transplantation site affects the outcomes of adipose-derived stem cell-based therapy for retinal degeneration", Stem Cells International, vol. 2020, p. 1-12, 2020. https://doi.org/10.1155/2020/9625798

16. J. Soucy, L. Todd, E. Kriukov, M. Phay, T. Reh, & P. Baranov, "Introduced chemokine gradients guide transplanted and regenerated retinal neurons toward their natural position in the retina", 2022. https://doi.org/10.1101/2022.09.29.510158

17. A. Ozga, M. Chow, & A. Luster, "Chemokines and the immune response to cancer", Immunity, vol. 54, no. 5, p. 859-874, 2021. https://doi.org/10.1016/j.immuni.2021.01.012

18. G. Xiu, X. Li, Y. Yin, J. Li, B. Li, X. Chenet al., "Sdf-1/cxcr4 augments the therapeutic effect of bone marrow mesenchymal stem cells in the treatment of lipopolysaccharide-induced liver injury by promoting their migration through pi3k/Akt signalling pathway", Cell Transplantation, vol. 29, p. 096368972092999, 2020. https://doi.org/10.1177/0963689720929992

19. K. Shimizu, Y. Maeda, M. Kuwabara, M. Hosogai, T. Mitsuhara, M. Takedaet al., "Impact of cranial bone-derived mesenchymal stem cell transplantation for functional recovery in experimental spinal cord injury", 2022. https://doi.org/10.21203/rs.3.rs-2238108/v1

20. K. Kohli, V. Pillarisetty, & T. Kim, "Key chemokines direct migration of immune cells in solid tumors", Cancer Gene Therapy, vol. 29, no. 1, p. 10-21, 2021. https://doi.org/10.1038/s41417-021-00303-x

21. Y. Chen, Z. Shao, E. Jiang, X. Zhou, L. Wang, H. Wanget al., "Ccl21/ccr7 interaction promotes emt and enhances the stemness of oscc via a jak2/stat3 signaling pathway", Journal of Cellular Physiology, vol. 235, no. 9, p. 5995-6009, 2020. https://doi.org/10.1002/jcp.29525

22. H. Hahn, C. Daly, J. Little, N. Perry, E. Flores-Espinoza, A. Inoueet al., "Endosomal chemokine receptor signalosomes regulate central mechanisms underlying cell migration",, 2022.

23. Daher ID, Moura MI, Murad AC, Ferrari RS, Neiva EB, Liedtke FS, Zotarelli Filho IJ. Major clinical findings of cellular therapy for intravitreal use in ischemic retinopathy and macular degeneration: a systematic review. MedNEXT Journal of Medical and Health Sciences. 2022 Aug 28;3[3].

24. Soucy JR, Todd L, Kriukov E, Phay M, Reh TA, Baranov P. Introduced chemokine gradients guide transplanted and regenerated retinal neurons toward their natural position in the retina. bioRxiv. 2022 Oct 1:2022-09.

[DOI: 10.61882/ijbc.17.3.26]

25. Unachukwu UJ, Warren A, Li Z, Mishra S, Zhou J, Sauane M, Lim H, Vazquez M, Redenti S. Predicted molecular signaling guiding photoreceptor cell migration following transplantation into damaged retina. Scientific reports. 2016 Mar 3;6[1]:22392.

26. Enzmann V, Lecaudé S, Kruschinski A, Vater A. CXCL12/SDF-1-dependent retinal migration of endogenous bone marrow-derived stem cells improves visual function after pharmacologically induced retinal degeneration. Stem cell reviews and reports. 2017 Apr; 13:278-86.

27. Wang J, Zhang W, He GH, Wu B, Chen S. Transfection with CXCR4 potentiates homing of mesenchymal stem cells in vitro and therapy of diabetic retinopathy in vivo. International Journal of Ophthalmology. 2018;11[5]:766.

28. Sharma R, Khristov V, Rising A, Jha BS, Dejene R, Hotaling N, Li Y, Stoddard J, Stankewicz C, Wan Q, Zhang C. Clinical-grade stem cell–derived retinal pigment epithelium patch rescues retinal degeneration in rodents and pigs. Science translational medicine. 2019 Jan 16;11[475]: eaat5580.

29. Yanai A, Häfeli UO, Metcalfe AL, Soema P, Addo L, Gregory-Evans CY, Po K, Shan X, Moritz OL, Gregory-Evans K. Focused magnetic stem cell targeting to the retina using superparamagnetic iron oxide nanoparticles. Cell transplantation. 2012 Jun;21[6]:1137-48.

30. Xu, F., Shi, J., Yu, B., Ni, W., Wu, X., & Gu, Z. . Chemokines mediate mesenchymal stem cell migration toward gliomas in vitro. Oncology Reports, 23[6], 1561–1567.

31. Subramani M, Van Hook MJ, Qiu F, Ahmad I. Human Retinal Ganglion Cells Respond to Evolutionarily Conserved Chemotropic Cues for Intra Retinal Guidance and Regeneration. Stem Cells. 2023 Nov 1;41[11]:1022-36.

32. Pena J, Dulger N, Singh T, Zhou J, Majeska R, Redenti S, Vazquez M. Controlled microenvironments to evaluate chemotactic properties of cultured Müller glia. Experimental eye research. 2018 Aug 1; 173:129-37.

33. Fukushima Y, Okada M, Kataoka H, Hirashima M, Yoshida Y, Mann F, Gomi F, Nishida K, Nishikawa SI, Uemura A. Sema3E-PlexinD1 signaling selectively suppresses disoriented angiogenesis in ischemic retinopathy in mice. The Journal of clinical investigation. 2011 May 2;121[5]:1974-85.

34. Lee JP, Zhang R, Yan M, Duggineni S, Wakeman DR, Niles WL, Feng Y, Chen J, Hamblin MH, Han EB, Gonzalez R. Chemical mutagenesis of a GPCR ligand: Detoxifying "inflammo-attraction" to direct therapeutic stem cell migration. Proceedings of the National Academy of Sciences. 2020 Dec 8;117[49]:31177-88.

[DOI: 10.61882/ijbc.17.3.26]