

Insights into stem cell therapy for diabetic retinopathy: a bibliometric and visual analysis

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Abstract

Stem cells have been confirmed to be involved in the occurrence and development of diabetic retinopathy; however, the underlying mechanisms remain unclear. In this study, we used Citespace software to visually analyze 552 articles exploring the stem cell-based treatment of diabetic retinopathy over the past 20 years, which were included in the Web of Science Core Collection. We found the following: (1) a co-citation analysis of the references cited by all 552 articles indicated 15 clusters. In cluster #0, representing the stem cell field, some highly cited landmark studies emerged between 2009–2013. For example, endothelial progenitor cells and diabetic retinopathy gradually received the full attention of scholars, in terms of their relationship and therapeutic prospects. Some researchers also verified the potential of adipose-derived stem cells to differentiate into stable retinal perivascular cells, using a variety of animal models of retinal vascular disease. All of these achievements provided references for the subsequent stem cell research. (2) An analysis of popular keywords among the 552 articles revealed that, during the past 20 years, a relative increase in basic research articles examining stem cells and endothelial progenitor cells for the treatment of diabetic retinopathy was observed. The contents of these articles primarily involved the expression of vascular endothelial growth factor, vascular regeneration, oxidative stress, and inflammatory response. (3) A burst analysis of keywords used in the 552 articles indicated that genetic and cytological research regarding the promotion of angiogenesis was an issue of concern from 2001 to 2012, including several studies addressing the expression of various growth factor genes; from 2014 to 2020, mouse models of diabetic retinopathy were recognized as mature animal models, and the most recent research has focused on macular degeneration, macular edema, neurodegeneration, and inflammatory changes in diabetic animal models. (4) Globally, the current authoritative studies have focused on basic research towards the stem cell treatment of diabetic retinopathy. Existing clinical studies are of low quality and have insufficient evidence levels, and their findings have not yet been widely accepted in clinical practice. Major challenges during stem cell transplantation remain, including stem cell heterogeneity, cell delivery, and the effective homing of stem cells to damaged tissue. However, clinical trials examining potential stem cell-based treatments of diabetic retinopathy, including the use of pluripotent stem cells, retinal pigment epithelial cells, bone marrow mesenchymal stem cells, and endothelial progenitor cells, are currently ongoing, and high-quality clinical evidence is likely to appear in the future, to promote clinical transformation.

Key Words: diabetes; diabetic retinopathy; epithelial cells; macula; progenitor cells; retina; stem cells; visual analysis

Chinese Library Classification No. R453; R364.5; R741

Introduction

Existing treatments for diabetic retinopathy primarily include laser photocoagulation, the intravitreal injection of anti-vascular endothelial growth factor (VEGF) antibodies, and vitrectomy (Wong et al., 2016; Fiori et al., 2018). However, these treatments only aim to delay or prevent this persistent degenerative disease, and few studies have explored the pathogenesis and etiology of this disease. Numerous studies have confirmed that stem cells are involved in the occurrence and development of diabetic retinopathy, and the underlying

mechanisms are still being explored (Megaw and Dhillon, 2014; Gaddam et al., 2019).

Stem cells have the potential to delay the progression of diabetic retinopathy and to reduce the symptoms of such diseases (Bhattacharya et al., 2017; Kuriyan et al., 2017; Nirwan et al., 2019). In recent years, cell regenerative therapies for diabetic retinopathy have been preliminarily confirmed to be effective in some experimental animal studies, consolidating the preclinical research foundations in this field. The cell types that have been explored for use

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during regenerative therapy include cell-specific endogenous stem cells, endothelial progenitor cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells. Recent studies examining mesenchymal stem cells, endothelial progenitor cells, and adipose stromal cells have shown that cell-based therapies may be viable options for the prevention of neurovascular damage and the promotion of retinal regeneration (Megaw and Dhillon, 2014; Gaddam et al., 2019).

In this paper, we visually analyzed the research hotspots related to stem cell use for the treatment of diabetic retinopathy over the past 20 years and the expectations for the future development of cell therapy for similar diseases.

Data and Methods

Retrieval strategy

The first author retrieved all articles regarding the stem cell treatment of diabetic retinopathy indexed in the Web of Science (WOS) Core Collection and ClinicalTrials.gov.

Databases retrieved

WOS core Collection and ClinicalTrials.gov database.

Search strategy

The search terms and strategies used for the WOS database are shown in **Table 1**.

For the ClinicalTrials.gov database, the search terms used were “Stem Cell, Progenitor Cell, Mother Cell, Diabetic Retinopathy,” and the search strategy was as follows: (Stem Cell OR Progenitor Cell OR Mother Cell) AND Diabetic Retinopathy.

Time range for the literature search

Articles from 2000 to 2020 were included in the search.

Qualification

A full-text search was performed.

Inclusion criteria

WOS Core Collection database: after reading the titles and abstracts, all articles related to stem cell treatment of diabetic retinopathy were selected, irrespective of article styles, including original research articles, meta-analyses, reviews, commentaries, and case reports.

ClinicalTrials.gov database: after reading the titles and study protocol information, clinical trials exploring the stem cell treatment of diabetic retinopathy were selected.

Number of articles included

A total of 552 articles identified in the WOS Core Collection were selected. Nine clinical trials indexed in ClinicalTrials.gov were selected.

The deadline for publications was 2020-04-20.

Literature visual analysis

(1) A total of 552 articles were selected for the generation of a citation analysis report. Citespace 5.2.R1 software was used to visually analyze the references cited by the 552 included articles, as described by Dr. Chao-Mei Chen, a scholar at Drexel University, USA (Chen, 2014; Chen et al., 2014; Chen and Song, 2019).

(2) Research hotspots regarding the use of stem cells for the treatment of diabetic retinopathy were sorted, followed by a keyword co-occurrence analysis.

The keyword co-occurrence analysis generated a visual map of the keywords used by all included articles, which appear as nodes, with the node sizes indicating how often the keywords appear. The keywords used by the 552 articles were selected as required for the co-occurrence analysis, to generate a keyword co-occurrence network map.

Table 1 | Search strategy for the Web of Science database

#1 *Stem Cell
#2 *Progenitor Cell
#3 Mother Cell
#4 #1 OR #2 OR #3
#5 Therapy
#6 Treatment
#7 Cell Transplantation
#8 #5 OR #6 OR #7
#9 Diabetic Retinopathy
#10 #4 AND #8 AND #9

(3) Co-citation analysis of the references was performed, to analyze the time-varying upward trend in citations concerning the use of stem cells in the treatment of diabetic retinopathy.

Reference co-citation indicates that both literature A and B were referenced by literature C.

The author performed a co-citation analysis of all 17,446 references cited by the 552 included articles to generate a co-citation network map and, then, generated a timeline map of the co-citation network, according to the clusters of the co-cited references.

(4) A burst detection of the subject headings was performed, to identify hot words in the field stem cells use in diabetic retinopathy treatment.

A burst term is defined as a keyword that appears with an abrupt change in frequency within the literature, during a specific period, which is also considered to be a hot word in this field at this stage of research.

The burst detection in CiteSpace software was based on the algorithm developed by Goldberg et al. (2002).

(5) Interpretation of the visual map identifications used in the analysis of articles concerning the use of stem cells in the treatment of diabetic retinopathy.

Citation tree rings: In a map drawn using Citespace software, a circular region, termed the citation tree rings, represents the citation history of a paper. The color of the most central citation tree ring indicates the publication year of the paper.

Node circles: The size of the radius indicates the number of publications in the author’s co-authored network and the institutional co-authored network and indicates the frequency of keywords that appear in the keyword co-occurrence network.

Links between nodes: A link between nodes indicates the presence of a co-authorship or a co-occurrence relationship. The node colors indicate different years and gradually change from cold colors to warm colors. For example, blue represents earlier years, and yellow represents recent years. Cluster #: A cluster analysis was performed based on the generated map, and each cluster was labeled by citing the title, keywords, and subject headings in the abstract of the cited reference (each label can be divided into several categories, such as #0, #1, #2...).

Results

Citation frequency of the 552 WOS-indexed articles examining stem cell treatment for diabetic retinopathy

(1) From 2000 to 2020, a yearly increase in the citation frequency of articles regarding the stem cell treatment of diabetic retinopathy was observed, with a peak in 2019. Therefore, the interest in research hotspots associated with the stem cell treatment of diabetic retinopathy appears to be gradually increasing each year (**Figure 1**).

(2) Representative examples of highly cited articles: Four highly

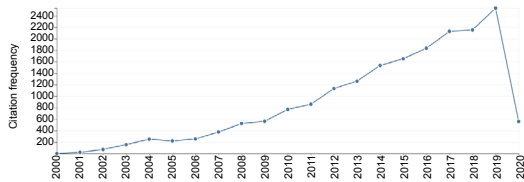


Figure 1 | Trends in the citation frequency of the 552 included articles from 2000 to 2020.

From 2000–2019, the citation frequency has increased yearly. Relevant publications indexed in the Web of Science that were published prior to April 20, 2020, are included, but data for the entirety of 2020 is not yet available.

cited articles were identified, concerning the therapeutic strategies for the use of pericytes, human embryonic stem cells, hematopoietic stem cells, and endothelial precursor cells during diabetic retinopathy treatment (Grant et al., 2002; Otani et al., 2002; Armulik et al., 2011; Schwartz et al., 2012; **Table 2**).

The study performed by Armulik et al. (2011) was the first to introduce the potential application of pericytes that are differentiated into stem cells to the treatment of diabetic retinopathy and was cited 1,086 times. Schwartz et al. (2012) were the first group to describe the subretinal transplantation of retinal pigment epithelium, derived from human embryonic stem cells, for the treatment of retinopathy, and this study was cited 807 times. In this study, the patient’s vision recovered, to some extent, after treatment, and no obvious rejection reaction had occurred within 4 months. Although this study was a one-arm study, with a small sample size and short follow-up time, the interest in the findings has increased. Two animal experiments reported the effectiveness of hematopoietic stem cells on retinopathy, from different aspects, and were cited 523 and 253 times (Grant et al., 2002; Otani et al., 2002; **Table 2**).

(3) Four types of stem cells have regularly been reported for the treatment of diabetic retinopathy, with increasing incidence over time. Current research on the stem cell treatment of diabetic retinopathy primarily focuses on the treatment of early retinopathy but not on proliferative diabetic retinopathy. Some types of stem cells secrete special growth factors, which, in turn, exert neuroprotective effects on the diabetic retina; other types of stem cells can reduce and repair capillary occlusion, reducing the loss of peripheral cells, and can differentiate into peripheral cells and endothelial cells, protecting blood vessels damaged by diabetic retinopathy. Some of the potential stem cells explored for the treatment of diabetic retinopathy are as follows.

Mesenchymal stem cells: Recent studies have reported that mesenchymal stem cells may represent the optimal therapeutic agent for disease treatment and tissue replacement. The treatment of diabetic retinopathy using mesenchymal stem cells has gradually become a research hotspot in recent years (Gong et al., 2018; **Table 2**). However, mesenchymal stem cells have not been used in clinical practice to treat diabetic retinopathy, and the optimal approach for the administration of mesenchymal stem cells remains controversial. The effectiveness and safety of mesenchymal stem cells in clinical applications require further evaluation.

Endothelial progenitor cells: Compared with other differentiated and mature endothelial cells, endothelial progenitor cells display a stronger ability to resist oxidative stress (Caballero et al., 2007) (**Table 2**). A successful therapeutic method that targets retinal angiogenesis is likely to include the elimination of retinal ischemia caused by diabetic retinopathy.

Adipose-derived stem cells: Adipose-derived stem cells can lower blood glucose levels and play a role in neurovascular protection (Elshaer et al., 2018; **Table 2**). However, whether adipose stem cells indirectly improve the retinal

Table 2 | Hotspot analysis of the representative articles, sorted from the 552 included articles regarding stem cell therapy for diabetic retinopathy

Study	Type of cells	Research hotspots
Armulik et al. (2011)	Pericytes	Pericytes can differentiate into various stem cells and participate in the development of diabetic retinopathy and tissue fibrosis.
Schwartz et al. (2012)	Embryonic stem cells	To investigate the safety and tolerability of subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelium in patients with macular dystrophy and dry age-related macular degeneration.
Decembrini et al. (2014)	Embryonic stem cells	Injection of embryonic stem cells improves the vision of the mouse model of retinal degenerative disease.
Grant et al. (2002)	Hematopoietic stem cells	To explore the role of hematopoietic stem cells in ischemic retinal vascular reconstruction.
Otani et al. (2002)	Endothelial progenitor cells and hematopoietic stem cells	Selectively targeting Lin (-) hematopoietic stem cells (non-hematopoietic stem cells) may be an effective method for treating various eye diseases.
Caballero et al. (2007)	Endothelial progenitor cells	CD34 ⁺ endothelial progenitor cells have been used as a potential therapy in mouse models of ischemic retinopathy such as diabetic retinopathy and ischemia-reperfusion.
Gong et al. (2018)	Mesenchymal stem cells	Mesenchymal stem cells have the function of paracrine nutrition and immune regulation. Transplantation of mesenchymal stem cells can delay the occurrence and development of diabetic retinopathy.
Elshaer et al. (2018)	Adipose stem cells	Adipose-derived stem cells and secreted paracrine factors can treat early retinal complications of diabetic mice.

microenvironment by triggering blood glucose reductions or directly play roles in damaged tissues remains unclear.

Pluripotent stem cells: Pluripotent stem cells have the ability to differentiate into any type of mature cell. Induced pluripotent stem cells are primarily derived from embryonic stem cells. Studies have shown that embryonic stem cells are beneficial for visual acuity improvements in mouse models of retinal degeneration (Decembrini et al., 2014; **Table 2**). In animal models of diabetes, damage to the tight junctions of the retinal pigment epithelium can destroy the retinal pigment epithelium barrier, indicating that cell replacement therapies using retinal pigment epithelium cells may be important for the treatment of diabetic retinopathy (Xu and Le, 2011).

Co-citation results of the cited references associated with research hotspots in the field of stem cell treatment of diabetic retinopathy

The cited references of the 552 included articles, published from 2000 to 2020, can be divided into 15 cluster categories

A landscape, generated using clusters of co-cited references, presented the following 15 cluster groups, as shown in **Figure 2**: #0 stem cell, #1 vascular stem cell, #2 laser, #3 health economics, #4 kidney disease, #5 optic nerve, #6 wnt, #7 muller cell, #8 cell death, #9 retinal capillary endothelium, #10 biomaterial, #11 Nrf2, #12 blood-brain barrier, #13 mononuclear phagocytes, and #14 angiotensin.

A timeline view of the cited references in the 552 included articles reveals changes in the citation frequency of classic literature over time

Based on the generated cluster map, a timeline map of co-cited references could be obtained, in which the Y-axis is defined as the cluster No. and the X-axis is defined as the publication year. The timeline map showed the time span and research progress of the development and evolution of the 15 identified cluster sub-fields, as shown in **Figure 3**.

Taking #0 stem cells, in **Figure 3**, as an example, three highly cited landmark studies emerged from 2009 to 2013, which

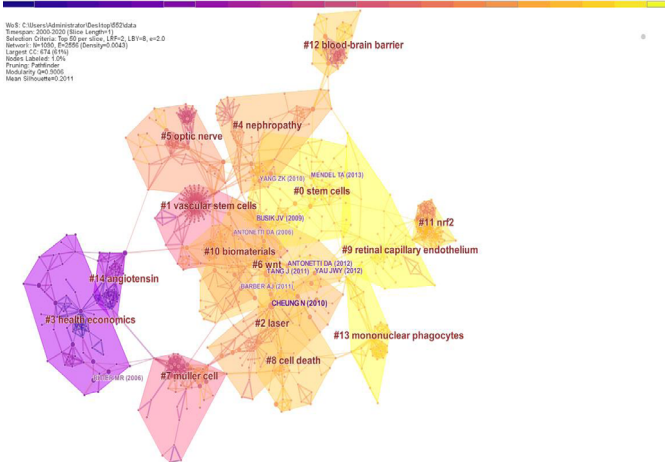


Figure 2 | Reference co-citation network for the 522 included articles (clustered according to index terms).

Colors, moving from blue to yellow, indicate the citation time from 2000 to 2020, respectively. Different cluster blocks (# 0–14) are distinguished by different colors. The color of each cluster block indicates the year in which the co-citation relationship first occurred in each cluster. Publications in the blue block were published earlier than those in the green block, and those in the yellow block were published later than those in the green block. Several nodes can be found in each cluster block, and each node represents one reference. The size of each node circle represents the number of times each reference has been cited. The connection lines between nodes indicate the pathways of citation, and the color of each line represents the time of the first citation. Only a few highly co-cited references, such as Cheung et al. (2010) and Busik et al. (2009), are shown, due to the threshold limit.

were the most authoritative studies in the field of stem cell therapy for diabetic retinopathy:

Busik et al. (2009) reported an animal experiment examining the association between diabetic retinopathy and endothelial progenitor cells and relevant treatment prospects, which has been cited 18 times, including 5 times in 2014 (**Figure 4A and B**).

Robinson et al. (2012) updated several animal models of diabetic retinopathy and introduced relevant cytological features, and this study has been cited 11 times, 5 of which were in 2014 (**Figure 4C and D**).

Mendel et al. (2013) tested the ability of adipose-derived stem cells to differentiate into pericytes, which stabilize the retinal blood vessels in various animal models of retinal vascular disease. This study has been cited 17 times, including 5 times in 2014, 5 times in 2016, and 5 times in 2018 (**Figure 4E and F**).

Citation analysis of 10 classic articles, as references cited by the 552 articles

Among the top 10 highly-cited articles, 5 were reviews (Cheung et al., 2010; Barber et al., 2011; Tang et al., 2011; Antonetti et al., 2012; Yau et al., 2012) regarding the pathogenesis, risk factors, and treatment prospects of diabetic retinopathy (**Table 3**), whereas the other 5 were animal studies that introduced the relationships between diabetic retinopathy and endothelial progenitor cells, derived bone marrow progenitor cells, adherent white blood cells, adipose-derived mesenchymal stem cells, and adipose-derived stem cells (Joussen et al., 2004; Ritter et al., 2006; Busik et al., 2009; Yang et al., 2010; Mendel et al., 2013; **Table 3**).

Keywords for hotspots regarding the stem cell-based treatment of diabetic retinopathy, over time, based on the burst analysis of high-frequency keywords in the 552 articles
Hot keywords based on the burst analysis of high-frequency keywords in the 552 articles

Among the 552 articles, the top 3 high-frequency keywords were “diabetic retinopathy” (221 times), “endothelial growth factor” (110 times), and “expression” (91 times), “Angiogenesis,” “retina,” “oxidative stress,” “stem cells,”

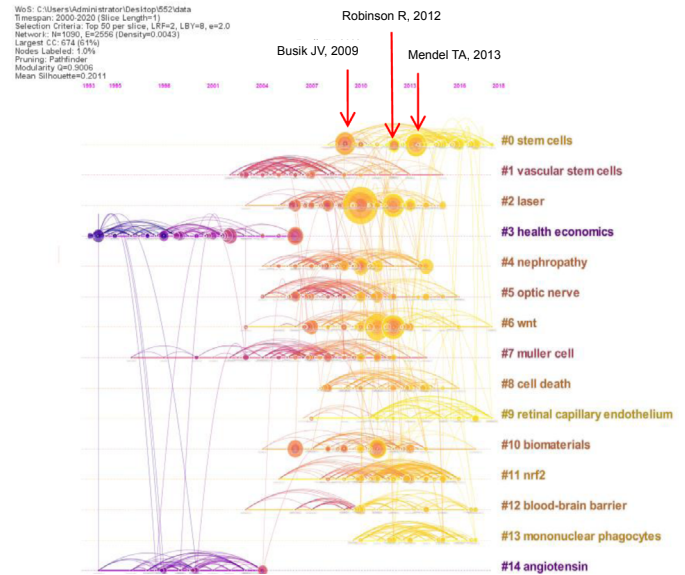


Figure 3 | Timeline view of the citation trends identified in the 552 included articles.

The timeline map reveals changes in reference co-citations over time. The circular areas represent citation tree rings, which represent the citation history of each article. The color of the most central area of the citation tree ring represents the year of publication. Each node represents a cited reference. The size of the node indicates the citation frequency. Lines represent relationships between references. The node colors represent different years, which gradually change from cold to warm moving from 2000 to 2020, respectively. Blue color indicates an earlier publication year, and red color indicates the most recent publication year. The longer color line segments indicate larger time spans cited. The cluster labeling on the right shows the research hotspot category associated with each reference. A red annual ring that appears in the node annual rings indicates that the citation frequency increased rapidly or continues to increase rapidly. The distribution of cited time can be judged by the color of each annual ring. On the timeline map, each cluster is arranged in chronological order, and adjacent clusters often correspond to related topics (co-citation between clusters). The flow of knowledge between clusters can also be observed over time (from cool to warm colors).

“endothelial progenitor cells,” and “inflammation” ranked 4–10, among which, “stem cells” and “endothelial progenitor cells” appeared 49 times and 42 times, respectively. These findings indicated that relatively more studies were performed to examine the effects of stem cells and endothelial progenitor cells on diabetic retinopathy, involving the expression of vascular endothelial growth factor, vascular regeneration, oxidative stress, and inflammatory reactions (**Figure 5**).

Two stages for keyword bursting among the 552 articles

As shown in **Figure 6**, there are two stages for keyword bursting. The first stage: From 2001 to 2012, the primary burst words were neovascularization, cells, endothelial growth factor, central nervous system, gene expression, vitreous fluid, progression, proliferative diabetic retinopathy, endothelial cell, *in vivo*, and growth factor. “Neovascularization” acted as a burst word from 2001 to 2011, with which continued for 11 years, which indicated that the promotion of neovascularization was the primary research focus for the use of stem cells in the treatment of diabetic retinopathy at this stage, with a focus on genetics and cytology, including the expression characteristics of various growth factors at the mRNA level. The second stage: From 2014 to 2020, the primary hot keywords were mouse model, glaucoma, macular degeneration, diabetic macular edema, neurodegeneration, degeneration, nuclear factor kappa B, and inflammation, each of which had relatively shorter burst times, generally 3–4 years. A mouse model is currently an accepted animal model of diabetic retinopathy. In recent years, studies regarding stem cell therapy in diabetic animals have primarily mostly focused on pathological improvements in macular degeneration, macular edema, neurodegeneration, and inflammation.

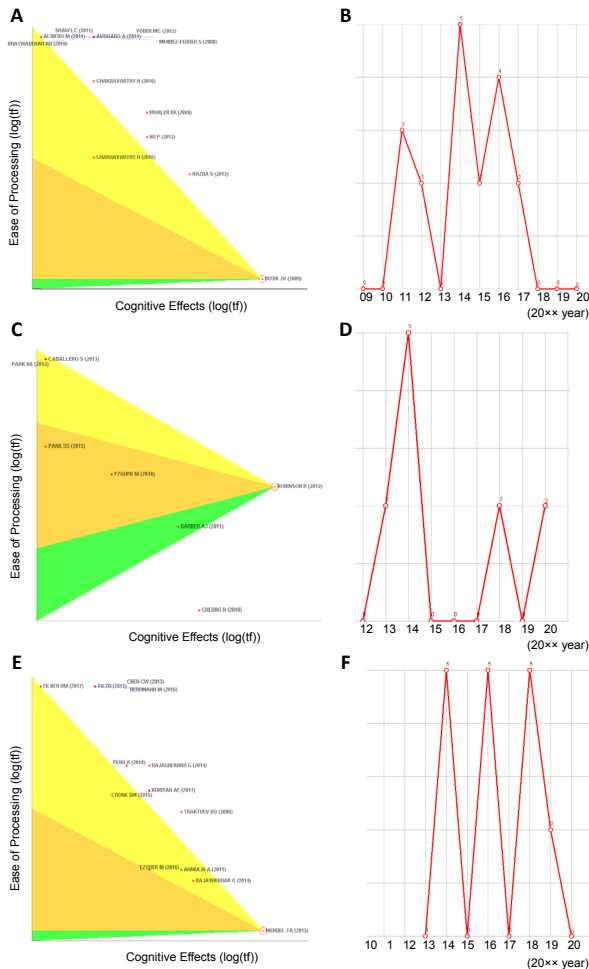


Figure 4 | Co-citation status of three representative articles in the #0 stem cell category in the timeline view.

(A, C, and E) The pennant diagrams of Busik et al. (2009), Robinson et al. (2012), and Mendel et al. (2013), respectively, which can be used to view the information for the references directly connected to a node. The figure shows the distribution of other literature that have established citation links with these three representative references. The positions of the references, from top to bottom, demonstrate that the number of citations gradually increases, and the bottom reference has been cited most frequently. (B, D, and F) The time trends showing the number of times that Busik et al. (2009), Robinson et al. (2012), and Mendel et al. (2013) are cited, respectively, with the top of the broken line representing the number of citations. All three articles were cited 5 times in 2014, indicating that research on stem cells was relatively concentrated in 2014.

Analysis of clinical research articles on the stem cell-based treatment of diabetic retinopathy

Examples of rare clinical studies from the 552 articles regarding the stem cell-based treatment of diabetic retinopathy

Gu et al. (2018) confirmed the safety and efficacy of intravenous injections of autologous bone marrow mesenchymal stem cells in 17 patients (34 eyes) with diabetic retinopathy; however, no placebo control group was used in this study and the best treatment window and infusion times remain uncertain.

Another clinical study (Liang et al., 2018) observed the safety of subretinal space transplantation using autologous bone marrow mesenchymal stem cells in four patients with proliferative diabetic retinopathy. No complications were observed after cell transplantation, and the transplanted cells played a local anti-inflammatory role. No hyperplasia and circulation improvements were found.

In the clinical trial by Bhattacharya et al. (2017), stem cells derived from fat or bone marrow were directly transplanted into the eye, to repair the damage to the retina caused

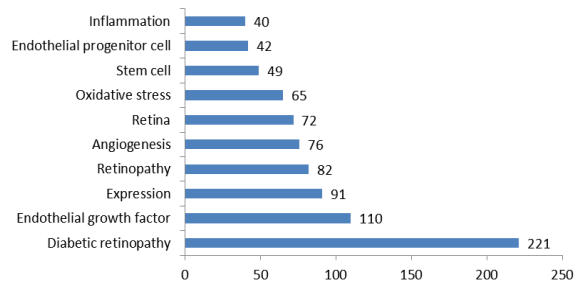


Figure 5 | Top 10 high-frequency keywords included in the 552 articles. The top three high-frequency keywords are “diabetic retinopathy,” “endothelial growth factor,” and “expression.” The numbers on the sides of the histogram represent the frequency of occurrence.

Keywords	Year	Strength	Begin	End	2000–2020 year
Neovascularization	2000	4.3757	2001	2011	[Timeline visualization]
Cell	2000	5.1853	2001	2008	[Timeline visualization]
Endothelial Growth Factor	2000	5.6606	2002	2007	[Timeline visualization]
Central Nervous System	2000	3.9950	2003	2006	[Timeline visualization]
Gene Expression	2000	4.7705	2006	2008	[Timeline visualization]
Vitreous Fluid	2000	3.1233	2007	2012	[Timeline visualization]
Progression	2000	4.3642	2007	2009	[Timeline visualization]
Proliferative Diabetic Retinopathy	2000	3.2628	2007	2010	[Timeline visualization]
Endothelial Cell	2000	3.4391	2008	2011	[Timeline visualization]
In Vivo	2000	3.1434	2009	2012	[Timeline visualization]
Growth Factor	2000	5.2583	2009	2012	[Timeline visualization]
Mouse Model	2000	3.3835	2014	2017	[Timeline visualization]
Glaucoma	2000	3.4957	2014	2016	[Timeline visualization]
Macular Degeneration	2000	3.2191	2016	2018	[Timeline visualization]
Diabetic Macular Edema	2000	3.4425	2016	2018	[Timeline visualization]
Neurodegeneration	2000	3.2743	2016	2018	[Timeline visualization]
Degeneration	2000	4.5117	2017	2020	[Timeline visualization]
Nuclear factor Kappa B	2000	3.1404	2017	2020	[Timeline visualization]
Inflammation	2000	8.0854	2018	2020	[Timeline visualization]

Figure 6 | Time trends of burst keywords included in the 552 articles.

Two stages are identified: the range marked by the box indicates the first stage (2000–2009), whereas the second stage is outside the dotted box. “Neovascularization” is the keyword with the highest burst intensity. In the figure, Year represents the earliest year in which the keywords appeared, Strength represents the citation strength, and Begin and End represent the time when the burst started and ended, respectively.

by age-related macular degeneration and other blinding diseases. Human clinical trials examining the retinal stem cell transplantations of pluripotent stem cells and induced pluripotent stem cells are currently underway. These pluripotent stem cells have the same morphology as photoreceptor cells and retinal pigment epithelial cells (Yoder and Ingram, 2009).

Analysis of the nine clinical trials examining the stem cell-based treatment of diabetic retinopathy that were registered with ClinicalTrials.gov

Nine clinical trials examining the stem cell-based treatment of diabetic retinopathy were registered on ClinicalTrials.gov, which primarily focused on endothelial progenitor cells (NCT01927315), induced pluripotent stem cells (NCT03403699), hematopoietic stem cells (NCT01972438), embryonic stem cells (NCT02749734 and NCT03046407), autologous CD34⁺ stem cells (NCT03981549), and autologous bone marrow stem cells (NCT03011541, NCT01920867, NCT01736059, and NCT02280135; **Table 4**).

In an ongoing trial (NCT01736059), the intravitreal injection of CD34⁺ bone marrow mesenchymal stem cells is being used to treat irreversible vision loss caused by retinal degenerative diseases or retinal vascular diseases, including diabetic retinopathy (**Table 4**).

Another clinical trial (NCT03403699) explored the ability of

Table 3 | Ten classic articles regarding stem cells and diabetic retinopathy cited by the 552 articles

Study	Citation counts	Design or type of articles	Type of cell	Article highlights
Cheung et al. (2010)	29	Review	No specific cell information description	The outlook for future treatment modalities, such as inhibition of other antigenic factors, regenerative therapy, and topical therapy, is promising.
Tang et al. (2011)	20	Review	No specific cell information description	Discuss the potential of anti-inflammatory approaches to inhibit development of different stages of the retinopathy
Antonetti et al. (2012)	19	Review	Neuronal, glial, and vascular cells in the retina	To explore the molecular interactions of neuronal, glial, and vascular cells in the retina as the basis of the neurovascular unit and examine the effect of diabetes on the function of the neurovascular unit to highlight new therapeutic approaches.
Yau et al. (2012)	19	Review	No specific cell information description	To examine the global prevalence and major risk factors for diabetic retinopathy and vision-threatening diabetic retinopathy among people with diabetes
Busik et al. (2009)	18	Animal experiment	Endothelial progenitor cells	This reduction in the circadian peak of endothelial progenitor cells release led to diminished reparative capacity, resulting in the development of the hallmark feature of diabetic retinopathy, acellular retinal capillaries.
Mendel et al. (2013)	17	Animal experiment	Human Adipose-derived stem cells	Adipose-derived stem cells-derived pericytes can integrate with retinal vasculature, adopting both pericyte morphology and marker expression, and provide functional vascular protection in multiple murine models of retinal vasculopathy.
Barber et al. (2011)	15	Review	Neural and vascular cells in the retina	Review some of the evidence supporting apoptotic cell death as a contributing mechanism of diabetic retinopathy, explore some of the potential causes, and discuss the potential links between apoptosis and loss of visual function in diabetic retinopathy.
Ritter et al. (2006)	14	Animal experiment	Derived myeloid progenitor cells	Using a model of oxygen-induced retinopathy, we demonstrate that a population of adult bone marrow-derived myeloid progenitor cells migrated to avascular regions of the retina, differentiated into microglia, and facilitated normalization of the vasculature
Jousen et al. (2004)	14	Animal experiment	Adherent leukocytes	Chronic, low-grade subclinical inflammation is responsible for many of the signature vascular lesions of diabetic retinopathy.
Yang et al. (2010)	13	Animal experiment	Adipose-derived mesenchymal stem cells	Adipose-derived mesenchymal stem cells may serve as a promising therapeutic approach for diabetic retinopathy.

Table 4 | Nine clinical trials exploring the stem cell-based treatment of diabetic retinopathy that were registered with ClinicalTrials.gov

Status/NCT number	Study title	Conditions	Sample size (n)	Interventions	Study type	Study design
Completed/ NCT01927315	Effects of fenofibrate on endothelial progenitor cells in diabetes	Diabetes; diabetic retinopathy	41	Drug: Fenofibrate 145 mg; Drug: Placebo	Interventional	Allocation: Randomized; intervention model: Parallel assignment; Masking: single (participant)
Recruiting/ NCT03403699	Human iPSC for repair of vasodegenerative vessels in diabetic retinopathy	Diabetes complications; diabetic retinopathy	20	Biological: Generation of inducible pluripotent stem cells	Observational	Observational model: Cohort
Enrolling by invitation/ NCT01736059	Clinical trial of autologous intravitreal bone-marrow CD34 ⁺ stem cells for retinopathy	Behcet's syndrome; non-exudative age-related macular degeneration	15	Drug: CD34 ⁺ bone marrow stem cells intravitreal	Interventional	Masking: none (open label); Model: single group assignment
Recruiting/ NCT03011541	Stem cell ophthalmology treatment study II	Diabetic retinopathy; retina vein occlusion; retinal disease	500	Procedure: Arm 1	Interventional	Masking: None (open label); Allocation: non-randomized
Enrolling by invitation/ NCT01920867	Stem cell ophthalmology treatment study	Age-related macular degeneration;retinitis pigmentosa; retinal disease	300	Procedure: Arm 2; Procedure: Arm 3; Procedure: Retrobulbar	Interventional	Intervention model: Parallel assignment; masking: None (open label); Allocation: non-randomized
Has Results/ NCT02749734	Clinical study of subretinal transplantation of human embryo stem cell derived retinal pigment epitheliums in treatment of macular degeneration diseases	Macular degeneration	15	Drug: Saline; Procedure: Subretinal transplantation	Interventional	Intervention model: Single group assignment;
Recruiting/ NCT03046407	Treatment of dry age related macular degeneration disease with retinal pigment epithelium derived from human embryonic stem cells	Stargardt's macular dystrophy; dry age-related macular degeneration	10	Biological: Retinal pigment epithelium transplantation	Interventional	Masking: None (open label); Intervention model: Single group assignment
Recruiting/ NCT03981549	Treatment of central retinal vein occlusion using stem cells study	Central retinal vein occlusion	20	Biological: Autologous bone marrow CD34 ⁺ stem cells	Interventional	Intervention model: Single group assignment; Masking: None (open label)
Completed/ NCT02280135	Clinical trial of intravitreal injection of autologous bone marrow stem cells in patients with retinitis pigmentosa	Retinitis pigmentosa	8	Biological: Intravitreal injection of autologous bone marrow stem cell; Other: Subconjunctival injection of saline	Interventional	Allocation: Randomized; Intervention model: Parallel Assignment; Masking: double (participant, investigator)

induced pluripotent stem cells to differentiate into endothelial cells and pericytes in the capillary degeneration region, after diabetic retinopathy (**Table 4**).

Two prospective non-randomized, controlled trials (NCT03011541, 500 cases included; NCT01920867, 1,000

cases included) investigated the effectiveness of bone marrow mesenchymal stem cell transplantation for retinopathy treatment, including age-related macular degeneration, retinitis pigmentosa, retinal diseases, diabetic retinopathy, retinal vein occlusion, and retinal diseases (**Table 4**). The

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results of these trials, which examined relatively large sample sizes, warrant further consideration. The other registered clinical trials included relatively smaller sample sizes and did not present prospective, large sample, randomized, controlled clinical evidence.

Discussion

Current status of research articles on stem cell-based treatments of diabetic retinopathy

Endothelial progenitor cells, mesenchymal stem cells, and hematopoietic stem cells have been found to exert repairing effects on retinal microvascular endothelial cells and pericytes and to inhibit the formation of pathological neovascularization. However, further investigation examining the potential use of other stem cells, such as adult stem cells and induced pluripotent adult stem cells, remains necessary. Currently, few internationally recognized authoritative studies exist examining the stem cell-based treatment of diabetic retinopathy, and most of the published articles are opinion articles, review articles, and animal experiment articles. Most relevant studies remain in the basic research stage, and few representative clinical trials have been documented.

Limitations and challenges

Although tremendous progress has been made in the application of stem cell-based therapies to treat diabetic retinopathy and other diabetic complications, challenges for clinical transformation remain, which must be resolved as soon as possible. Due to the toxic and pathological characteristics of diabetic retinopathy, the affected retina is an unfavorable environment for homing, which represents a primary obstacle for treatment with mesenchymal stem cells. Methods for the exogenous injection of stem cells should be well-clarified to obtain better transplantation results. The limited proliferation and differentiation of certain cell types, such as retinal progenitor cells, represent other obstacles that must be overcome during the development of stem cell-based therapies. Another challenge for the translation of pre-clinical research to applied stem cell-based therapies is the inability of animal models to perfectly represent human conditions. Mismatched clinical endpoints between animal models and humans make predicting the effects of stem cell-based therapies impossible to predict based on existing clinical parameters (Kern et al., 2019). Due to the limitations of the Citespace software, the present article only analyzes the literature indexed in the Web of Science database, whereas other databases, such as PubMed, have not been fully analyzed. Therefore, the 552 articles included in the article only represent the information indexed in the Web of Science and are not yet fully representative of all available information in this field, which is the primary limitation of this article.

Prospects

Stem cell heterogeneity, cell delivery, and the effective homing of stem cells to damaged tissues remain major challenges faced by stem cell transplantations for the treatment of diabetic retinopathy. Some potential clinical trials are ongoing, which primarily focus on the treatment of diabetic retinopathy using pluripotent stem cells, retinal pigment epithelial cells, bone marrow mesenchymal stem cells, and endothelial progenitor cells. Hopefully, high-quality clinical evidence will be obtained in the future.

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