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Practical application of stem cell therapy in retinoblastoma

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Abstract

Retinoblastoma (RB), recognized as the most prevalent intraocular malignancy in pediatric populations, continues to pose considerable therapeutic challenges due to its genetic etiology, tumor heterogeneity, and resistance to standard treatment modalities. Recent progress in stem cell biology has introduced innovative approaches for both disease modeling and therapeutic intervention. The utilization of induced pluripotent stem cells (iPSCs) and retinal organoids has enabled the in vitro recapitulation of retinal development and RB pathogenesis, thereby facilitating precision drug screening and elucidation of underlying mechanisms. Additionally, the identification of cancer stem cells (CSCs) within RB has redirected therapeutic strategies toward targeting pathways involved in self-renewal, mechanisms of drug resistance, and tumor propagating cells, to prevent relapse and metastasis. Mesenchymal stem cells (MSCs) have emerged as promising vectors for tumor-targeted therapy, leveraging paracrine effects and exosome-mediated delivery of therapeutic agents, thus offering minimally invasive and systemic approaches to overcoming drug resistance and modulating tumor behavior. Furthermore, hematopoietic stem cell (HSC) rescue has improved the safety profile of high-dose chemotherapy regimens by mitigating treatment-associated toxicities. Collectively, these stem cell-based strategies underscore the multifaceted role of cellular therapies in RB, heralding a future characterized by integrated, personalized, and less invasive therapeutic modalities.

Keywords: Retinoblastoma, Stem cell, Therapy, Translational elements

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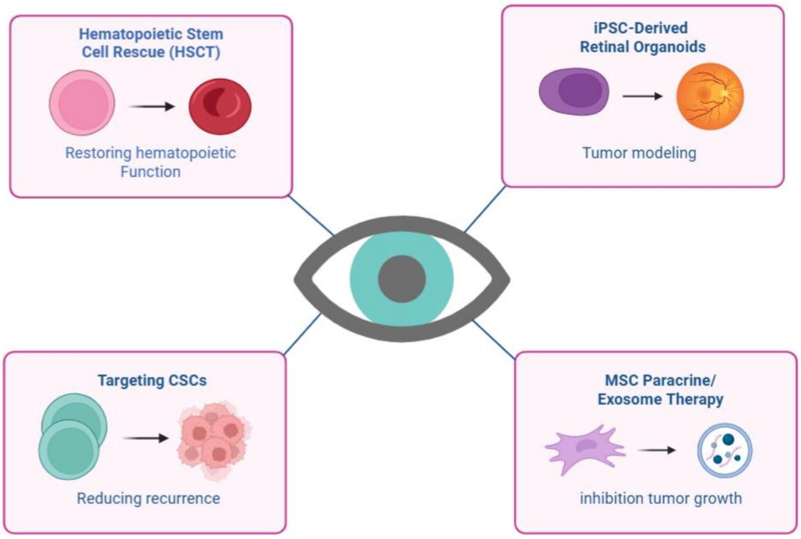
Abstract



Introduction

RB represents the most prevalent primary intraocular malignancy occurring in pediatric populations and is predominantly attributed to biallelic mutations in the RB1 gene (1), and occurs with an incidence of approximately 15,000 to 20,000 live births (2). Traditional interventions, including systemic chemotherapy, intra-arterial chemotherapy, radiotherapy, and enucleation, are effective in achieving tumor control; however, long-term adverse effects and vision impairment continue to pose significant challenges. Consequently, there is a pressing need for innovative therapeutic approaches, with stem cell-based therapies emerging as promising modalities for both treatment and disease modeling (1). Although these treatments have significantly improved patient outcomes, they are associated with long-term complications, including secondary malignancies, growth disturbances, and severe visual impairment (3). Furthermore, resistance to standard chemotherapy is increasingly acknowledged, in part attributable to the presence of CSCs within RB tumors, which contribute to tumor recurrence and metastasis (4). Stem cells can be utilized as adjunctive therapy, exemplified by hematopoietic stem cell transplantation (HSCT), which serves to restore bone marrow function following high-dose chemotherapy (5). iPSCs and retinal organoids serve as disease models for investigating the pathogenesis of RB and for evaluating the efficacy of novel therapeutic agents, as possible therapeutic targets, concentrating on CSC populations within tumors and in the context of cellular delivery systems, where MSCs or their extracellular vesicles (EVs) are employed to transport therapeutic molecules directly to tumor locations. These varied applications underscore the significance of stem cell research (5-7).

Different Types of RB

The RB1 gene, situated at the chromosomal locus 13q14, encodes the RB protein, which plays a critical role in controlling the G1/S transition of the cell cycle through the suppression of E2F transcription factors (8). The inactivation of both functional RB1 alleles results in the deregulation of retinal cell proliferation, ultimately contributing to tumorigenesis (9). RB manifests in both heritable or germline and non-heritable or sporadic forms. In the heritable variant, which follows an autosomal dominant inheritance pattern, approximately 40% of cases involve children inheriting or acquiring a germline mutation in one allele of the RB1 tumor suppressor gene. This mutation is found in all somatic cells, including germ cells, making it heritable to subsequent generations (10). The two-hit hypothesis posits that tumor development necessitates a second somatic mutation, resulting in the biallelic inactivation of the RB1 gene within retinal cells (11). Individuals with hereditary RB frequently exhibit bilateral and multifocal tumors, and there exists a 50% probability that they will transmit the mutant allele to their offspring (12). Significantly, they are also inclined to develop secondary malignancies, including osteosarcoma and soft tissue sarcomas (13). In the sporadic cases, in 60% of them, both RB1 mutations manifest somatically within a single retinal cell. This indicates the absence of a germline mutation, rendering the condition non-heritable (14). These patients generally exhibit unilateral, solitary tumors and do not possess an elevated risk of transmitting the disease to their progeny (10).

HPCS Rescue after High-Dose Chemotherapy

High-dose chemotherapy has been utilized in advanced and refractory RB cases to address resistance to conventional treatment protocols and to eliminate minimal residual disease (15, 16). Nevertheless, this intensive chemotherapy regimen is highly myeloablative, leading to severe and potentially life-threatening suppression of bone marrow function (17, 18). To mitigate this toxicity, HSCT, primarily utilizing autologous peripheral blood stem cells, has been established as a rescue approach aimed at reinstating hematopoietic function (19). Investigations in clinical settings have revealed that the use of autologous post high-dose chemotherapy leads to enhanced survival rates in patients diagnosed with extraocular or metastatic RB, concurrently upholding a tolerable safety profile (20). However, this method entails significant risks, such as infection, graft failure, and mortality associated with transplantation (21). Therefore, HSCT is generally indicated for pediatric patients presenting with relapsed or advanced stages of the disease, rather than for those exhibiting localized intraocular RB (22, 23).Current research efforts are focused on refining patient selection criteria, optimizing conditioning protocols, and reducing long-term complications associated with HSCT. Furthermore, the integration of HSCT with novel therapeutic approaches, including targeted molecular agents and immunotherapies, holds promise for augmenting its efficacy in the future management of RB (24-26). New methods are being investigated to lower transplant-related morbidity. Studies are assessing reduced intensity conditioning strategies aimed at minimizing toxicities while ensuring anti-tumor efficacy, particularly in very young pediatric patients (27). Moreover, the integration of HSCT with novel therapeutic approaches, including immune checkpoint inhibitors and targeted agents, has the potential to enhance long-term clinical outcomes by effectively targeting both the predominant tumor cell population and chemoresistant cancer stem-like cells (28, 29).

Stem Cells for Disease Modeling (iPSCs and Retinal Organoids)

iPSCs derived from patients have significantly advanced the investigation of human diseases, including RB (30, 31). These iPSCs are produced by reprogramming somatic cells, such as fibroblasts, into a pluripotent state, thereby conferring the capacity to differentiate into diverse cell types, including retinal cells (32, 33). This methodology facilitates the generation of retinal organoids as three-dimensional constructs that faithfully replicate the cellular organization and developmental dynamics of the human retina in vitro (34-36). iPSCs derived from patients harboring RB1 mutations enable the direct investigation of tumor initiation within a genetic context that closely replicates the patient's disease profile, thereby bridging the divide between experimental models and clinical scenarios (37, 38). This approach is particularly advantageous given the inherent challenges of studying RB in vivo, which stem from its rarity, heterogeneity, and the ethical constraints associated with pediatric tumor research. The resultant retinal organoids comprise proliferative retinal progenitor cells that recapitulate the hyperplastic lesions characteristic of RB patients (39-41). Such models are instrumental for elucidating the molecular mechanisms underpinning tumorigenesis, including the regulatory pathways governing cell proliferation, apoptosis, and differentiation. Furthermore, retinal organoids facilitate the exploration of tumor microenvironment interactions. Co-culture systems integrating retinal organoids with immune or stromal cells permit the examination of the contributions of non-tumor cell populations to RB progression, immune evasion, and therapeutic resistance (42, 43). Another significant application lies in high-throughput drug screening, where organoid-based platforms enable the assessment of chemotherapeutic agents, targeted inhibitors, and gene silencing techniques under physiologically relevant conditions (44, 45). This methodology not only forecasts therapeutic efficacy but also aids in identifying patient-specific drug sensitivities, thereby advancing the prospects of precision oncology in RB (46). Additionally, advancements in bioengineering are propelling the field towards the development of vascularized and innervated retinal organoids, which can more accurately replicate the metabolic demands and stress responses of tumors. These next-generation models may yield insights into the mechanisms of hypoxia-induced resistance and angiogenesis in RB (47). iPSCs and retinal organoids together constitute a progressively advancing set of methodologies that surpass traditional modeling approaches. These tools are increasingly essential for elucidating the biology of RB, investigating tumor host interactions, and facilitating the development of personalized therapeutic interventions (48).

Targeting RB CSCs

One of the new paradigms in RB research is the acknowledgment of CSCs as a vital factor in tumor initiation, progression, therapeutic resistance, and recurrence. CSCs found in RB tumors demonstrate the ability for self-renewal, multipotency, and tumorigenicity, resembling normal stem cells, albeit with dysregulated pathways that govern proliferation and differentiation (49). Crucially, these cells are believed to persist following conventional treatments, including chemotherapy and radiotherapy, thereby serving as a reservoir for disease recurrence (50). Several molecular signaling pathways, notably Notch, Hedgehog (HH), Wingless-related Integration Site / β-catenin (Wnt/β-catenin), and Phosphoinositide 3-kinase/ Protein Kinase B/ mammalian Target Of Rapamycin (PI3K/Akt/mTOR), are frequently involved in sustaining the CSC phenotype in RB. Dysregulated activation of these pathways facilitates survival signaling, epithelial to mesenchymal transition (EMT), and metabolic reprogramming, enabling CSCs to adapt to hypoxic or nutrient-deprived microenvironments. Accordingly, therapeutic interventions targeting these pathways, such as Gamma Secretase Inhibitors (GSIs) for Notch, Smoothened (SMO) antagonists for HH, and Wnt pathway inhibitors, have garnered considerable interest in preclinical studies (51, 52). Additionally, immunotherapeutic strategies specifically directed against CSCs represent a promising avenue. For example, CSCs in RB frequently overexpress markers including ATP-binding cassette subfamily G member 2 (ABCG2), Cluster of Differentiation 44 (CD44), and Aldehyde Dehydrogenase Family 1 (ALDH1), which may serve as viable therapeutic targets. Approaches employing monoclonal antibodies, chimeric antigen receptor T (CAR-T) cells, or antibody drug conjugates designed to eradicate CSCs selectively have demonstrated preclinical efficacy in other solid tumors and hold potential for adaptation in RB treatment (53, 54). Furthermore, the inhibition of drug efflux transporters such as ABCG2 may increase the sensitivity of CSCs to chemotherapy, potentially addressing the issue of multidrug resistance (55). In addition, epigenetic regulation has emerged as a critical factor influencing CSC survival in RB. Aberrant patterns of histone modifications and deoxyribonucleic acid (DNA) methylation contribute to the maintenance of stemness-associated gene expression. Consequently, epigenetic inhibitors, including histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors, are under investigation for their capacity to induce differentiation in CSCs and enhance their responsiveness to therapeutic interventions (56, 57). Collectively, targeting CSCs in RB signifies a paradigm shift from traditional treatments that predominantly focus on eliminating the rapidly proliferating tumor mass. By specifically eradicating the rare, therapy-resistant CSC population, it may be possible to achieve sustained remission and reduce recurrence rates. The integration of CSC targeted strategies with current treatment modalities, such as intra-arterial chemotherapy and focal therapies, holds promise for improving long-term therapeutic outcomes in patients with RB (58).

Targeting CSCS Signaling in RB

CSCs depend on developmental signaling pathways to maintain their self-renewal capabilities and ensure their survival. Investigating and therapeutically targeting these pathways presents a promising approach for the eradication of CSCs and the enhancement of treatment efficacy (59) **(Table 1)**. The Wnt/β-catenin signaling pathway plays a vital role in sustaining CSC self-renewal. Abnormal activation of Wnt signaling has been observed in RB, which fosters cell proliferation and confers resistance to standard therapies. The pharmacological blockade of Wnt signaling through the use of small molecules or inhibitors can inhibit the nuclear translocation of β-catenin, diminish the expression of CSC markers, and make tumor cells more susceptible to chemotherapy **(Figure 1)**. Additionally, targeting Wnt signaling may reduce metastatic capabilities by disrupting EMT processes (60)**.**

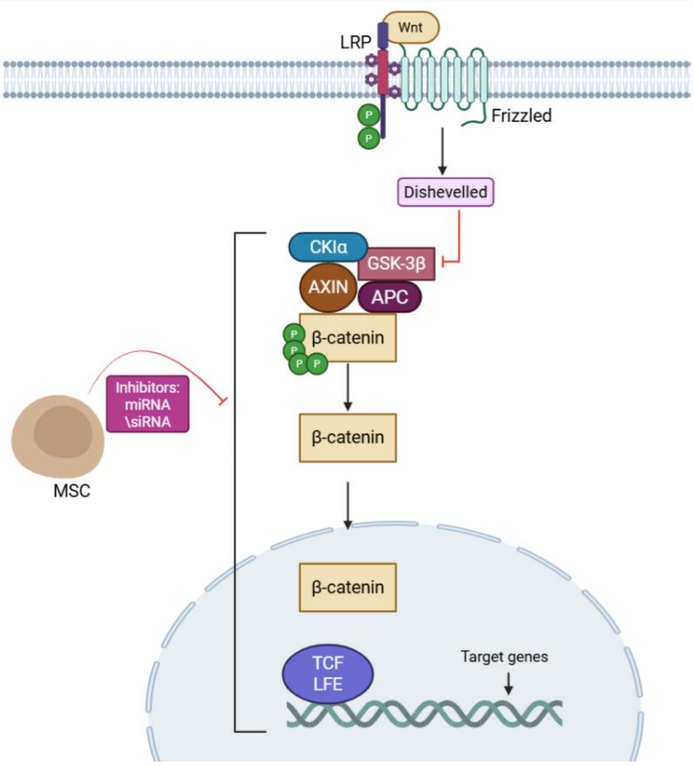


Figure 1. Activation of the β-catenin pathway in RB leads to β-catenin accumulation and transcription of target genes that promote tumor growth and stem cell maintenance. MSCs, through secreted factors and messenger RNAs(mRNAs), can inhibit this pathway, suppressing β-catenin activity and reducing tumor proliferation.

Notch signaling is key to controlling cell development and supporting stem cell maintenance. In RB, overactive Notch pathways promote blood vessel growth and help CSCs survive (60). Lab studies show that drugs like GSIs and antibodies blocking Notch receptors can slow CSC growth and reduce tumor blood vessels, potentially making standard chemotherapy more effective by overcoming drug resistance. Similarly, the HH pathway, especially Sonic Hedgehog (SHH), drives tumor growth and CSC survival by interacting with Patched receptors to activate SMO and GLI proteins, which control genes for cell growth and stem-like traits (61). Drugs like vismodegib and sonidegib, which block SMO, have been shown to shrink CSC populations and slow RB tumor growth in lab models. The PI3K/AKT/mTOR pathway also plays a major role in CSC survival, growth, and metabolism, contributing to drug resistance in RB. Using targeted drugs to block PI3K, AKT, or mTOR can trigger CSC death, reduce their ability to self-renew, and make tumors more responsive to standard treatments (62, 63). Combining therapies that target PI3K/AKT/mTOR with those hitting Wnt or Notch pathways may create stronger anti-CSC effects **(Figure 2)**.

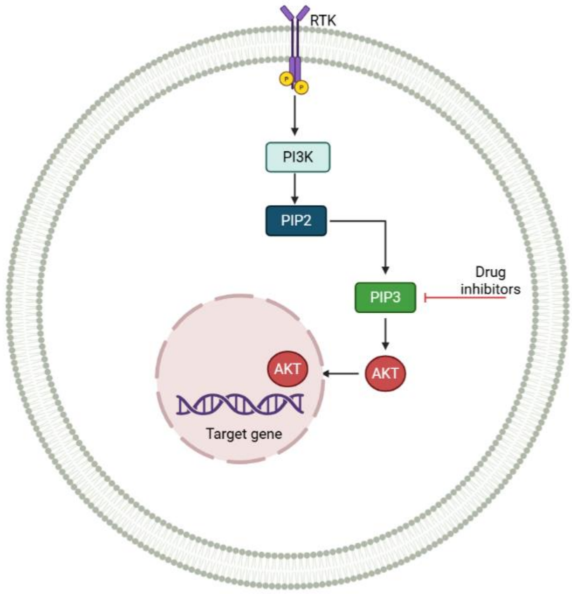


Figure 2. PI3K/AKT signaling pathway modulated by MSC-derived exosomes in RB. Activation of RTK leads to PI3K-mediated phosphorylation of PIP2 to PIP3, triggering AKT activation and subsequent transcription of genes promoting survival, proliferation, and drug resistance. Targeted inhibitors can block this pathway to suppress tumor progression.

Focusing on the molecular pathways of CSCs in RB offers a hopeful strategy to tackle tumor regrowth and drug resistance. Combining CSC-specific treatments with traditional chemotherapy or radiation could target both the main tumor cells and the resistant CSC group, improving long-term outcomes and lowering the chance of the cancer returning (64, 65). Further lab and human studies are needed to refine drugs that target these pathways and to develop effective treatment combinations.

Table 1. Stem Cell Signaling in RB. Multiple signaling pathways, including Wnt/β-catenin, Notch, HH, and PI3K/Akt/mTOR, play pivotal roles in regulating the self-renewal, proliferation, and survival of CSCs in RB. Aberrant activation of these pathways contributes to tumor growth, angiogenesis, and therapeutic resistance. Targeted inhibition of these signaling cascades has shown promise in suppressing CSC activity, improving drug sensitivity, and potentially enhancing the overall effectiveness of conventional treatments.

Signaling pathway	Role in CSCs	Targeted inhibition strategy	Effect on RB treatment
Wnt/ß-catenin	Maintains CSCs' self-renewal, promotes proliferation and EMT, and contributes to therapy resistance	Small molecule inhibitors, monoclonal antibodies, β-catenin nuclear translocation blockers	Reduces CSC population, sensitizes tumor cells to chemotherapy, and decreases metastasis potential
Notch	Regulates stem cell maintenance, angiogenesis, and survival of CSCs	GSIs, Notch receptor blocking antibodies	Inhibits CSC proliferation, reduces angiogenesis, enhances chemotherapy efficacy
SHH	Controls CSC-driven proliferation and stemness via GLI transcription factors	SMO antagonists	Reduces CSC numbers, suppresses tumor growth, and may improve response to other therapies
PI3K\AKT\mTOR	Promotes survival, proliferation, and chemoresistance in CSCs	PI3K inhibitors, AKT inhibitors, mTOR inhibitors	Induces CSC apoptosis, decreases self-renewal, sensitizes tumors to chemotherapy, and combination therapy can enhance overall efficacy

Paracrine and Exosome-Mediated Roles of MSCs

MSCs are versatile cells that can develop into bone, fat, or cartilage cells (66). Beyond this ability, MSCs release signaling molecules like cytokines and growth factors, which shape the tumor environment, immune responses, and tissue healing in RB (67). In RB treatment, MSCs are studied for their ability to fight tumors through these molecules and as carriers for targeted drug delivery. They produce factors that affect tumor growth, cell death, blood vessel formation, and immune cell activity, helping to control tumors (68). A key way MSCs communicate is through tiny vesicles called exosomes, which carry proteins, ribonucleic acids (RNAs), and microRNAs to RB cells and nearby tissue, influencing pathways like Wnt/β-catenin, PI3K/AKT, and Notch. These pathways drive tumor growth, drug resistance, and cancer stem cell behavior (69, 70). Preclinical investigations have demonstrated that MSC-derived exosomes can serve as therapeutic delivery platforms, facilitating the targeted transport of anticancer agents, small interfering RNAs (siRNAs), or gene editing tools directly to tumor cells. This strategy enhances targeting specificity, minimizes systemic toxicity, and can overcome physiological barriers within the ocular environment (71, 72). However, MSC effects depend on the tumor setting, as some conditions may lead MSCs or their exosomes to encourage tumor growth, making it critical to understand these interactions for safe RB therapy (73). Using MSC exosomes instead of whole cells reduces risks like unwanted cell changes or cancer formation. Early lab tests in eye cancer suggest that injecting exosomes into the eye can alter the tumor environment, block blood vessel growth, and deliver targeted drugs (74). Exosomes are also easier to produce and store, making them practical for consistent RB treatments **(Figure 3)**. In summary, MSCs and their exosomes offer a promising approach for RB, either by adjusting the tumor environment or delivering precise therapies, advancing personalized cancer care (75, 76).

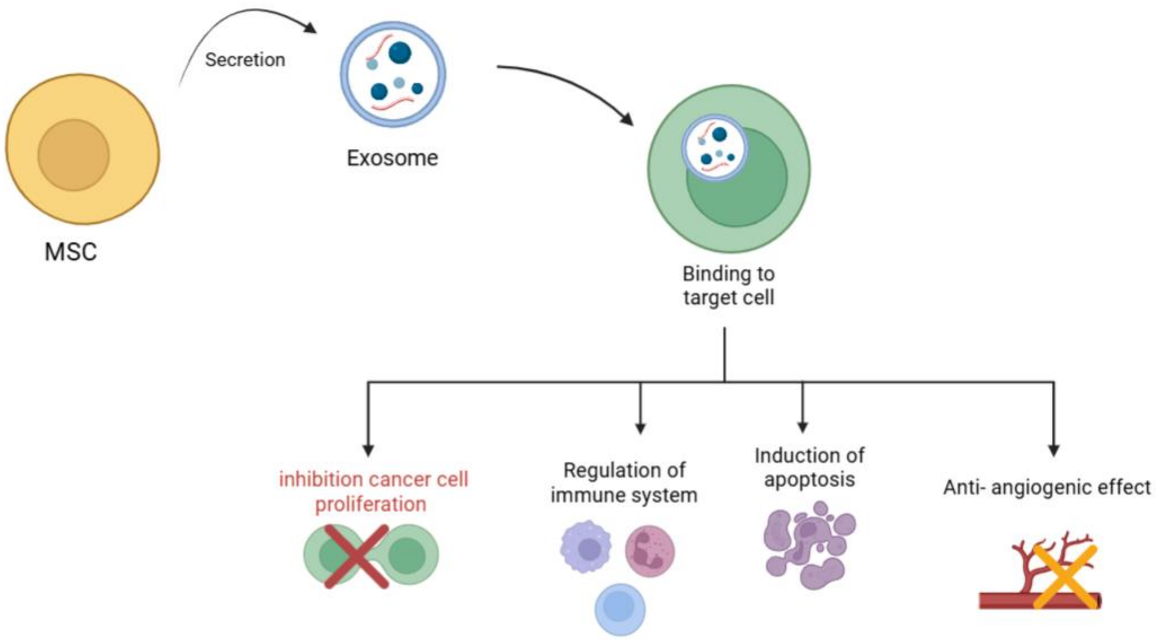


Figure 3. MSC-derived exosome–mediated therapeutic mechanisms in RB. This schematic illustrates how MSC-derived exosomes exert therapeutic effects in RB. MSCs release nanosized exosomes enriched with bioactive molecules such as microRNAs, siRNAs, growth factors, and cytokines, which can be internalized by tumor cells. These exosomal contents regulate multiple cellular pathways, including PI3K/AKT, Wnt/β-catenin, and apoptotic cascades, leading to the inhibition of tumor proliferation, angiogenesis, and chemoresistance, while promoting apoptosis. Moreover, MSC-derived exosomes demonstrate low immunogenicity and can act as natural carriers for targeted drug delivery, enhancing therapeutic precision and minimizing systemic toxicity.

Stem Cells as Carriers for Targeted Therapies

Stem cells, such as MSCs and neural stem cells (NSCs), are increasingly recognized for their ability to deliver cancer treatments directly to tumors, thanks to their natural attraction to RB cells (77, 78). This feature allows stem cells to carry drugs or other agents straight to RB tumors, minimizing harm to healthy tissues and boosting treatment effectiveness. By modifying stem cells genetically, they can produce proteins that trigger tumor cell death, such as apoptosis-inducing factors or cancer-blocking genes, activated specifically within the tumor environment (79). MSCs can also be equipped with chemotherapy drugs or tiny particles, released at the tumor through vesicles or signaling molecules, increasing drug levels locally while reducing side effects (80, 81). Additionally, stem cells can transport viruses that attack RB cells selectively, protecting the viruses from immune defenses and improving treatment outcomes (82). Combining stem cell delivery with immune therapies or standard chemotherapy enhances anti-cancer effects. For instance, MSCs carrying drug-filled vesicles alongside immune-boosting drugs can target tumors and adjust the immune environment simultaneously (70, 83). Lab studies show these delivery systems are precise, effective, and potentially safer than traditional treatments, though challenges like ensuring stem cell safety, preventing tumor growth promotion, and fine-tuning delivery timing remain (81). In summary, stem cells offer a flexible approach to RB treatment, delivering diverse therapies with high accuracy and low off-target effects, making them a promising tool for personalized cancer care (84) **(Table 2).**

Table 2. Types of cell therapy approaches in RB. This table provides an overview of the main cell therapy approaches in RB, summarizing their mechanisms, therapeutic potential, and key advantages and limitations. These strategies aim to control tumor growth, prevent recurrence, modulate the tumor microenvironment, and support retinal regeneration, offering promising avenues for improving current treatments while highlighting challenges that require further research.

Cell type\ Method	Applications in RB	Advantage	Disadvantage\challenges
HSCT	Patients with advanced or metastatic RB	Bone marrow recovery increases chemotherapy tolerance	Risk of infection, transplant rejection, and transplant-related death
iPSC-derived retinal organoids	Study of tumorigenesis, Testing of new drugs	Human model, Personalization	High cost, time-consuming, and Technical limitations
Targeting CSCs	Reducing tumor recurrence, Combating drug resistance	Reduce risk of recurrence, long-term effect	Accurate identification of CSCs, risk of side effects
MSC paracrine\Exosome therapy	Tumor growth inhibition, Drug delivery	Safe, low invasive, reduces systemic toxicity, and Accurate targeting	Variable effects in different Tumorigenic risk
Stem cells as a carrier	Targeted drug and gene delivery	Reduce systemic toxicity, Precise targeting	Safety, tumorigenic effects, and limited delivery

Limitations and Challenges

Stem cell therapies hold great potential for treating RB, but significant hurdles must be addressed before they can be widely used in clinics. MSCs have dual roles: they can deliver anti-cancer agents or modify the tumor environment, but they may also release factors that unintentionally promote tumor growth, blood vessel formation, or spread (85). To ensure MSCs only provide benefits, careful analysis and modification of these cells are crucial. Long-term safety remains a major concern, with risks including the potential for transplanted cells to form tumors, trigger immune reactions, or cause unintended effects, especially in children with RB. Genetically altered stem cells require rigorous testing to avoid risks like gene mutations or activation of cancer-causing genes. Despite their ability to target tumors, getting stem cells to reach eye tumors consistently is difficult due to barriers like the blood-retina barrier, fluid dynamics in the eye, and immune defenses. Optimizing delivery methods, cell doses, and timing is key to improving treatment success (86). RB's genetic and cellular diversity, including resistant CSCs, complicates stem cell treatments and highlights the need for therapies tailored to each patient's tumor profile (2, 87). Producing and testing stem cells consistently, including their exosomes, is vital for clinical use. Factors like growth conditions, cell passage, and donor differences can affect treatment outcomes, requiring strict protocols to meet regulatory standards (88). Most stem cell research for RB is still in lab or animal studies, with few human trials. While these models provide useful insights, clinical studies are needed to evaluate long-term effects, ideal dosing, and combinations with standard treatments (89). In summary, stem cell therapies offer exciting possibilities for RB, but thorough assessments of safety, tumor-specific effects, delivery approaches, and compliance with regulations are essential. Addressing these obstacles will unlock the full potential of stem cells in personalized RB treatment.

Conclusion

Stem cell technologies are reshaping the landscape of RB research and treatment. iPSCs and retinal organoids have become essential tools for uncovering disease mechanisms and testing new drugs, paving the way for personalized cancer care. The identification of CSCs underscores the need to target tumor-initiating cells to ensure lasting remission and address drug resistance. Meanwhile, MSC-derived factors and exosomes provide powerful carriers for delivering anticancer therapies directly to tumors, reducing harm to healthy tissues. HSC support remains a key complement to standard chemotherapy, enabling higher doses while limiting long-term side effects. Together, these strategies highlight how stem cell advances deepen our understanding of RB and lay the groundwork for innovative, patient-tailored treatments. Looking ahead, progress will depend on combining lab-based models with clinical applications, ensuring safety, and maximizing the combined impact of cellular and molecular therapies..

Author contribution

EB and **AN** designed the study, as well as collected and analyzed the data. **MM** was responsible for drafting and revising the manuscript. **PMS** provided supervision for the study and ensured the scientific accuracy of its content. All authors critically reviewed and gave their approval for the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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