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Review

Functional characterization and therapeutic potential of human umbilical cord blood mononuclear cells

Yu Zhang [a, b, c, 1], Yueda Lu [a, b, c, 1], Xinyue Hu [a, b, c, 1], Mengxing Jiang [a, b, c], Zhixiu Chen [a, b, c], Lingkun Jin [a, b, c], Min Li [a, b, c, ***], Chen Chen [d, **], Jianye Wang [a, b, c, *]

[a] Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, No 218 Jixi Road, Hefei 230022, Anhui, China
[b] The First Clinical College of Anhui Medical University, No 81 Meishan Road, Hefei 230032, Anhui, China
[c] Engineering Research Center of Biopreservation and Artificial Organs, Ministry of Education, No 81 Meishan Road, Hefei 230032, Anhui, China
[d] Department of Surgical Oncology, Anhui Provincial Children's Hospital, No.39 East Wangjiang Road, Hefei 230022, Anhui, China

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ABSTRACT

Human umbilical cord blood mononuclear cells (hUCB-MNCs) are a population of cells derived from neonatal cord blood, encompassing various stem cells and immune cells. The unique characteristics of hUCB-MNCs endow them with distinctive multifunctionality, including the promotion of angiogenesis, acceleration of tissue repair, regulation of immune responses, neuroprotection, alleviation of inflammatory reactions, enhancement of antioxidant capacity, reduction of fibrosis processes, and inhibition of apoptosis. These diverse biological properties underscore the significant clinical therapeutic potential of hUCB-MNCs, which are widely applied in the treatment of various diseases. This review aims to summarize the underlying mechanisms responsible for the multifunctional attributes of hUCB-MNCs, elucidating their potential modes of action in disease management and providing novel theoretical insights and practical guidance for their expanded application across different disease domains. By synthesizing current research findings, this review may provide insights into the potential clinical applications of hUCB-MNCs in the fields of regenerative medicine and cell therapy.

Contents

* Corresponding author. Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, No 218 Jixi Road, Hefei 230022, Anhui, China.
** Corresponding author. Department of surgical oncology, Anhui provincial children's hospital, No 39 Wangjiang Road, Hefei 230022, Anhui, China.
*** Corresponding author. Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, No 218 Jixi Road, Hefei 230022, Anhui, China.
E-mail addresses: liminzhi2009@126.com (M. Li), ccahsertyy@163.com (C. Chen), wangjianye9@126.com (J. Wang).
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[1] Yu Zhang, Yueda Lu and Xinyue Hu contributed equally to this work.

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1. Introduction

Human umbilical cord blood mononuclear cells (hUCB-MNCs) represent a highly promising cellular resource, extracted from the umbilical cord blood of newborns [1]. This population encompasses a variety of stem cells and immune cells [2]. The uniqueness of hUCB-MNCs lies in their multifunctionality. They not only effectively promote angiogenesis, which is crucial for improving blood circulation and repairing damaged blood vessels [3,4], but also accelerate the repair process of injured tissues, providing the possibility for rapid tissue recovery.

Moreover, the immunomodulatory capabilities of hUCB-MNCs are not to be underestimated. They can adjust the intensity and direction of the immune response according to the body's needs, which is vital for treating diseases caused by immune system imbalances [5]. hUCB-MNCs also exhibit significant efficacy in neuroprotection [6], anti-inflammatory [7], antioxidant [8], anti-fibrotic [8], and apoptosis-inhibiting biological processes [9]. These characteristics make hUCB-MNCs a cell therapy resource with broad therapeutic potential.

Currently, hUCB-MNCs have been applied in variety of diseases, encompassing fields such as cardiovascular diseases [10], neurological disorders [11], and autoimmune diseases [11]. Their therapeutic efficacy and safety have been validated to a certain extent, but to gain a deeper understanding and better utilize this resource, we need to explore the underlying molecular mechanisms more thoroughly.

The purpose of this paper is to systematically review and analyze existing research findings, aiming to delve into the multifunctional properties of hUCB-MNCs and their intrinsic molecular mechanisms. By analyzing their mechanisms of action in different disease models in detail, this paper will uncover the potential therapeutic mechanisms of hUCB-MNCs in disease treatment.

2. Human umbilical cord blood mononuclear cells

Mononuclear Cells (MNCs), primarily of diverse immune cells and hematopoietic stem cells, are a cell population defined by the presence of a single nucleus within the blood or tissue. Based on their source, MNCs can be classified into three types: bone marrow-derived (Bone Marrow Mononuclear Cells, BM-MNCs), peripheral blood-derived (Peripheral Blood Mononuclear Cells, PB-MNCs), and umbilical cord blood-derived (hUCB-MNCs). While these three types of MNCs share certain similarities, they also exhibit notable differences. The following table (Table 1) presents a comprehensive comparison of the characteristics of MNCs derived from these distinct origins.

hUCB-MNCs are a heterogenous population of mononuclear cells isolated from cord blood, comprising diverse stem cells and immune cells including hematopoietic stem cells, cord blood mesenchymal stem cells, endothelial progenitor cells, lymphoblasts, embryonic-like stem cells, and various lymphocyte subsets. The sourcing of these cells is widespread, with a non-invasive and safe extraction process that avoids ethical concerns. In comparison to BM-MNCs, UCB-MNCs demonstrate decreased immunogenicity due to the lower antigen presentation capacity and reactivity of their immature immune cells. Additionally, the incidence of graft-versus-host disease (GVHD) in allogeneic cord blood grafts is low, which contributes to the clinical safety of hUCB-MNCs [12]. hUCB-MNCs exhibit a broad expression of pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, and metalloproteinases [13], conferring upon them anti-inflammatory, angiogenic, chemotactic, and neuroprotective properties [14]. These attributes have established hUCB-MNCs as valuable assets in the field of regenerative medicine.

hUCB-MNCs, isolated from umbilical cord blood, include a minor population of umbilical cord mesenchymal stem cells, endowing them with certain mesenchymal stem cell (MSC) characteristics [15,16]. However, significant differences in biological properties, immunoregulatory functions, proliferative capacity, and differentiation potential exist between hUCB-MNCs and MSCs derived from other sources, such as bone marrow mesenchymal stem cells (BM-MSCs) and adipose tissue mesenchymal stem cells (AT-MSCs) (Table 2). hUCB-MNCs are a heterogeneous cell population comprising various immune cells and expressing diverse immunophenotypes, which collectively confer strong immunoregulatory capabilities [17]. Additionally, these cells harbor hematopoietic progenitor and stem cells with potent differentiation potential. hUCB-MNCs exhibit rapid proliferation and a low rate of cellular senescence [16]. In contrast, BM-MSCs are well-known for their robust differentiation capacity, although this potential diminishes with advancing age. The proliferative ability of BM-MSCs also declines with age [18]. Notably, the immunoregulatory function of BM-MSCs is less pronounced compared to that of hUCB-MNCs and AT-MSCs [19]. On the other hand, AT-MSCs are abundant, readily accessible, and characterized by low immunogenicity. Their immunoregulatory capacity exceeds that of BM-MSCs [20]. Furthermore, AT-MSCs exhibit strong proliferative and differentiation capacities; however, they are prone to cellular aging after multiple passages [21]. Despite the promising potential of hUCB-MNCs, BM-MSCs, and AT-MSCs in regenerative medicine, it is crucial to carefully consider their unique attributes when selecting the most suitable cell type for specific clinical applications.

2.1. hUCB-MNCs isolation

The isolation of mononuclear cells from human umbilical cord blood can be achieved through several well-established techniques (Table 3). The density gradient centrifugation is common method is density gradient centrifugation. This process leads to the formation of a distinct layer within the gradient, facilitating the retrieval of MNCs [22]. During the process of density centrifugal separation, hUCB-MNCs may encounter contamination from red blood cells and nucleated erythroid precursor cells. A novel technique has been developed utilizing mouse monoclonal antibodies targeting human glycophorin A and mouse immunoglobulin-coated magnetic beads.

Table 1
Comparison of mononuclear cells from three different origins.

Characteristic/ Origins	BM-MNCs	PB-MNCs	hUCB-MNCs
Collection method	Bone marrow puncture, painful and complex procedure.	Venous blood collection, relatively simple and convenient.	Cord blood collection, by-product of neonatal birth, painless.
Post-collection recovery time	Longer, donors need considerable time to recover.	Faster, donors return to normal activities shortly.	No recovery needed, does not affect donor health.
Cell types	Pluripotent stem cells, hematopoietic stem cells, immune cells.	Lymphocytes, monocytes, plasma cells	Hematopoietic stem cells, immune cells
Immune cell activity	High	High	Moderate
Cryopreservation	Requires cryopreservation, high demands on cryopreservation conditions.	Better short-term cryopreservation, long-term may affect cell viability.	Better long-term cryopreservation, less impact on antitumor activity
Application fields	Suitable for treating various malignant hematologic tumors and genetic diseases	Suitable for immune cell therapy, such as antitumor, antiviral, etc.	Suitable for treating various malignant hematologic tumors and genetic diseases.
Collection difficulty	High, requires professional operation and anesthesia.	Low, simple procedure, no anesthesia required.	Less ethical issues, considered a social by-product, no donor consent needed.
Ethical issues	Donor consent is required, potential ethical controversies.	Less ethical issues, considered a social by-product, no donor consent needed.	Less ethical issues, considered a social by-product, no donor consent needed.
Incidence of GVHD	High	High	Low

Table 2
Comparison of hUCB-MNCs and mesenchymal stem cells from different sources.

Characteristic/Cell Type	UCB-MNCs	BM-MSCs	AT-MSCs
Source	Umbilical cord blood	Bone marrow	Adipose tissue
Immunophenotype	Various immune cells, multiple phenotypes	Predominantly mesenchymal stem cell phenotype	Mesenchymal stem cell phenotype, low immunogenicity
Immune regulatory ability	High	Moderate	High
Proliferative capacity	Rapid proliferation, slow senescence	Decreased with age	High proliferation
Differentiation potential	High, including hematopoietic progenitors	High, age-dependent	High proliferation and differentiation, potential aging with passages
Acquisition difficulty	Relatively easy	Invasive procedure required	Relatively easy, obtainable via liposuction
Immunogenicity	Low	Moderate	Low
Age influence	Minimal	Proliferation and differentiation decline with age	Proliferation and differentiation may decline after multiple passages

Table 3
Comparison of five different separation methods.

Items/Methods	Density Gradient Centrifugation	Antibody-Magnetic Bead Purification	Modified Ficoll-Paque Gradient Method	Targeted CD45 Negative Selection	Endothelial Cell Conditioned Medium Culture
Principle	Uses cell density differences to separate on a density gradient medium through centrifugation	Uses specific antibodies and magnetic beads to remove unwanted cells	Improved gradient centrifugation method, enhances separation efficiency	Uses targeted CD45 markers to remove unwanted cell types	Cultivates in specific medium to promote monocyte differentiation
Purity	Moderate, prone to contamination from red blood cells and nucleated erythroid precursors	High, can obtain highly purified mononuclear cells	High, the number of separated cells exceeds that of the classic method	High, effectively enriches mononuclear cells	Moderate, targeted for the separation of specific types of progenitor cells
Cell viability	Moderate, lysis with ammonium chloride may damage cell function	High, reduces damage to lysosomal function	High	Moderate	High, suitable for cell differentiation
Time/Cost efficiency	Moderate	High	High, saves time and cost	Moderate	Low, requires long-term culture
Complexity of operation	Simple	Complex	Moderate	Complex	Complex
Special requirements	Requires density gradient medium	Requires specific antibodies and magnetic beads	Requires specific Ficoll-Paque medium	Requires precise technique	Requires specific culture medium

This innovative method enables the efficient purification of cord blood mononuclear cells, resulting in high purity, substantial yield, and enhanced cell viability [23]. Jia et al. employed a modified Ficoll-Paque gradient method to isolate the hUCB-MNCs. The number of cells isolated by this method far exceeded that of the classic approach, significantly saving time and cost [24].

An alternative method involves the targeted removal of unwanted cell types, such as red blood cells and granulocytes, by focusing on the CD45 marker. This selective approach enables the enrichment and isolation of mononuclear cells through the negative selection of CD45 [25]. Furthermore, a distinct method involves culturing mononuclear cells from human umbilical cord blood in

endothelial cell conditional medium to generate various endothelial progenitor cell subtypes [26]. In conclusion, the extraction of mononuclear cells from human umbilical cord blood commonly involves techniques such as density gradient centrifugation, negative selection based on CD45, and culture under specific conditions to obtain diverse cell subpopulations.

2.2. hUCB-MNCs proliferation

The proliferation capacity of hUCB-MNCs plays a pivotal role in their regenerative potential. Various studies have investigated the factors and conditions that influence the proliferation of hUCB-MNCs. IL-15 can enhance the expression of CD4+ CD45RA+ cells within hUCB-MNCs and reduce the expression of CD45RO+ cells [27]. Researchers investigated the effects of IL-15 and IL-12 on the apoptosis and proliferation of hUCB-MNCs, finding that both factors, when used alone or in combination, reduced cell viability. The combined treatment also increased the apoptosis rate of CD8+ and CD56+ subsets, the percentage of proliferating cells, and elevated the expression level of CD95 [28].

Research has found that type 4 phosphodiesterase is involved in the proliferation of hUCB-MNCs. After adding inhibitors of different types of phosphodiesterases, only the type 4 and non-selective inhibitors were able to suppress the proliferation of hUCB-MNCs, indicating that type 4 phosphodiesterase plays a role in the regulation of cell proliferation, and enhancing its activity may promote cell proliferation [29]. The proliferation of mononuclear cells in human umbilical cord blood plays a critical role in their regenerative and therapeutic potential. Understanding the factors and conditions influencing their proliferation is imperative for maximizing the utility of these cells across various medical applications.

2.3. hUCB-MNCs storage

The storage methods for hUCB-MNCs primarily consist of cryopreservation at low temperatures and lyophilization for room temperature storage. Cryopreservation at low temperatures halts the metabolic processes of cells, delaying cell aging and death, thereby extending cell lifespan. Moreover, cryopreservation preserves the morphological structure and biological function integrity of cells, reducing the risk of cell damage during storage [30]. However, cryopreservation may induce freezing damage, impacting cell secretion function and viability. Therefore, the development of an optimal cryopreservation medium is essential. Parekh et al. introduced a cryopreservation solution with taurine as the central component. Experimental validation revealed that the optimal taurine concentration in the cryoprotective solution is 3 mmol/L. At this concentration, the survival rate of hUCB-MNCs reached 89 % (compared to 83 % in the control group), with a 50 % reduction in apoptotic cells. Additionally, transcription factors exhibited significantly higher expression levels compared to conventional preservation methods [31]. This approach not only enhances the viability of hUCB-MNCs but is also straightforward, feasible, and cost-effective, presenting a new option for cell cryopreservation.

Lyophilization for room temperature storage offers improved cell viability compared to cryopreservation at low temperatures. Nonetheless, lyophilized cells often display compromised membrane integrity and reduced viability. To tackle this challenge, researchers optimized lyophilization conditions and supplemented the cryoprotective solution with the antioxidant EGCG, which mitigated cell membrane damage and enhanced cell viability [32]. The following table offers the comparison of the two storage methods (Table 4).

3. Functional characteristics of HUCB-MNCs

hUCB-MNCs exert therapeutic effects on a wide range of diseases primarily through the secretion of various cytokines [14,33]. They exhibit diverse functionalities, including the promotion of angiogenesis [34–36], regulation of immune responses [37], anti-inflammatory and antioxidant activities [38], neuroprotection [6], reversal of fibrosis [10], enhancement of tissue regeneration [9], and inhibition of apoptosis [39] (Fig. 1).

3.1. Angiogenesis

Angiogenesis, the process of new blood vessel growth from pre-existing vessels, plays a crucial role in tissue development following injury, wound healing, and the restoration of blood flow and oxygen supply. Regarding the molecular mechanisms underlying the promotion of angiogenesis by hUCB-MNCs, numerous studies have been conducted, with conclusions primarily focusing on two key aspects: the release of relevant cytokines or differentiation into vascular endothelial cells (Fig. 2).

hUCB-MNCs can secrete various angiogenic and endothelial cell proliferation factors (such as VEGF, IGF-1, CD31+) to facilitate angiogenesis [39–42]. And the secretion of these cytokines by hUCB-MNCs is significantly enhanced under hypoxic conditions, surpassing 100 % of the levels observed under normal aerobic conditions. In recent years [39], emerging studies have utilized gene engineering to produce adenovirus-transfected hUCB-MNCs, which have shown promising outcomes for vascular regeneration. Salafutdinov et al. found that genetic modification of hUCB-MNCs can lead to the simultaneous overexpression of vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and stromal cell-derived factor 1α (SDF1α), thereby promoting the formation of new blood vessels. Importantly, these genetically engineered cells maintain their cytokine and growth factor secretion profile, making them a safer and more effective option for angiogenesis treatment compared to direct gene therapy [35,36].

Moreover, hUCB-MNCs can stimulate angiogenesis through differentiation into vascular endothelial cells [43,44]. This is attributed to the presence of endothelial progenitor cells within hUCB-MNCs, which can directly contribute to the formation and repair of damaged blood vessels [45]. A comprehensive analysis of DNA methylation and gene expression has revealed that during the differentiation of hUCB-MNCs into oligodendrocyte precursor cells (OECs), alterations in DNA methylation occur and are closely associated with gene expression regulation. The study identified hypermethylated downregulated genes, such as CD74, VAV1, TLR8, and NCF4, as well as hypomethylated upregulated genes, including ECSCR, MCAM, PGF, and ARHGEF15. The hypermethylated downregulated genes are enriched in immune-related functions, while the hypomethylated upregulated genes are enriched in developmental processes and angiogenesis, indicating a significant role for DNA methylation in the regulation of differentiation [3].

The therapeutic potential of hUCB-MNCs in promoting angiogenesis has been validated in the clinical management of a wide array of diseases, including bronchopulmonary dysplasia [46,47], cardiovascular disorders such as myocardial infarction [10,41,48] and myocardial injury [49], and central nervous system diseases like stroke [11], ischemic brain injury [50], and spinal cord injury [51] (Table 5). The therapeutic mechanism of these cells primarily depends on the secretion of a diverse array of bioactive cytokines, which effectively stimulate vascular repair and regeneration. By releasing key cytokines, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (βFGF), and angiopoietins (Ang), hUCB-MNCs play a critical role in the reconstruction of the vascular network in damaged tissues, activating endogenous

Table 4
Comparison of two storage methods.

Characteristics/ Methods	Cryopreservation	Room temperature storage via lyophilization
Cell viability	Lead to cell death or functional impairment due to freezing damage	Higher cell viability, further improved by optimizing freeze-drying conditions
Cell structure	Better preservation of cell morphology and biological function integrity	Forms a stable solid structure, protecting cells from environmental factors
Preservation damage	Freezing damage may lead to cell death or functional impairment	Optimized to reduce cell membrane damage, improving cell viability
Preservation medium	Requires specific cryoprotective solutions, such as those with a taurine core	Requires optimized cryoprotective solutions and antioxidants, such as adding EGCG
Operational simplicity	Requires precise control of the freezing and storage conditions	Relatively simple and feasible by optimizing the lyophilization process
Cost-effectiveness	Cost may be higher, especially due to the need for low-temperature equipment	More cost-effective, suitable for large applications
Environmental stability	Requires a stable low-temperature environment, sensitive to temperature changes	Stable solid structure, less affected by environmental factors
Cell function	May affect the secretion function of cells	Better preservation of cell function, especially through optimized preservation methods
Preservation time	Can be stored for a long time	Can be stored for an extended period at room temperature

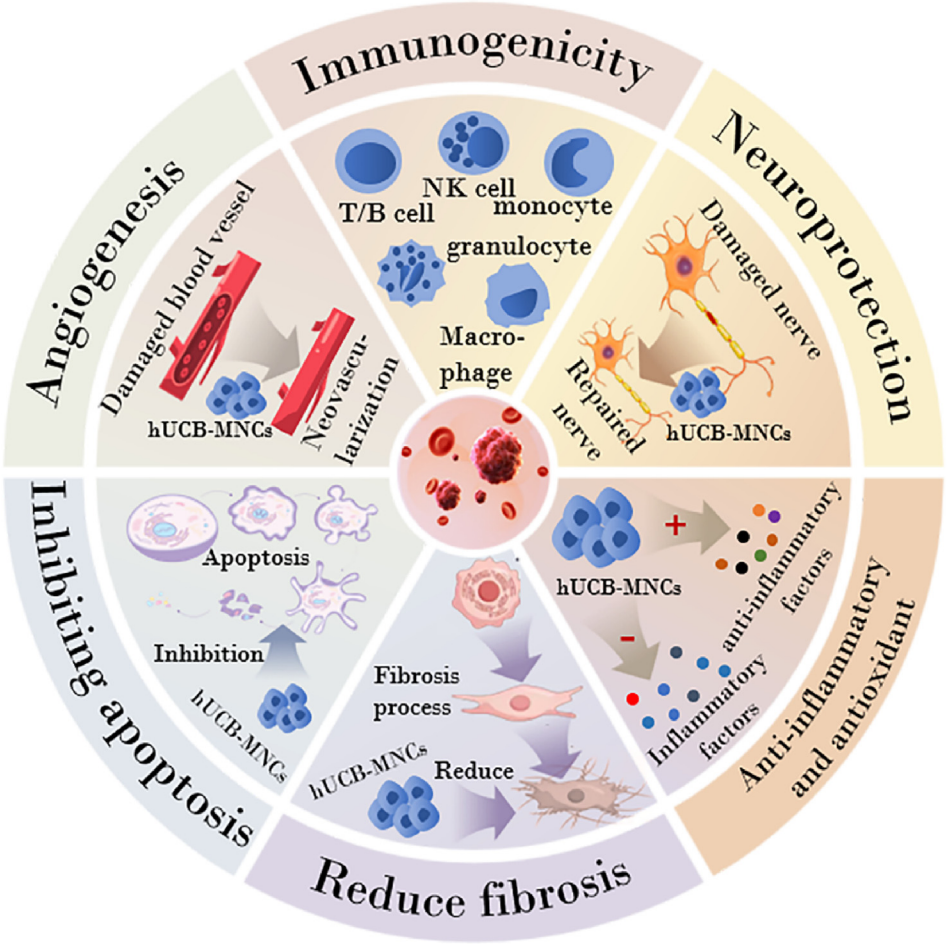

Fig. 1. The functional characteristics of human umbilical cord blood mononuclear cells (hUCB-MNCs).

repair processes. This paracrine effect not only expedites vascular repair but also provides crucial support for the functional recovery of impaired tissues, positioning hUCB-MNCs as a promising tool in the field of regenerative medicine. hUCB-MNCs exhibit significant potential for promoting angiogenesis and can be utilized in the treatment of various ischemic diseases and tissue injuries.

3.2. Immunogenicity

hUCB-MNCs possess the capacity to harbor or differentiate into various immune cell types, including common types such as monocytes/macrophages, B lymphocytes, T lymphocytes, natural killer (NK) cells, and dendritic cells (Fig. 3A). Functioning as

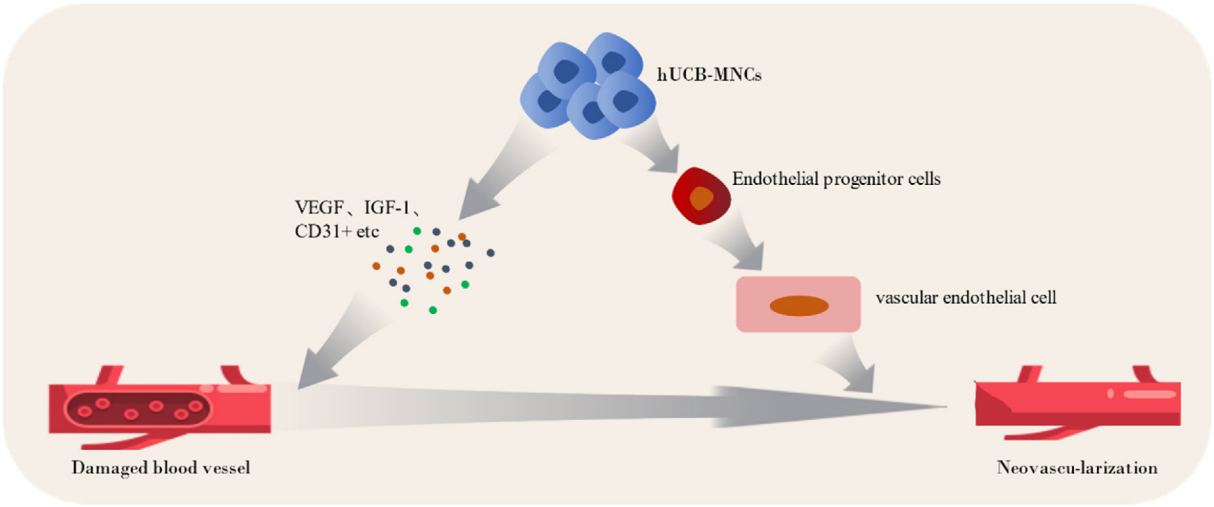

Fig. 2. hUCB-MNCs promote angiogenesis. hUCB-MNCs secreting cytokines (VEGF, IGF-1, CD31+ etc.) to promote angiogenesis; hUCB-MNCs contain endothelial progenitor cells that transform into vascular endothelial cells.

Table 5
The key factors mediating the angiogenic effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Bronchial dysplasia	[46]	2021	VEGF (+)
Myocardial infarct	[41]	2006	VEGF164(+), VEGF188(+)
Myocardial injury	[52]	2010	Ang-1(+), Ang-2(+), VEGF (+)
Stroke	[53]	2018	VEGF (+)
Ischemic brain injury	[50]	2017	VEGF (+), Ang-1(+), Tie-2(+)
Bladder dysfunction	[54]	2019	HIF-1α (+), VEGF (+)
Spinal cord injury	[55]	2017	VEGF (+)
Ischaemic bowel disease	[56]	2024	VEGF (+), βFGF (+)
Intrauterine adhesion	[42]	2024	VEGF (+), IGF-1(+)

antigen-presenting immune cells, they are characterized by significant amoeboid movements, enabling them to phagocytose and eliminate damaged, senescent cells and debris, while also defending against and eradicating invasive pathogens [37]. Studies have indicated that monocytes/macrophages derived from hUCB-MNCs exhibit a limited capacity for antigen presentation, attributed to their immature state [57,58].

Neonatal B lymphocytes can generate IgM antibodies comparable to those of adults, although they demonstrate reduced capability in producing IgG or IgA [59]. B lymphocytes within hUCB-MNCs are inclined to express IgM antibodies (Fig. 3B), with a majority of these IgM-positive B cells also expressing the CD5 antigen [60]. Research by Gluckman and colleagues has revealed that approximately 68 % of CD19-positive cord blood B cells exhibit CD5 antigen positivity [61].

Moreover, investigations have shown that the phenotypic analysis of T lymphocyte subsets (CD4, CD8) does not reveal significant differences between adult blood and cord blood. Neonatal T cells exhibit lower levels of IL-2 receptors and HLA-DR compared to adult T cells (Fig. 3B). Umbilical cord blood T cells produce IL-2 and express functional IL-2R complexes, particularly high-affinity IL-2R complexes and HLA-DR, at levels significantly lower than those of adult T cells. These functional attributes may be linked to the immaturity of cord blood T cells [17]. In terms of cord blood NK cells, research has identified four subsets: CD56hiCD16−, CD56loCD16−, CD56+CD16+, and CD56−CD16+ (Fig. 3B). Furthermore, it has been observed that cord blood NK cells can be categorized into the same four subsets, each exhibiting variations in the expression of adhesion molecules and memory cell markers [62].

Studies have utilized immunophenotypic comparison to evaluate the heterogeneity of unsorted and sorted hUCB-MNCs. The results suggest that sorted mononuclear cells are enriched with a population of primitive stem cells, while unsorted mononuclear cells and those with depleted mitochondria are abundant in progenitor cells. Consequently, the combined utilization of these two sorted populations may serve as a valuable alternative for the treatment of hematologic/heritable diseases. This research provides insights into the application of cell enrichment techniques in regenerative medicine for cell-based therapies [63].

hUCB-MNCs primarily exert potent immunostimulatory effects by generating immune cells with diverse immunophenotypes, a characteristic that has been extensively applied in the clinical treatment of various diseases, including chronic liver injury [64], asthma [65], ataxia [66], multiple system atrophy [67], as well as gastrointestinal cancer [68], and lymphoma [69] (Table 6). hUCB-MNCs can effectively boost the body's immune response by modulating the activity and function of immune cells, thereby promoting disease remission and recovery, and serving as a beneficial adjunct to traditional treatments for these conditions.

The relatively low immunogenicity of hUCB-MNCs positions them as an appealing resource for immunomodulatory transplantation, particularly for patients lacking fully matched HLA donors. However, when considering umbilical cord blood transplantation, it is crucial to assess HLA compatibility and evaluate potential immunological risks.

3.3. Neuroprotection

hUCB-MNCs play a crucial role in neuroprotection, involving unique mechanisms of action such as anti-inflammatory and antioxidant effects, immunomodulation, promotion of angiogenesis, secretion of trophic factors, and cellular differentiation [71]. Here, we examine the primary mechanisms of action of hUCB-MNCs in various neuroprotection scenarios based on several studies.

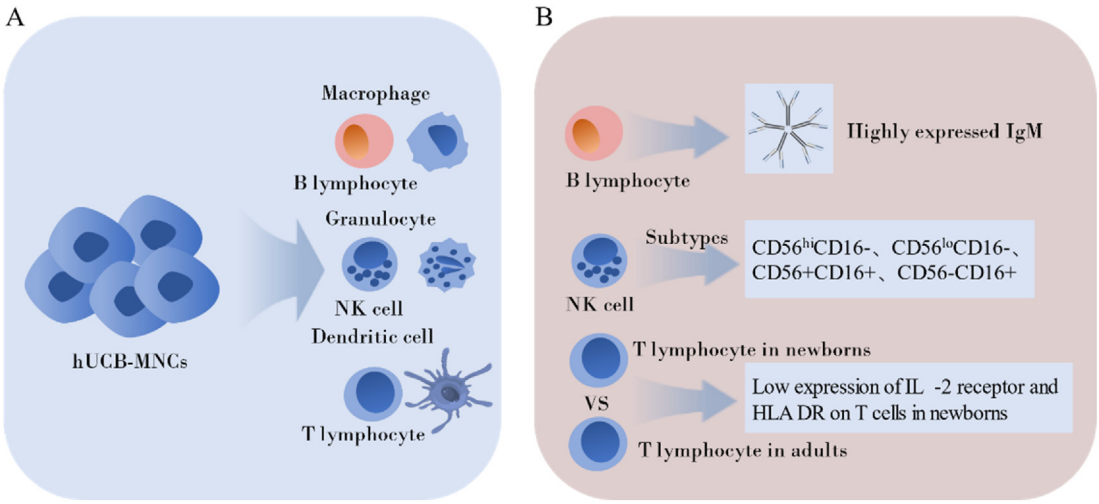

Fig. 3. Immunological functional characteristics of hUCB-MNCs. (A) hUCB-MNCs contain immune cells (B lymphocyte, macrophage, granulocyte, NK cell, dendritic cell, T lymphocyte etc.); (B) High expression of IgM antibodies in B lymphocytes of hUCB-MNCs; Four subtypes of NK cells in hUCB-MNCs; T lymphocytes in hUCB-MNCs express lower levels of IL-2 receptor and HLA DR compared to adult T lymphocytes.

Table 6
The key factors mediating the Immunogenicity effects of hUCB-MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Chronic liver injury	[64]	2009	CD45+T/B (+)
Asthma	[65]	2023	CD4+CD8+ T (−), CD4−CD8− T (−), CD4+CD8− T (+)
Ataxia	[66]	2011	IgG (+), IgA (+), Total T (+), CD 3+CD 4 T (+)
Multiple system atrophy	[70]	2021	CD4(−), CD 4/CD 8(+)
Gastrointestinal cancer	[68]	2017	CD 3 + T (+), CD 4 + T (+), CD 8 + T (+), IFNγ(+), TNFγ(+)
Lymphoma	[69]	2016	CD 3-CD 56 + NK (+), NKG 2A (−), NKp 44(+), CD 69(+)

Studies have shown that hUCB-MNCs can enhance the survival of microglial cells by modulating the autophagic process in response to bacterial infection. Specifically, hUCB-MNCs support the survival of microglial cells by reducing autophagy levels and downregulating the expression of cytokines TNF-α and IL-6 (Fig. 4A), which is beneficial for microglial cell survival [38]. However, a limitation of this study is the lack of detailed exploration into the specific mechanisms of action of hUCB-MNCs.

In the context of spinal cord injury, hUCB-MNCs may aid in the repair of the damaged area by secreting GDNF (glial cell-derived neurotrophic factor). GDNF, a neurotrophic factor, promotes the proliferation and migration of Schwann cells. These Schwann cells can migrate to the injured site and contribute to the formation of functional myelin, essential for nerve impulse transmission. Therefore, the mechanism through which hUCB-MNCs facilitate spinal cord injury repair may be linked to their capability to enhance GDNF secretion (Fig. 4B) [51,55,72–75].

hUCB-MNCs that overexpress GDNF have shown positive outcomes in Alzheimer's disease treatment [76]. In addressing neurodegenerative conditions like Parkinson's disease, hUCB-MNCs primarily exert therapeutic effects through differentiation into neurons and dopaminergic neurons [77]. A study involving the co-culture of murine fibroblasts with hUCB-MNCs revealed that these cells underwent neuronal differentiation, expressed specific pluripotent genes, and neuronal markers, offering a novel perspective on utilizing fibroblasts in neural regeneration and the management of neurological disorders [78].

In the realm of optic nerve injury treatment, hUCB-MNCs have been observed to elevate the levels of growth-associated protein-43 (GAP-43) and hypoxia-inducible factor-1α (HIF-1α) (Fig. 4C), indicating their potential to enhance axonal survival through systemic mechanisms involving GAP-43 and HIF-1α [79].

hUCB-MNCs exhibit the ability to attenuate neuronal apoptosis in conditions of cerebral ischemia and hypoxia (Fig. 4D), primarily attributed to the upregulation of Bcl-2 protein expression and the downregulation of Bax protein expression [80]. These discoveries collectively highlight the multifunctionality and promise of hUCB-MNCs in neural repair and treatment.

The neuroprotective properties of hUCB-MNCs make them a versatile candidate for treating neural [80] or spinal cord injuries [55], brain damage [81], and neurodegenerative diseases [82]. Despite the encouraging results from laboratory investigations and clinical trials, the utilization of hUCB-MNCs in clinical settings necessitates further exploration to validate their safety and efficacy, thereby defining their precise role in managing these intricate neurological conditions.

hUCB-MNCs play essential roles in neuroprotection and repair through the secretion of neurotrophic factors, showcasing significant therapeutic effectiveness in restoring impaired nervous systems. This mechanism has been substantiated and applied in the clinical management of diverse neurological ailments, including perinatal brain injury [83], stroke [11], ischemic brain injury [53], Alzheimer's disease [76], and spinal cord injury [55] (Table 7). The neurotrophic factors released by hUCB-MNCs promote neuronal survival, stimulate axonal regeneration, facilitate myelin repair, and modulate neuroinflammatory responses, offering a fresh perspective and potential therapeutic approaches for addressing these diseases clinically.

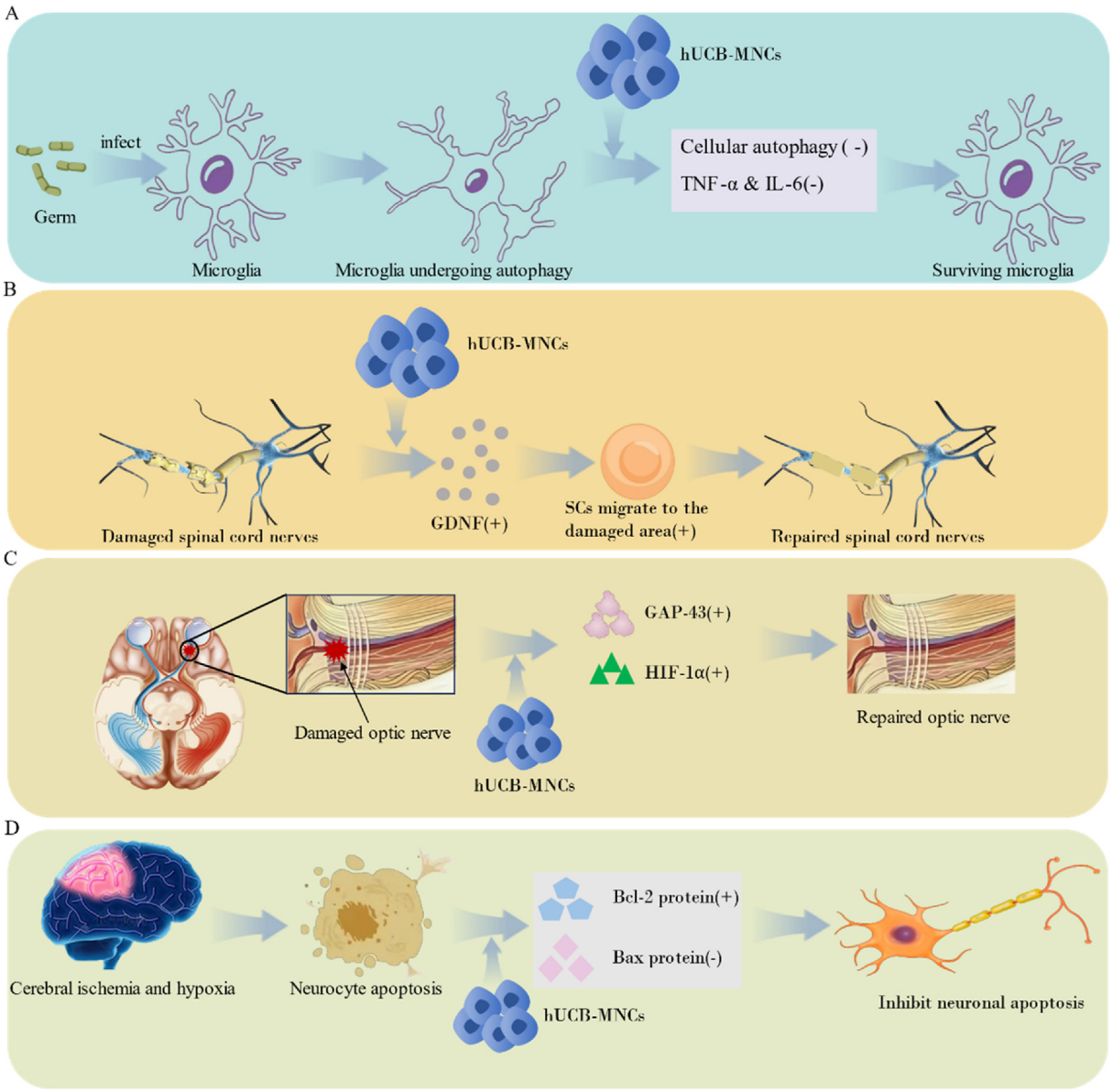

Fig. 4. The neuroprotective function of hUCB-MNCs. (A) hUCB-MNCs alleviate autophagy in microglia infected with bacteria; (B) hUCB-MNCs promote the repair of damaged spinal cord by promoting the secretion of GDNF; (C) hUCB-MNCs promote the repair of damaged optic nerves by increasing GAP-43 levels and HIF-1 α expression; (D) hUCB-MNCs can alleviate neuronal apoptosis under cerebral ischemia and hypoxia conditions.

3.4. Anti-inflammatory and antioxidant

hUCB-MNCs, contain multiple types of immune cell, demonstrate significant potential in anti-inflammatory and antioxidant capacities. hUCB-MNCs regulate immune responses by harboring diverse immature stem/progenitor cells capable of differentiating into T cells, natural killer cells, dendritic cells, and other immune cells. These cells modulate immune responses and diminish the production of inflammatory factors (interleukin-6, interleukin-2, tumor necrosis factor, etc.) (Fig. 5A), thereby exerting anti-inflammatory effects [17]. Moreover, they facilitate the resolution of inflammation by differentiating into macrophages, which can phagocytose and eliminate injured, aged cells and their debris in the inflammatory site (Fig. 5A), thereby aiding in the resolution of inflammation [5]. Additionally, hUCB-MNCs secrete anti-inflammatory factors such as interleukin-10 (IL-10), interleukin-13 (IL-13), and transforming growth factor (TGF) (Fig. 5A), which can mitigate inflammatory responses and alleviate tissue damage [33].

The anti-inflammatory characteristics of hUCB-MNCs serve as a solid foundation for their clinical application, with the key mechanism centered on enhancing the secretion of a range of anti-inflammatory factors while inhibiting the production of pro-inflammatory factors. This precise regulatory mechanism significantly dampens inflammatory responses, offering novel avenues for treating various diseases. The anti-inflammatory function of hUCB-MNCs is particularly crucial in managing common conditions like acute liver injury [9], renal interstitial fibrosis [85], ischemic brain injury [50], bronchopulmonary dysplasia [47], myocardial injury [52], and stroke [11] (Table 8). By modulating the inflammatory milieu, hUCB-MNCs not only directly alleviate inflammatory symptoms but also indirectly promote the repair and regeneration of damaged tissues, thereby enhancing the overall efficacy of disease treatment and improving patient recovery rates.

hUCB-MNCs exert antioxidant effects primarily encompass the following aspects. By scavenging free radicals, the cellular components of umbilical cord blood mononuclear cells can effectively eliminate free radicals in the body (Fig. 5B), such as superoxide anions and hydroxyl radicals, which are key contributors to oxidative stress [86]. By enhancing antioxidant enzyme activity, hUCB-MNCs can boost the levels of antioxidant enzymes in the body (Fig. 5B), such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), thereby enhancing cellular antioxidant capacity. For instance, hUCB-MNCs can induce antioxidant effects through the Keap1-Nrf2 pathway. hUCB-MNCs significantly elevate Keap1 activity, thereby enhancing Nrf2 activity (Fig. 5B). Moreover, Nrf2 can regulate the activity of its downstream enzyme, heme oxygenase-1 (HO-1), which aids in heme degradation. Heme is a molecule that can generate free radicals, leading to oxidative stress and cellular damage. HO-1 reduces free radical production by breaking down heme, thus reducing the risk of oxidative stress. The byproducts of heme degradation, such as bilirubin, biliverdin, and carbon monoxide, capable of promoting cell repair. Additionally, hUCB-MNCs promote cellular repair as the stem and progenitor cells exhibit robust proliferation and differentiation capabilities, facilitating the repair and regeneration of damaged cells (Fig. 5b), thereby mitigating oxidative stress-induced damage [87].

Table 7
The key factors mediating the Neuroprotection effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Perinatal brain injury	[12]	2022	GDNF (+), NGF (+), BDNF (+)
Stroke	[53]	2018	TUJ 1 (+)
Ischemic brain injury	[84]	2019	GFAP (+), MBP (+)
Apoplexy	[11]	2014	BDNF (+), reelin (+), GPx-4(+)
Alzheimer's disease	[76]	2019	GDNF (+)
	[82]	2017	NGF (+)
Parkinson	[77]	2016	Tuj 1(+), MAP 2(+), GFAP (+)
Optic nerve injury	[79]	2016	GAP-43(+), HIF-1α (+)
Spinal cord injury	[73]	2018	NTFs (+)
	[55]	2017	GDNF (+)

Table 8
The key factors mediating the anti-inflammatory effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Acute liver injury	[9]	2022	IL-6(−), TNF-α(−), IFNγ(−), IL-17α(−), Cxcl 1(−), Cxcr 1(−)
Renal interstitial fibrosis	[85]	2020	NLRP3(−)
Asthma	[65]	2023	IL-5(−), IL-13(−), IL-17(−)
Bronchial dysplasia	[47]	2013	IL-1β(−)
	[46]	2021	IL-6(−), IL-1β(−), TNFα(−),IL-10(−)
Myocardial injury	[52]	2010	TNF(−), IFNγ(−), IL-1β(−), IL-2(−), IL-6(−), IL-10(+)
Perinatal brain injury	[12]	2022	IL-10 (+)
Ischemic brain injury	[81]	2023	IL-6(−), TNF-α(−), IL-4(+), IL-10(+)
	[50]	2017	NF-κB(−), NLRP3(−)
	[89]	2020	TLR 4(−), pNF-κB (−), IL-6β(−)
Apoplexy	[11]	2014	IL-2(−), IL-6(−)
Multiple system atrophy	[70]	2021	TNF-α(−), IL-6(−)

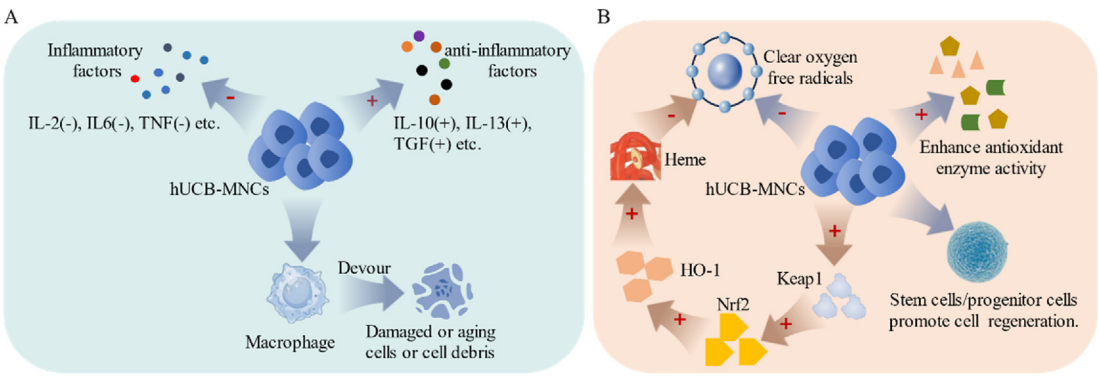

Fig. 5. The anti-inflammatory and antioxidant effects of hUCB-MNCs. (A) Secreting inflammatory factors (IL-2,IL-6, TNF etc.); hUCB-MNCs differentiate into macrophages to clear, engulf damaged, and senescent cells and cell debris; Secreting anti-inflammatory factors (IL-10, IL-13, TGF etc.); (B) hUCB-MNCs clear oxygen free radicals; hUCB-MNCs enhance antioxidant enzyme activity; hUCB-MNCs resist oxidation through the Keap 1-Nrf 2 pathway; Stem cells and progenitor cells in hUCB-MNCs promote the repair and regeneration of damaged cells, reducing oxidative stress-induced damage.

The antioxidant capabilities of hUCB-MNCs are a crucial aspect of their fundamental actions. In conjunction with their anti-inflammatory effects, they establish a dual defense mechanism against oxidative stress and inflammatory responses. Through their antioxidant properties, hUCB-MNCs efficiently eliminate free radicals from the body, reducing cellular damage induced by oxidative stress, and playing a beneficial role in the pathological processes of various diseases, including but not limited to, acute liver injury [9], renal interstitial fibrosis [85], ischemic brain injury [50], and diabetes skin wound [88] (Table 9). In this context, hUCB-MNCs not only alleviate stress-related tissue damage but also promote the repair and regeneration of damaged tissues by modulating inflammatory responses, thereby enhancing disease prognosis and improving patients' quality of life.

hUCB-MNCs exhibit significant clinical application value in the realms of anti-inflammation and antioxidation through various mechanisms, including immune response regulation, inflammation resolution promotion, free radical clearance, antioxidant enzyme activity enhancement, and cellular repair facilitation.

3.5. Reduce the progression of fibrosis

hUCB-MNCs have exhibited potential in inhibiting the fibrosis process, a pathological condition characterized by the excessive deposition of collagen and other extracellular matrix proteins, leading to tissue structural alterations and impaired organ function. The TGF-β-Smad2/3 signaling pathway plays a pivotal role in the fibrosis process [91]. Fibrosis is typified by the abnormal accumulation of extracellular matrix (ECM), resulting in tissue structural and functional abnormalities. In fibrotic disorders, the TGF-β-Smad2/3 signaling pathway is commonly dysregulated, facilitating fibrotic progression [92]. Through the inhibition of the TGF-β-Smad2/3 signaling pathway, hUCB-MNCs effectively downregulate the expression levels of TGF-β and Smad2/3, thereby markedly impeding fibrosis progression (Fig. 6A). Furthermore, hUCB-MNCs promote increased E-cadherin expression while reducing N-cadherin expression. These notable biological effects indicate that hUCB-MNCs possess the capability to reverse the epithelial-mesenchymal transition (EMT) process (Fig. 6A), offering novel perspectives and potential intervention strategies for fibrosis and related conditions [42].

hUCB-MNCs have demonstrated substantial therapeutic potential in attenuating the fibrotic process, primarily by effectively inhibiting the production of key substances that drive fibrosis. This mode of action involves multiple biological pathways, including suppression of fibrogenic factors expression, regulation of extracellular matrix deposition, and inhibition of inflammatory responses. hUCB-MNCs have been applied in the treatment of various fibrotic diseases, proving particularly effective in addressing common conditions such as renal interstitial fibrosis [85], bronchopulmonary dysplasia [13], and intrauterine adhesions [42] (Table 10). Through this mechanism, hUCB-MNCs not only decelerate fibrosis progression but also facilitate tissue structure and function repair, offering effective treatment for patients and playing a crucial role in enhancing disease prognosis.

Table 9
The key factors mediating the antioxidant effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Acute liver injury	[9]	2022	Duox 2(−), Nox 3(−)
Renal interstitial fibrosis	[85]	2020	ROS(−)
Renal injury	[8]	2020	MDA(−), SOD (−), Nrf2(−), HO-1 (−)
Ischemic brain injury	[50]	2017	ROS(−), GSH(−), SOD(−), CAT(−)
Diabetes	[88]	2014	CAT(+), NO(+), MDA(+)
Erectile dysfunction	[90]	2023	NOS/cGMP(−)
Ischaemic bowel disease	[56]	2024	NO(−)

Table 10
The key factors mediating the reduce fibrosis effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Renal interstitial fibrosis	[85]	2020	α-SMA(−)
Bronchial dysplasia	[47]	2013	TGF-β3(−)
	[46]	2021	TGF-β(−), MMP-9(−)
Intrauterine adhesion	[42]	2024	a-SMA(−), COL 1A1(−), TGF-β(−), Smad2(−), E-cadherin(+), N-cadherin(−)

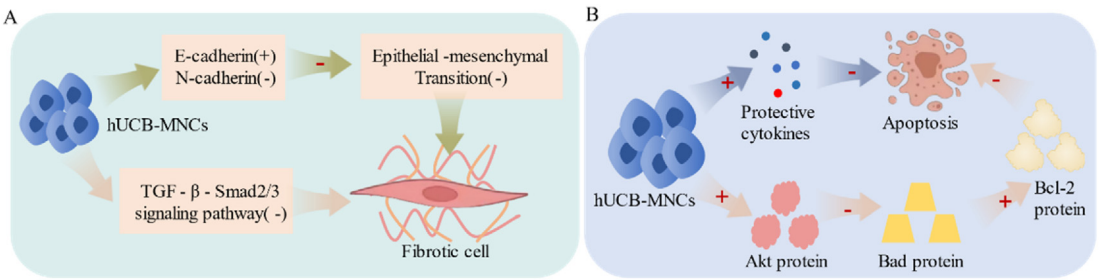

Fig. 6. hUCB-MNCs inhibit fibrosis process. (A) hUCB-MNCs inhibit the TGF - β - Smad2/3 signaling pathway; hUCB-MNCs promote the expression of E-cadherin, reduce the expression of N-cadherin, and reverse the EMT process; (B) hUCB-MNCs inhibit cell apoptosis through Akt/Bcl-2 signaling pathway; hUCB-MNCs secrete protective cytokines (SCF, IL-6, IL-10 etc.) to inhibit cell apoptosis.

Table 11
The key factors mediating the inhibiting apoptosis effects of hUCB MNCs in diverse therapeutic applications.

Disease Types	Related Research	Published Year	Key Factors
Renal interstitial fibrosis	[85]	2020	Caspase-3(−)
Myocardial infarction	[39]	2013	p-Akt(+), Bcl-2(+), eNOS(+)
Myocardial injury	[49]	2012	p-Akt(+), Bcl-2(+)
Perinatal brain injury	[12]	2022	TNF-α(−), TNFR 1(−), TNFR 2(−), CD 40(−), Fas(−), caspase-3(−)
Ischemic brain injury	[80]	2016	Bax(+), Bcl-2(+)

3.6. Inhibiting apoptosis

Apoptosis, also referred to as programmed cell death, comprises a series of regulated cellular death processes that hold significance in both normal physiological and pathological conditions [93]. Studies have demonstrated that hUCB-MNCs can impede apoptosis by activating survival proteins such as Akt and Bcl-2 family proteins, thereby inhibiting apoptosis. Akt protein kinase inhibits apoptosis by phosphorylating Bad proteins, which in turn activate Bcl-2-related proteins (Fig. 6B). Furthermore, Akt protein kinase stimulates nitric oxide synthase (eNOS) in endothelial cells to generate nitric oxide (NO), further suppressing apoptosis [39].

hUCB-MNCs not only possess the capability to inhibit apoptosis by secreting a range of protective cytokines, such as stem cell factor (SCF), interleukin-6 (IL-6), interleukin-10 (IL-10), among others (Fig. 6B) [14,33], but also effectively counteract the effects of apoptosis by promoting cell proliferation and differentiation, thereby playing a crucial role in maintaining tissue homeostasis and facilitating injury repair. hUCB-MNCs demonstrated a protective effect against CCl4-induced acute liver injury by upregulating IL-22. Experimental findings revealed that hUCB-MNCs treatment enhanced hepatic regeneration and activated STAT3 phosphorylation in a CCl4-induced liver injury model. This indicates that hUCB-MNCs ameliorate hepatocyte necrosis and stimulate liver regeneration by elevating IL-22 levels [9].

Through their distinctive paracrine function, hUCB-MNCs release various bioactive cytokines and effectively impede the apoptotic process by activating multiple signaling pathways. This mechanism serves as a crucial shield for protecting tissues from damage induced by diverse diseases. hUCB-MNCs not only decrease disease-related cell death but also promote cell survival. In clinical settings, this cytoprotective mechanism has demonstrated promising therapeutic potential in managing various diseases. For instance, in conditions like renal interstitial fibrosis [85], myocardial infarction [39], perinatal brain injury [12], and ischemic brain injury [80], the application of hUCB-MNCs has significantly reduced apoptosis, protecting affected tissues from further damage (Table 11). In this manner, hUCB-MNCs contribute to slowing disease progression, offering novel therapeutic avenues for patients and showcasing substantial potential in enhancing therapeutic effectiveness and patients' quality of life.

4. Future perspectives

Human umbilical cord blood mononuclear cells (hUCB-MNCs) hold significant promise for tissue repair and the treatment of various diseases. These cells have emerged as a focal point in regenerative medicine [79] owing to their straightforward isolation method, high proliferative potential, self-renewal capability, and low immunogenicity. However, the application of hUCB-MNCs is constrained by factors like inter-individual variances, genetic influences, and optimal timing of transplantation, which necessitate further exploration in future investigations [94].

In this review, we delve into the diverse mechanisms of action of hUCB-MNCs and their application across different diseases, emphasizing the key molecules involved. These diseases encompass a broad spectrum, including heart diseases, neurodegenerative disorders, liver conditions, immune system ailments, and cancers. While many studies are still in the animal model phase, these discoveries lay the groundwork for forthcoming clinical investigations and offer an optimistic outlook on the utilization of hUCB-MNCs in human disease treatment. To ensure the safety and efficacy of hUCB-MNCs therapy and to enhance comprehension of their mode of action, future endeavors should entail more extensive, multicenter clinical trials. We anticipate that these trials will afford patients with more precise and innovative medical interventions, ushering in novel treatment avenues [95].

At the current forefront of research, numerous scientists are actively exploring novel approaches to integrate emerging technologies with hUCB-MNCs to further elucidate their potential in fostering tissue repair and advancing regenerative medicine. These investigations encompass not only gene editing and tissue engineering methodologies but also insights from interdisciplinary realms such as bioinformatics and systems biology. Through this strategy of integrating multiple technologies, researchers are assessing the synergistic effects of hUCB-MNCs in cell therapy and their therapeutic applications across diverse disease models.

The utilization of gene editing techniques has the potential to enhance the targeted differentiation of hUCB-MNCs, enabling more efficient transformation into the desired cell types. Some researchers have genetically modified hUCB-MNCs by introducing specific genes into these cells using recombinant adenoviral vectors to induce overexpression of VEGF, FGF2, and bone SDF1α, assessing their impact on angiogenesis [35]. In a comparable study, researchers generated 12 cDNA libraries from hUCB-MNCs obtained from six individual donors. These cells were genetically modified using recombinant adenoviral vectors (Ad-EGFP or Ad-VEGF165). Subsequent gene sequencing and bioinformatics analyses revealed a significant increase in the expression levels of the modified genes, EGFP and VEGF, when compared to the control group. Importantly, the genetic modification did not elicit significant alterations in the global transcriptome of the cells, which is of considerable significance for the evaluation of the safety and efficacy of gene therapy [13]. Other investigators have introduced GDNF [76] or NGF [82] genes into hUCB-MNCs via adenoviral vector transduction and evaluated their therapeutic efficacy by transplanting these cells into Alzheimer's disease mouse models.

Furthermore, bioinformatics analysis can aid researchers in gaining a deeper understanding of the molecular mechanisms underlying hUCB-MNCs' role in tissue repair, while systems biology approaches can unveil intricate interactions with the local microenvironment. In a study focusing on hUCB-MNCs for bronchial dysplasia treatment, a research team systematically explored diverse RNA networks through whole transcriptome sequencing, identifying reliable biomarkers and therapeutic targets for bronchial dysplasia-related pathogenesis using various bioinformatics analysis techniques. This study offered new insights into initiating and regulating hUCB-MNCs in the treatment of neonatal lung injury [46].

In the future, researchers may endeavor to integrate a wider array of cutting-edge technologies with human umbilical cord

blood-derived mononuclear cells (hUCB-MNCs) for their application in the treatment of clinical diseases. In my view, one promising approach could involve the combination of hUCB-MNCs with hydrogels, utilizing these matrices as carriers for the repair of cavernous organs such as the uterus and fallopian tubes [96], or for the regeneration of damaged skin [97]. Hydrogels not only prevent cell loss but also provide a conducive environment for cellular functions [98]. Furthermore, stimulus-responsive characteristics could be introduced, such as conductive gels [99] or thermosensitive hydrogels [100]. Another strategy I propose is the co-administration of hUCB-MNCs with platelet-rich plasma (PRP). PRP is a concentrate of platelets at high levels, which contains a wealth of growth factors and is primarily used to promote repair of injuries [101]. The body's self-repair process requires the regulation of multiple growth factors, and PRP is rich in such factors [102]. The combined use of hUCB-MNCs and PRP can create and enhance the microenvironment for hUCB-MNCs, thereby improving their survival rate and therapeutic efficacy [103].

As nanomedicine continues to flourish, numerous research teams have been investigating new pathways for its integration with stem cell therapy. They have skillfully incorporated nanotracers, antioxidant nanomaterials, and magnetic nanomaterials into stem cell therapeutic strategies, endowing stem cells with a series of innovative properties. The application of nanotracers allows researchers to effectively label stem cells, enabling real-time monitoring of their distribution, migration pathways, survival, and differentiation processes within the body [104]. Concurrently, the introduction of antioxidant nanomaterials has significantly enhanced the survival rate of stem cells, protecting them from oxidative stress damage post-transplantation [105]. Moreover, the utilization of magnetic nanomaterials, through their interaction with external magnetic fields, allows for precise control of stem cell proliferation and differentiation, providing a novel means for the precise regulation of stem cell therapy [106]. This technology can also be applied to the treatment involving hUCB-MNCs. These interdisciplinary research efforts are poised to bring revolutionary advancements to the field of hUCB-MNCs therapy, offering a brighter outlook for future clinical applications.

The integration of these interdisciplinary technologies not only propels advancements in hUCB-MNCs research but also establishes a critical scientific foundation for future personalized medicine and precision therapy. As these investigations progress, there is optimism that the application of hUCB-MNCs will bring about transformative changes in the fields of tissue repair and regenerative medicine.

5. Conclusion

This review meticulously expounds on the multiple functional characteristics of hUCB-MNCs and their therapeutic potential in the treatment of various diseases. The research data has unveiled the significant efficacy of hUCB-MNCs in promoting cell regeneration, tissue repair, and the restoration of organ function, thereby affirming their importance and vast application value in the field of regenerative medicine. The findings presented in this paper not only provide a solid theoretical foundation and practical guidance for researchers currently working in the field of hUCB-MNCs but also offer robust scientific support for the exploration of new strategies and therapeutic approaches in this domain. These discoveries are expected to advance the clinical application of hUCB-MNCs, bringing new treatment options and hope to numerous patients.

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Authors contributions

YZ, YL, XH, MJ, ZC and LJ participated in the literature search, data interpretation, writing. JW, CC and ML participated in data collation, article framework construction and critical revision. All authors read and approved final manuscript.

Data availability statement

Data and materials were available in the manuscript.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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