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Review Article

EXPLORING THE ROLE OF UMBILICAL CORD AND CORD BLOOD IN REGENERATIVE MEDICINE

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ABSTRACT

UC/umbilical cord blood (UCB) has become an important option as sources of various types of stem cells to treat chronic diseases of various origins (blood disorders, autoimmune disorders, neurodegenerative diseases, cardiac diseases, diabetes, cancer, gastric and liver diseases, etc.). This is because these stem cells have demonstrated the potential to differentiate into mature cells and also to activate the endogenous progenitor cells to regenerate the tissue. In addition, a subpopulation of stem cells known as Mesenchymal Stem cells (MSCs) has the unique ability to modulate the immune cell response through cell-to-cell interactions and/or by the abundant production of various growth factors, cytokines, and extracellular vesicles. UC and UCB-derived stem cells have emerged as superior alternatives due to their ethical acceptability, ease of procurement, and robust regenerative potential. Many clinical trials are being run using MSCs for the treatment of various disorders. Most importantly, the cells derived from these sources are readily available and present no serious ethical challenges, thereby making them an important therapeutic candidate in clinical settings. This review uniquely synthesizes the mechanistic pathways of UCB and Umbilical Cord (UC) across different major therapeutic areas and critically appraises the translational challenges from a clinical perspective. Moreover, we have also provided insights on the use of UCB/UC and its derivatives as vehicles for the delivery of therapeutic agents to the target tissue. These findings underscore the potential of UCB and UC not only as standalone treatments but also as innovative platforms for enhancing the efficacy of existing therapies. In addition, this review also highlighted the preclinical and clinical results that have been obtained using UCB and UC in various fields, as well as the challenges and regulatory limitations of those products in clinical settings. Future research should focus on overcoming regulatory hurdles and optimizing delivery systems to maximize patient outcomes.

Keywords: Umbilical cord blood, Umbilical cord tissue, Mesenchymal stem cells, Regeneration, Immunomodulation, Pre-clinical, Clinical, Therapy.

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INTRODUCTION

Regenerative medicine is a novel and rapidly advancing field over the past two decades, driven by innovations in cell therapy, tissue engineering, and biomaterials aimed at restoring function in damaged or diseased tissues. This rapidly developing field offers the possibility of changing treatments for a variety of diseases and injuries. Scientists aim to develop treatments that harness the body's natural healing mechanisms to repair or regenerate damaged tissues and organs. In the medical field, approaches such as stem cell therapy, tissue engineering, and gene therapy are employed to stimulate and enhance these intrinsic repair processes.

The main therapeutic approach in regenerative medicine employs stem cell or stromal cell therapy (a kind of cell that has a unique ability to renew itself and give rise to specialized cell types), such as induced pluripotent stem cells, embryonic stem cells, and adult stem cells, to give rise to new tissue and alleviate numerous clinical conditions [1]. Regardless of the benefits shown in patients (Fig. 1), these cellular therapies are certainly accompanied by limitations that restrict their clinical application, such as scientific complexities, genomic regulation, undesired differentiation, safety issues like tumor risk, ethical debates, particularly around embryonic sources, and practical issues such as high cost, lack of long-term data, and regulation. On the other hand, stem cell research and their differentiation pathways serve as primary research areas in the field because they expand disease development understanding for discovering fresh therapeutic targets [2]. Despite the growing clinical interest, a comprehensive mechanistic understanding of how UC/umbilical cord blood (UCB)-derived stem cells exert therapeutic effects across diverse disease conditions remains incompletely defined. Furthermore, the translational pathway from bench to bedside faces several scientific, regulatory, and manufacturing challenges that require critical evaluation. This review focuses specifically on consolidating mechanistic insights, therapeutic applications, and translational barriers associated with UC/UCB-derived stem cells, offering a refined perspective distinct from broader regenerative medicine reviews.

SOURCES OF STEM CELLS AND CHARACTERISTICS FEATURES

Stem cells can be isolated from various tissues in the body, such as embryonic, umbilical cord, placenta, bone marrow, and adipose tissue, and have distinct characteristics that can be utilized in the clinical settings based on the specific clinical condition (Fig. 2) [3-6]. Among the different types of stem cells, UC and UCB-derived stem cells have emerged as superior alternatives due to their ethical acceptability, ease of procurement, and robust regenerative potential.

Table 1 reflects the key characteristics of various stem cell types, detailing their sources, differentiation potential, and other notable features. It provides a concise comparison of stem cells like embryonic, mesenchymal, and hematopoietic, thus helping to distinguish their therapeutic potential, ethical considerations, and regenerative properties.

BIOLOGY OF UCB/TISSUE

Until 1974, umbilical cords and their derivatives were considered as biological waste material. It was later that hematopoietic stem cells (HSC), progenitor cells, and mesenchymal stem cells (MSCs) were found to have been extracted from the UCB and tissue [7-9].

MSCs are a plastic adherent clonogenic population of cells first isolated by Friedenstein, morphologically a fibroblastic-like cell type and multipotent in nature, that is, these cells can differentiate into cartilage, bone, muscle, tendon, ligament, and fat to name a few. It is hypoimmunogenic, exhibiting no or very low expression of MHC-II antigens under standard conditions, thereby supporting its potential for use across human leukocyte antigen (HLA) barriers. This groundbreaking revelation opened new avenues for medical research and treatments, highlighting the potential of cord blood and tissue in regenerative medicine. Today, MSCs, HSCs, and progenitor cells play a crucial role in treating various blood disorders and offer hope for future therapies.

STRUCTURE AND COMPOSITION

The umbilical cord is an important fetus structure, and it consists of one vein and two arteries surrounded with Wharton's jelly (Latin word, Substantia Gelatinea funiculi Umbilicalis) (mainly composed of MSCs, collagen fibers, proteoglycans, glycosaminoglycans, and a large amount of water) that is specialized to provide cushioning [10]. It is lined with amniotic epithelium on the outside and becomes a pathway of blood flow between fetus and placenta (Fig. 3) [11].

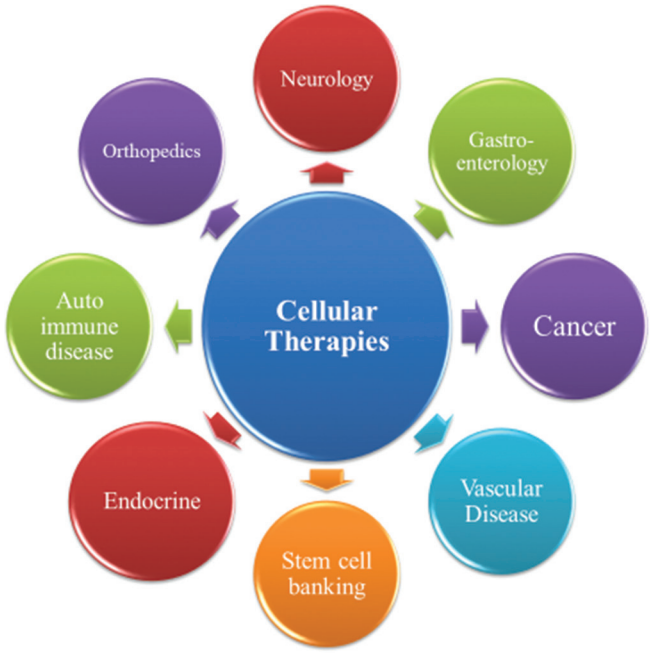

Fig. 1: Cellular therapies over different areas

Umbilical Cord (UC) Consists of

- HSCs,
- Mesenchymal stem cells (MSCs),
- Unrestricted somatic stem cells,
- Cord blood-derived embryonic-like stem cells, and
- Multipotent progenitor cells.

The characterization of UC and UCB, focusing on stem cell populations, surface markers, differentiation capacity, and related properties, is mentioned in Table 2 each one offers distinct types of prospects in regeneration and therapeutics [12]. These cells play major roles in cell renewal, differentiation, and tissue repair, thereby emphasizing the umbilical cord and its derivatives a useful resource in regenerative medicine and to treat various other disorders such as diabetes, liver cirrhosis, rheumatoid arthritis, osteoarthritis, myocardial infraction, vascular disease, and acute renal disease [3,4,13].

MECHANISTIC APPROACHES OF UC/UCB STEM CELL THERAPY

UC and UCB stem cells achieve therapeutic benefits through multiple biological mechanisms that lead to tissue repair, immune modulation, and regeneration (Fig. 4).

UC-MSCs support regeneration in various degenerative diseases through multiple synergistic mechanisms [14,15]. They release a rich array of paracrine factors, including cytokines (interleukin [IL]-10, transforming growth factor-beta [TGF-β]), growth factors (vascular endothelial growth factor [VEGF], insulin-like growth factor-1 [IGF-1]), and extracellular vesicles, which modulate inflammation, enhance cell survival, and stimulate repair [16]. UC-MSCs exert strong immunomodulatory effects through mediators such as IL-10, TGF-β, Indoleamine 2,3-Dioxygenase, HLA-G, and prostaglandin E2, shifting the immune environment towards a neuroprotective state. Guided by the SDF-1/CXCR4 axis, integrins, and selectins, they home to damaged sites, where they can differentiate into desired cell type in the target tissue. In addition, UC-MSCs promote angiogenesis through VEGF, fibroblast growth factor 2 (FGF-2), and angiopoietins and thereby improving oxygen and nutrient delivery to injured regions efficiently. Their anti-apoptotic and anti-fibrotic actions, mediated by Bcl-2, hepatocyte growth factor (HGF), tumor necrosis factor (TNF)-stimulated gene-6, and matrix metalloproteinases (MMPs), help prevent cell death, reduce

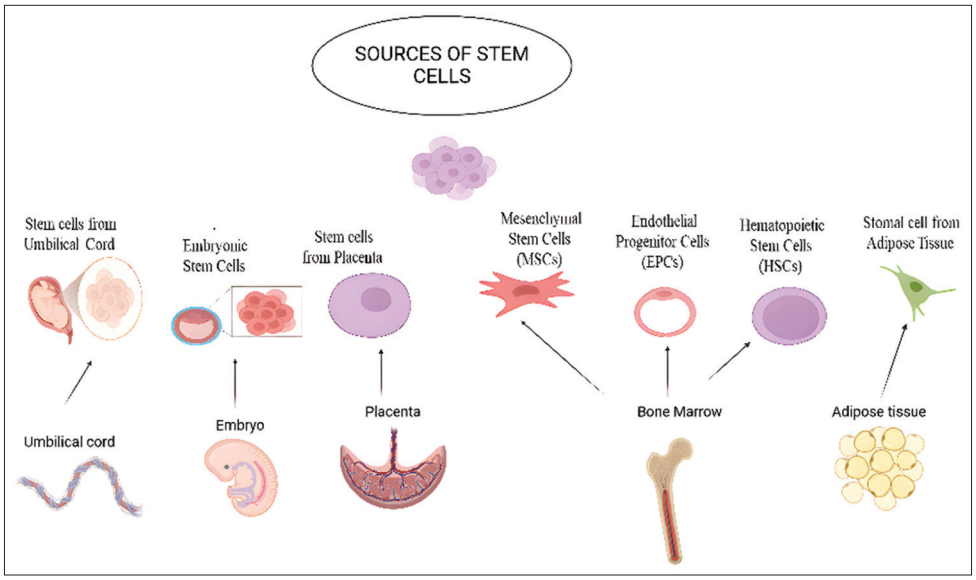

Fig. 2: Various types of stem cells and their respective source origins

Table 1: Characteristic features of stem cell sources

Stem cell type	Source	Cell type	Features
Umbilical cord stem cells	Umbilical cord blood/tissue (UC)	Multipotent	Non-invasive, low immunogenicity, rich in primitive stem cells, postnatal source
Embryonic stem cells	Inner cell mass of embryo	Pluripotent	Can form all germ layers, unlimited proliferation, ethical issues, tumor risk
Placental stem cells	Placenta (post-delivery)	Multipotent	Immunomodulatory, ethically safe, non-invasive, moderate differentiation potential
Mesenchymal stem cells (MSCs)	Bone marrow, fat, umbilical cord	Multipotent	Differentiate into bone, cartilage, fat; immune-regulating, low tumor risk
Endothelial progenitor cells	Bone marrow, peripheral blood	Multipotent: Give rise to vascular progenitors	Support blood vessel formation, helpful in cardiac repair, limited expansion
Hematopoietic stem cells	Bone marrow, cord, peripheral blood	Multipotent	Forms all blood cells, used in bone marrow transplant, restores immune system
Adipose tissue stromal cells	Adipose (fat) tissue	Multipotent	Easy to harvest, used in cosmetic/soft-tissue repair, limited bone differentiation

Table 2: Characterization of umbilical cord blood and umbilical cord (UC) tissue

Source	Cell types	Surface markers	Differentiation potential	Special features
Umbilical cord blood	HSCs mesenchymal stem cells (MSCs) USSCs CBEs	HSCs: $CD34^+$, $CD45^+$, USSCs: $CD45^-$, HLA Class II^-, CBEs: ESC-like markers such as; OCT4, SOX2, NANOG SSEA-3, SSEA-4 TRA-1-60 and TRA-1-81 – glycoproteins and MSCs Markers.	HSCs: All blood cell lineages USSCs: All 3 germ layers CBEs: Lineage-specific cell types etc.	Non-invasive collection Rich in primitive stem cells Lowers GvHD risk Long telomeres
Umbilical Cord (UC)	Wharton's Jelly-derived MSCs	Positive: CD105 (SH2), CD73 (SH3, SH4), CD90, CD166 Negative: CD14, CD31, CD34, CD45, CD86	Differentiate into cells of mesodermal origin.	Easy expansion *in vitro* Immunomodulatory Paracrine effects Ethical sourcing

CBEs: Cord blood-derived embryonic-like stem cells, USSCs: Unrestricted Somatic Stem Cells, HSC: Hematopoietic stem cells

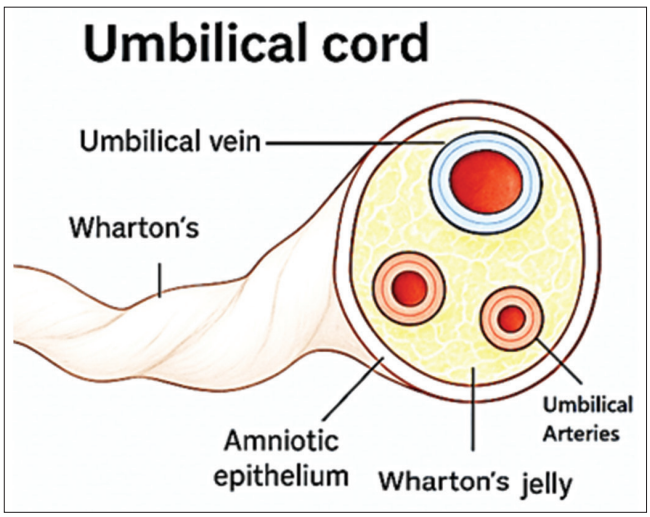

Fig. 3: Structure of umbilical cord tissue

scar tissue formation, and preserve functional tissue, collectively facilitating structural and functional recovery [17-19].

MECHANISMS OF ACTION IN REGENERATIVE PROCESS

Neurodegenerative disease

UC-MSCs exert their therapeutic efficacy in neurodegenerative conditions through a multifaceted mechanism involving paracrine secretion of neurotrophic factors, potent immunomodulation, and exosome-mediated delivery of therapeutic microRNA (miRNA). They promote neuronal survival, synaptic plasticity, and neurogenesis while suppressing inflammation through microglial phenotype switching and inflammasome inhibition (Fig. 5 and Table 3).

UC-MSCs exert regenerative effects in neurodegenerative diseases by targeting multiple pathological processes. They protect against neuronal loss and apoptosis through the secretion of neurotrophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and VEGF and activating survival pathways like PI3K/Akt and mitogen-activated protein kinase (MAPK)/ERK which results in an increased neurotrophin levels and a marked reduction in neuronal injury markers such as neurofilament light chain [20]. UC-MSCs modulate neuroinflammation by releasing anti-inflammatory molecules such as IL-10 and TGF-β, which aid in shifting microglia from a proinflammatory to a neuroprotective phenotype, reflected by reduced levels of TNF-α and IL-1β. They enhance neurogenesis by stimulating endogenous neural progenitors through paracrine growth factor secretion and stimulation of Wnt/β-catenin pathway, as evidenced by enhanced expression of doublecortin and magnetic resonance imaging-based hippocampal volume changes. By promoting angiogenesis through VEGF, angiopoietins, and HGF secretion, UC-MSCs improve cerebral blood flow [21,22]. UC-MSCs-derived exosomes and microvesicles can restore mitochondrial function and reduce oxidative stress by transferring healthy mitochondria to the damaged or dysfunctional cells. In addition, UC-MSCs secrete antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which can reduce lipid peroxidation and thereby lowering malondialdehyde levels and improving the mitochondrial potential. Furthermore, UC-MSCs support synaptic repair and plasticity by upregulating synaptic proteins (synaptophysin, PSD-95) mediated through extracellular vesicles containing miR-133. In demyelinating conditions, UC-MSCs activate oligodendrocyte precursor cells to promote remyelination, as evidenced by increased myelin basic protein and reduced myelin

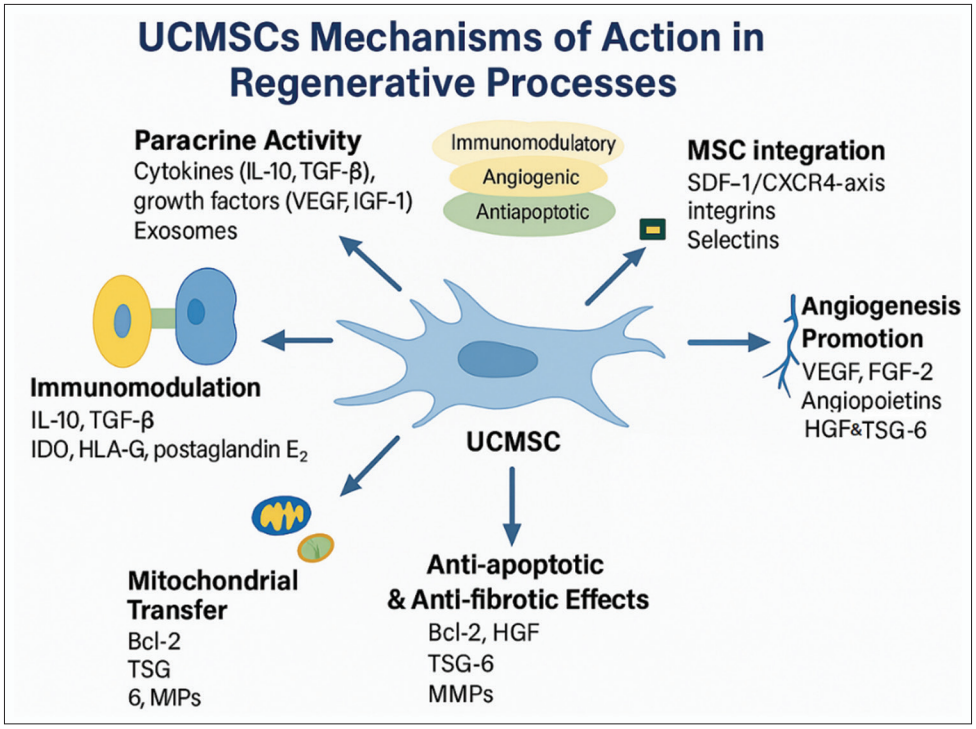

Fig. 4: Key mechanisms of UC/umbilical cord blood stem cell therapy alongside their molecular mediators, biological effects, and clinical relevance

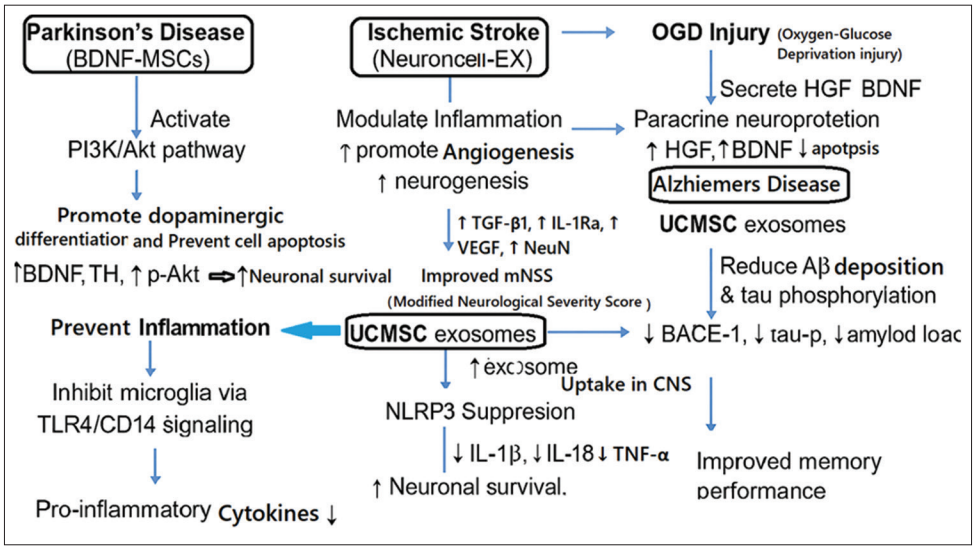

Fig. 5: Mechanistic insight into UC-MSCs efficacy in neurodegenerative conditions

debris in cerebrospinal fluid. This multifaceted action makes UC-MSCs a promising therapeutic strategy, with well-defined molecular and imaging biomarkers available to monitor treatment response.

Cancer

UCB contains HSCs, which are capable of differentiating into blood and immune cells such as natural killer (NK) cells and T cells. Although advanced nanotechnologies offer improved drug stability, targeted delivery, and enhanced therapeutic efficiency, the paper highlights several major challenges that limit their clinical translation. These include potential nanoparticle toxicity, unpredictable long-term safety, difficulties in large-scale production, instability during storage, high manufacturing cost, and strict regulatory barriers [23]. But on the other side, UCB has well-established roles in HSC transplantation, where it replaces the cells from bone marrow following high-dose chemotherapy or radiotherapy, particularly for hematologic malignancies such as leukemia, lymphoma, and myelodysplastic syndromes. NK cell–based immunotherapy has also been explored, utilizing unmodified UCB-derived NK cells for the treatment of hematologic cancers and chimeric antigen receptor-NK cells targeting CD19 in B-cell malignancies. Experimental approaches are investigating gene-modified UCB-derived cells to secrete pro-apoptotic factors such as TNF–related apoptosis-inducing ligand (TRAIL) and interferon-beta, cytokines including IL-12 and granulocyte–macrophage colony-stimulating factor (GM-CSF), or enzymes that activate prodrugs within the tumor microenvironment [24,25].

Umbilical cord (UC) tissue, on the other hand, is rich in MSCs and endothelial progenitors. While UC tissue-derived cells currently have no established role in routine cancer care, they are being actively studied for their tumor-homing properties as potential delivery vehicles for anticancer therapeutics. Experimental strategies include the use of MSCs to deliver chemotherapeutic drugs, oncolytic viruses, and cytokines

directly to tumors, as well as to modulate tumor-associated immune responses. Gene-modified MSCs can be designed to secrete targeted anticancer molecules or activate prodrugs within tumor tissue, thereby enhancing therapeutic specificity and reducing systemic toxicity [26].

At the molecular level, both UCB and UC-derived cells can reduce tumor burden through multiple mechanisms: Inducing apoptosis via TRAIL and caspase activation, targeted prodrug activation, NK cell–mediated cytotoxicity, immune checkpoint modulation, anti-angiogenesis through VEGF inhibition, immune system reprogramming with cytokines like IL-12 and GM-CSF, and oncolytic virus delivery (Fig. 6). This multi-pronged approach offers both direct tumor cell killing and also modulation of the tumor microenvironment, making them promising tools for next-generation cancer immunotherapy and targeted treatment strategies.

Diabetes

Umbilical cord–derived stem cells, such as UC-MSCs and UCB-HSCs, hold a strong potential for both Type 1 and Type 2 diabetes through

Table 3: UC-MSCs in neurodegenerative diseases: Pathophysiology insights and response indicators

Pathophysiological features in neurodegeneration	UC-MSCs action/mechanism	Measurable response indicators
Demyelination	Stimulate oligodendrocyte precursors for the production of myelin sheath. UC-MSCs release growth factors (Such as BDNF, IGF-1, NT-3, PDGF), which are crucial for oligodendrocyte precursor cell survival, proliferation, and differentiation of myelin sheath formation around axons.	↑ MBP, ↓ myelin debris in CSF, ↑ nerve conduction velocity
Synaptic loss and plasticity deficits	↑ Synaptophysin, (PSD-95) through miR-133b exosome delivery	Synaptic Protein Markers Synaptophysin, SNAP-25, VGLUT1, Bassoon PSD-95, Homer1, AMPA receptor subunits (GluA1/2), NMDA receptor subunits (NR2A/NR2B) Neuronal activity and network excitability Behavioral/Functional Outcomes
Mitochondrial dysfunction and oxidative stress	Exosome-mediated mitochondrial transfer; Secretion of SOD and catalase enzymes.	↓ MDA, ↑ antioxidant enzymes, restored mitochondrial potential.
Cerebral hypoperfusion	VEGF, angiopoietin, and HGF-mediated angiogenesis	↑ Serum VEGF, ↑ cerebral blood flow.
Impaired neurogenesis	Stimulate neural progenitors; activate Wnt-Frizzled receptors and co-receptors LRP5/6 on neural progenitor cells. β-catenin survival pathway- TCF/LEF transcription factors to induce gene expression.	↑ DCX expression, ↑ hippocampal volume.
Neuroinflammation	Secretion of IL-10 and TGF-β; microglial shift from proinflammatory to anti-inflammatory M1→M2	↓ TNF-α, IL-1β; ↑ IL-10; ↓ Translocator protein in the concentrations (cells supernatant)
Neuronal loss and apoptosis	Secretion of BDNF, GDNF, NGF; PI3K/Akt and MAPK/ERK activation (survival pathway)	↑ BDNF, GDNF (CSF/serum), ↓ NfL, ↓ cleaved caspase-3

BDNF: Brain-derived neurotrophic factor, IGF-1: İnsulin-like growth factor-1, SOD: Superoxide dismutase, VEGF: vascular endothelial growth factor, HGF: Hepatocyte growth factor, IL: Interleukin, TGF: Transforming growth factor, GDNF: Glial cell line-derived neurotrophic factor, NGF: Nerve growth factor, MAPK: Mitogen-activated protein kinase, CSF: cerebrospinal fluid, DCX: Doublecortin, MDA: Malondialdehyde, MBP: Myelin basic protein, PDGF: Platelet-derived growth factor, NMDA: N-methyl-D-aspartate, TCF/LEF: T cell factor/lymphoid enhancer factor family

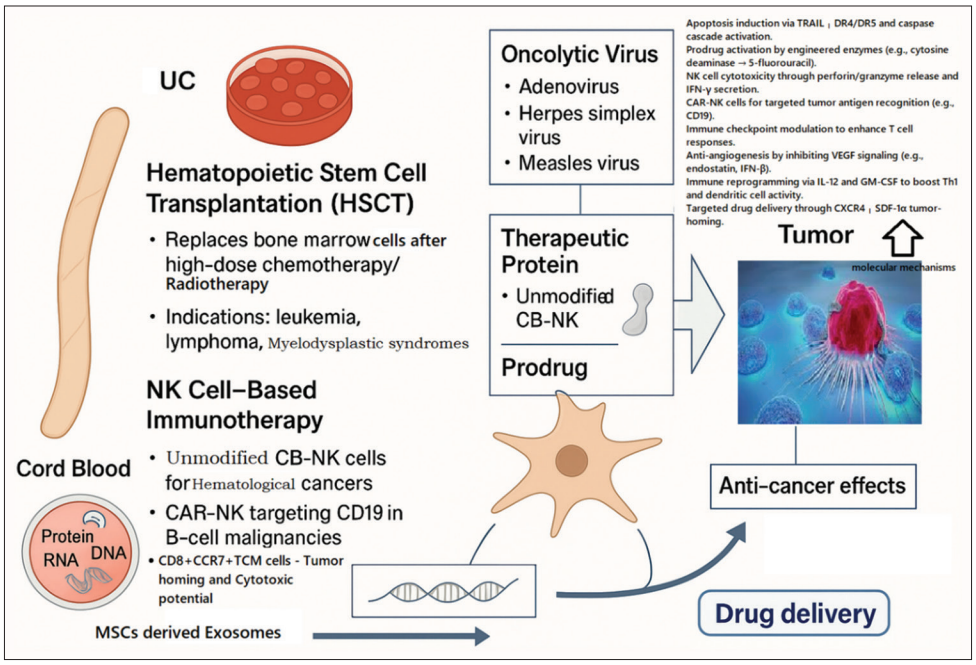

Fig. 6: Therapeutic roles of umbilical cord blood and umbilical cord tissue-derived cells in cancer

multi-targeted actions. Their primary therapeutic effects arise from paracrine signaling: Secretion of growth factors, immunoregulatory cytokines, and extracellular vesicles, which drive: (Fig. 7) [27].

- β-cell protection and regeneration through PI3K/Akt and MAPK/ERK pathways, enhancing cell survival and proliferation.
- Immune modulation by reducing autoimmune destruction (in T1D) through Treg induction, Th1/Th17 suppression, and tolerogenic dendritic cell promotion.
- Anti-inflammatory effects by lowering pro-inflammatory cytokines (TNF-α, IL-6) and suppressing nuclear factor kappa B (NF-κB) signaling.
- Metabolic improvements through AMP-activated protein kinase and ınsulin receptor substrate-1/AKT activation, boosting glucose uptake, GLUT4 translocation, and insulin sensitivity.
- Microvascular repair by promoting angiogenesis (VEGF) and endothelial function.

Clinical findings UC-MSCs showed improved C-peptide levels in early onset of T1D patients, reduced HbA1c and fasting glucose in Type 2 diabetes mellitus, decreased insulin requirements, and UCB-HSCs showed improved vascular/wound healing outcomes [28,29].

Gasteroenterology

UCB and UC-derived cells are becoming increasingly relevant in the field of gastroenterology, mainly for regenerative medicine, immune modulation, and anti-inflammatory therapies in diseases affecting the gastrointestinal (GI) tract. Deriving immune cells from UCB and UC-MSCs from UC are emerging as promising therapies in gastroenterology field due to their multi-mechanistic therapeutic potential (Fig. 8).

They offer benefits in:

- Inflammatory bowel disease: By suppressing inflammation, modulating immune cells, and promoting mucosal healing.

Liver diseases

- By supporting liver regeneration, reducing fibrosis, and improving immune regulation.

GI cancers

- By providing novel immunotherapy options and targeted drug delivery through exosomes.

Short bowel syndrome and intestinal injury

- By enhancing angiogenesis and epithelial repair.

At the molecular level, these cells exert anti-inflammatory, anti-fibrotic, regenerative, promoting immune tolerance and anti-apoptotic effects via pathways such as NF-κB inhibition, TGF-β/Smad modulation, Wnt/β-catenin activation, and PI3K/Akt signaling. Overall, UCB/UC cell–based approaches present a versatile and low-immunogenic therapeutic platform for a wide range of GI disorders, but require standardized protocols, large-scale trials, and long-term safety data before widespread clinical adoption [30,31].

Rheumatology and orthopedics

UCB and UC-MSCs show strong therapeutic potential in both rheumatologic and orthopedic disorders due to their combined immunomodulatory, anti-inflammatory, and regenerative properties (Table 4).

In rheumatology, UC-MSCs reduce autoimmune-driven inflammation by shifting immune balance (↓ Th1/Th17, ↑ Tregs), suppressing

Fig. 7: Immune regulation, β-cell support and metabolic improvement with umbilical cord blood/UC-MSCs

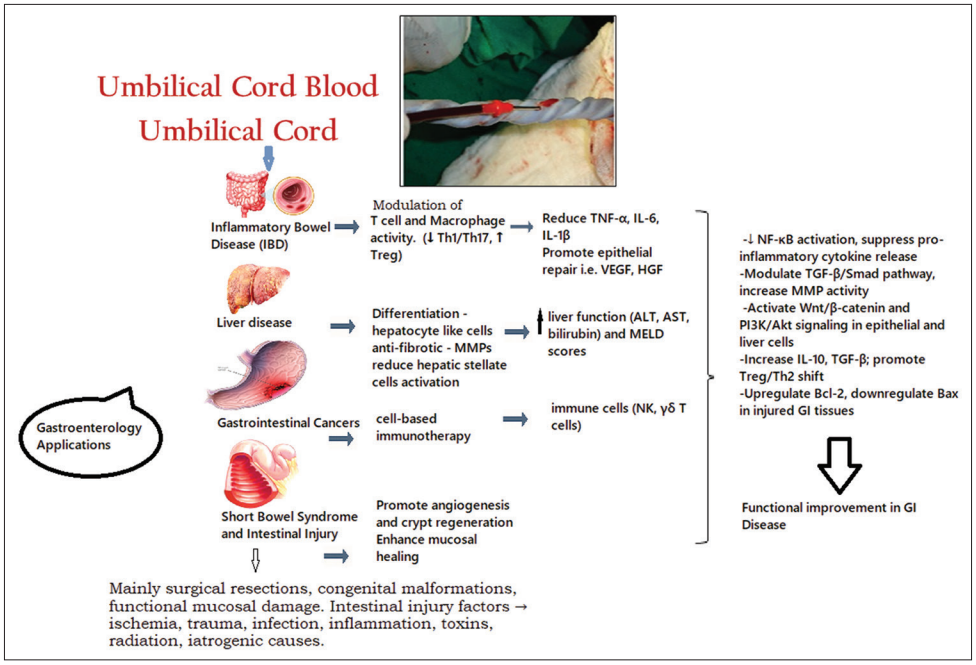

Fig. 8: Functional improvement in gastrointestinal disease by umbilical cord blood/UC tissue

Table 4: UC-MSCs in rheumatology and orthopedics diseases: Mechanism insights and response indicators

Specialty	Conditions	Mechanisms of action	Key clinical evidence
Rheumatology	RA, SLE, AS, SS	Immunomodulation: ↓ Th1/Th17, ↑ Tregs; inhibit B cell overactivation (↓ autoantibodies) [32,33]. Cytokine regulation: ↓ TNF-α, IL-6, IL-17, IFN-γ; ↑ IL-10, TGF-β [32,33]. Synovial tissue protection: Suppress fibroblast-like synoviocyte proliferation, ↓ MMP activity→less cartilage degradation [32]. Tissue repair: Growth factor release (VEGF, HGF) supports vascular and synovial restoration [32].	RA: UC-MSCs+methotrexate lowered disease activity score using 28 joints (DAS28 scores), ↓ inflammatory cytokines [32]. SLE: UC-MSC infusions improved renal function, ↓ anti-dsDNA titers [33]. AS: Reduction in pain and inflammatory markers in pilot trials [34]. SS: Suppressing autoreactive T/B cells, shifting immune balance toward Treg/M2 phenotype, Reducing autoantibody production, Promoting epithelial survival and repair through paracrine/exosome signaling.
Orthopedics	Osteoarthritis (OA), Avascular necrosis (AVN), Bone fractures/non-union, Intervertebral disc degeneration (IVDD)	Anti-inflammatory: ↓ IL-1β, TNF-α, MMPs in joint microenvironment [35]. Bone repair: Osteogenic differentiation (↑ Run×2, ALP, osteocalcin); VEGF-mediated angiogenesis [36]. Disc repair: ECM synthesis (proteoglycans, collagen) in nucleus pulposus regeneration; ↓ apoptosis and inflammation [37]. Cartilage regeneration: Chondrocyte differentiation; ↑ collagen II, aggrecan synthesis [35,38].	AVN: Core decompression+UC-MSCs delayed femoral head collapse [36]. Fractures: Faster healing, ↑ bone density [36]. IVDD: Early trials showed pain relief and improved disc hydration on MRI [37]. OA: Intra-articular infusion of UC-MSCs improved WOMAC and VAS scores (measure of pain, stiffness and physical function); MRI showed cartilage gain [35, 38].

RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, AS: Ankylosing spondylitis, SS: Sjögren's syndrome, OA: Osteoarthritis, AVN: Avascular necrosis, IVDD: Intervertebral disc degeneration, TNF-α: tumor necrosis factor, IL: Interleukin, TGF: Transforming growth factor, IFN-γ: interferon-beta, MMP: matrix metalloproteinases, VEGF: vascular endothelial growth factor, HGF: Hepatocyte growth factor, ECM: Extracellular matrix, MRI: Magnetic resonance imaging, VAS: Visual analogue scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

proinflammatory cytokines (TNF-α, IL-6, IL-17), inhibiting autoantibody-producing B cells, and protecting synovial tissues from degradation. These effects translate clinically into reduced disease activity in rheumatoid arthritis patients, improved renal and serological parameters in refractory systemic lupus erythematosus, and symptomatic relief in ankylosing spondylitis.

In orthopedics, UC-MSCs contribute to structural repair through differentiation into chondrocyte- and osteoblast-like cells, stimulation of extracellular matrix (ECM) synthesis, angiogenesis promotion, and suppression of joint and disc inflammation. Clinical evidence supports cartilage regeneration and pain reduction in osteoarthritis, delayed femoral head collapse in avascular necrosis, accelerated fracture healing, and improved disc hydration in early intervertebral disc degeneration.

Collectively, UCB and UC-MSCs therapies offer a dual-action approach: restoring immune balance in inflammatory conditions while regenerating damaged musculoskeletal tissues. While early-phase trials demonstrated safety and efficacy, large-scale randomized trials are required to establish standardized protocols, optimal dosing, and long-term outcomes.

Cosmetology

In cosmetology and esthetic dermatology, UCB and UC-derived stem cells, particularly mesenchymal stem cells (MSCs) and their secretome/

extracellular vesicles, are the subject of commercial and clinical research for applications including skin rejuvenation, anti-aging, scar reduction, and hair restoration (Table 5). They are not used as whole cells in most cosmetic applications (due to regulatory issues), but as cell-free derivatives (conditioned media, growth factors, extracellular vesicles). UCB and UC-derived MSCs, along with their secretome and extracellular vesicles (or exosomes), are emerging as powerful tools in cosmetic dermatology. Their regenerative effects stem from a rich repertoire of growth factors (e.g., TGF-β, FGF, VEGF), cytokines, and extracellular vesicles that stimulate collagen and elastin synthesis, promote angiogenesis, modulate pigmentation, reduce inflammation, and enhance tissue repair.

Clinically, these bioactive products are applied via topical formulations, micro needling, or intradermal injections to achieve skin rejuvenation, wrinkle reduction, scar remodeling, improved skin hydration, brightening, and hair regrowth. Current cosmetic use is largely cell-free, minimizing immune rejection risks and regulatory barriers while maintaining high regenerative potency. Despite promising results in both experimental and clinical settings, challenges remain in standardizing product quality, optimizing delivery methods, reducing costs, and establishing long-term safety. Nonetheless, UCB/UC-based interventions represent a rapid advancing frontier in regenerative esthetics, offering minimally invasive solutions for age-related skin and hair concerns.

Cardiology

UC-MSCs, cord blood-derived mesenchymal stem cells, cord blood-derived HSCs, and endothelial progenitor cells (EPCs) have shown promise in repairing damaged cardiac tissue. Their therapeutic potential in cardiological diseases is mediated largely through paracrine effects rather than long-term engraftment. UC/UCB stem cells promote cardiomyocyte regeneration by differentiating into cardiomyocyte-like cells and stimulating endogenous repair mechanisms. They enhance angiogenesis via secretion of vascular growth factors such as VEGF, HGF, bFGF, and angiopoietin-1. In addition, anti-apoptotic and anti-fibrotic effects are achieved through activation of PI3K/Akt, ERK1/2 pathways, and modulation of MMP/tissue ınhibitors of metalloproteinases (TIMP) balance. UC-MSCs-derived exosomes carry miRNAs (e.g., miR-126, miR-21, miR-210) that regulate vascular growth, inflammation, and oxidative stress [46-50] (Fig. 9).

In clinical studies, intracoronary or intravenous administration UC derived MSCs post myocardial infarction improved left ventricular ejection fraction by ~5–8% compared to control groups, reduced scar size, and enhanced perfusion. Importantly, because they are immunomodulatory and hypoimmunogenic, the body reduces the risk of rejection and enhances the therapeutic efficacy eventually. Cord blood EPCs rapidly migrated to ischemic myocardium and contributed to the formation of new vasculature. While promising, limitations include inconsistent long-term engraftment, delivery method variability, and a need for larger, long-term randomized controlled trials to confirm clinical benefit.

Vascular disease

UCB is a rich source of regenerative cell populations: EPCs, endothelial colony-forming cells (ECFCs), mesenchymal stromal cells (MSCs), and HSCs that contribute to vascular repair through complementary mechanisms (Table 6). EPCs and ECFCs promote angiogenesis and endothelial regeneration through VEGF-VEGFR2, PI3K/Akt, and MAPK/ERK pathways, restoring vascular integrity and perfusion. MSCs exert potent anti-inflammatory effects, by secreting HGF and IL-10 while suppressing NF-κB activation, thereby protecting the vasculature from inflammatory injury. In addition, they prevent fibrosis through TGF-β/Smad modulation and maintaining MMP/TIMP balance. HSCs support EPC mobilization, immune regulation, and structural vessel remodeling through PDGF, FGF, and notch signaling. Collectively, these actions enhance blood flow, reduce inflammation, preserve vessel elasticity, and improve functional recovery in vascular disease contexts [51-57].

UCB and cord tissue cells, particularly UC-MSCs, have emerged as promising therapeutic tools in nephrology due to their multifaceted

Table 5: UCB and UC-derived MSCs, along with their secretome and extracellular vesicles in cosmetic application

Mechanism	Biological effect	Cosmetic application
Collagen and elastin stimulation	MSC secreted growth factors (TGF-β, FGF, VEGF) promote fibroblast proliferation	Wrinkle reduction, skin tightening [39]
Anti-inflammatory and antioxidant	Cytokines (IL-10, IL-1RA) and antioxidant enzymes from MSCs reduce oxidative damage	Anti-aging, photodamage repair [40]
Angiogenesis	Secretion of VEGF and PDGF from MSCs or and UCB improve microcirculation	Skin glow, healing after procedures [41,42]
Melanogenesis modulation	MSC-secreted factors regulate melanin synthesis such as Tyrosinase (TYR), Tyrosinase-related protein-1 (TRP-1), and Tyrosinase-related protein-2 (TRP-2/DCT)	Hyperpigmentation treatment [43]
Hair follicle stimulation	Wnt signaling activation, VEGF-mediated follicular vascularization	Hair loss therapy [44]
Scar remodeling	MMPs and TIMPs balance to remodel the extracellular matrix	Acne scar, surgical scar treatment [45]

UCB: Umbilical cord blood, TGF-β: Transforming growth factor-beta, FGF: Fibroblast growth factor 2, VEGF: Vascular endothelial growth factor, IL: Interleukin, MMPs: Matrix metalloproteinases, TIMPs: Tissue ınhibitors of metalloproteinase

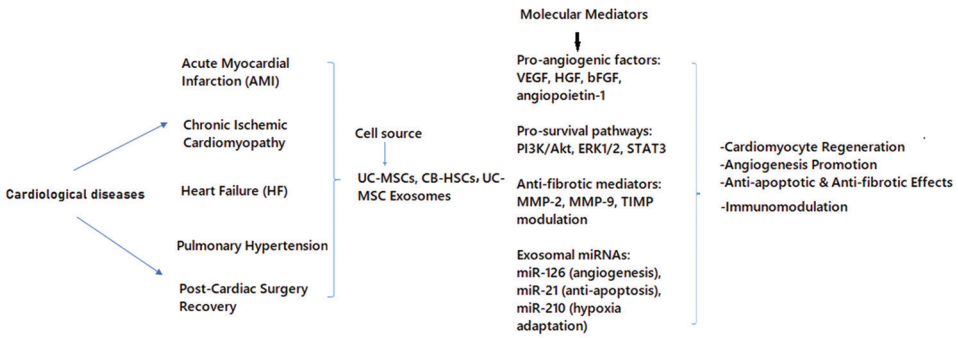

Fig. 9: Overview of umbilical cord and cord blood stem cell applications in cardiology

Table 6: UCB- and UC-derived MSCs contribute to vascular repair through distinct complementary mechanisms

Mechanism	Cell type	Markers	Molecular pathways/mediators	Vascular effect
Angiogenesis stimulation	EPCs, ECFCs	Surface markers: $CD34^+$, $CD133^+$, $VEGFR2^+$ (KDR), $CD31^+$, $CD146^+$, $CD105^+$Functional markers: eNOS, vWF (von Willebrand factor), VE-cadherin i.e., CD144 or cadherin-5	VEGF–VEGFR2 signaling, PI3K/Akt, MAPK/ERK	New capillary formation, improved perfusion
Endothelial repair	EPCs, ECFCs		NO production via eNOS activation, ICAM-1/VCAM-1 downregulation	Restores vascular integrity
Paracrine trophic support	MSCs	Surface markers: $CD73^+$, $CD90^+$, $CD105^+$, $HLA\text{-}DR^-$, $CD45^-$, $CD34^-$ Secretory markers: VEGF, HGF, Ang-1, IL-10	Secretion of VEGF, HGF, Ang-1, IL-6, IL-10	Promotes survival of endothelial cells, reduces apoptosis
Anti-inflammatory effect	MSCs		NF-κB pathway suppression via release of anti-inflammatory cytokines	Reduces vascular inflammation
Fibrosis prevention	MSCs		TGF-β/Smad modulation, MMP/TIMP balance maintenance.	Maintains vessel elasticity
Vascular remodeling	HSCs, MSCs		PDGF, FGF, Notch signaling	Structural repair of damaged vessels

UCB: Umbilical cord blood, EPCs: Endothelial progenitor cells, ECFCs: Endothelial colony forming cells, VEGF: Vascular endothelial growth factor, eNOS: endothelial function, HGF: Hepatocyte growth factor, TGF-β: Transforming growth factor-beta, MMPs: Matrix metalloproteinases, TIMPs: Tissue ınhibitors of metalloproteinase

regenerative, anti-inflammatory, antifibrotic, antioxidant, and immunomodulatory properties [58-63].

- In acute kidney injury, they promote tubular regeneration, reduce ischemia-reperfusion injury, and improve renal function through the secretion of growth factors such as HGF and VEGF.
- In chronic kidney disease and renal fibrosis, they inhibit TGF-β/smad signaling, reduce ECM deposition, and protect podocytes.
- In diabetic nephropathy, UC-MSC-derived exosomes restore mitochondrial function, decrease oxidative stress, and preserve glomerular structure.
- In autoimmune glomerular diseases (e.g., lupus nephritis), they modulate immune responses by enhancing Tregs and suppressing autoreactive lymphocytes.
- In kidney transplantation, they help induce donor-specific tolerance, reduce rejection risk, and support graft survival.

Mechanistically, they act majorly through paracrine signaling which includes exosome-mediated delivery of microRNAs, suppression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), upregulation of anti-inflammatory mediators (IL-10), reduction of oxidative stress (↑SOD, ↓robot operating system), and prevention of apoptosis (↑Bcl-2, ↓Bax) (Fig. 10). Overall, UCB and UC-based therapies hold high translational potential for renal diseases, but large-scale, controlled clinical trials are necessary to validate long-term efficacy and safety before routine clinical use.

Infertility

UC and UCB are rich in mesenchymal stem/stromal cells, HSCs, and plasma containing growth factors that support fertility restoration. They promote ovarian regeneration by stimulating folliculogenesis and repairing granulosa cells, endometrial repair by enhancing angiogenesis and reducing fibrosis, and male reproductive recovery by restoring spermatogenesis. Their anti-inflammatory effects help in autoimmune-related infertility, and they protect reproductive tissues from chemotherapy/radiotherapy damage (Table 7).

Preclinical and early clinical studies showed improved ovarian reserve markers, menstrual regularity, endometrial thickness, and positive pregnancy outcomes, with promising results in both female and male infertility. UC/UCB therapy is ethically acceptable, low in immunogenicity, and has strong regenerative potential, but widespread use is limited by the need for standardized protocols and large-scale clinical trials. Emerging strategies include UC-MSCs–derived exosomes and bioengineered scaffolds for reproductive tissue reconstruction [68, 69].

Although combining metformin with regenerative or nano-delivered therapies offers theoretical benefits, several challenges limit its translational success, particularly in complex metabolic disorders such as polycystic ovary syndrome (PCOS) and diabetes. Metformin's therapeutic effects are largely metabolic and do not directly address the chronic inflammation, tissue fibrosis, microvascular injury, and impaired cellular regeneration that characterize these conditions [70].

This gap highlights the importance of integrating biologically active cell-based strategies. Polycystic ovarian disease/PCOS is a complex endocrine metabolic disorder characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology, often with low-grade chronic inflammation, oxidative stress, and fibrosis in ovarian stroma (Table 8) [71,72]. UC and UCB-derived MSCs possess intrinsic anti-inflammatory, anti-fibrotic, angiogenic, and tissue-repair properties that can target pathophysiological factors that metformin and nanocarriers alone cannot correct. Moreover, nanoparticle-enhanced delivery of metformin still faces issues such as biocompatibility, long-term safety, and limited ability to repair damaged tissue. Therefore, combining metformin with UCB-derived MSC-based regenerative therapy offers a more comprehensive approach by simultaneously improving metabolic regulation and promoting structural and functional tissue recovery.

Pre-clinial evidence and clinical application

UCB- and UC-derived cells represent a versatile and promising cell source for regenerative and immunotherapeutic applications, bridging preclinical success with emerging clinical translation (Table 9).

Limitations of current evidence and ongoing challenges

Despite promising outcomes across neurological, cardiovascular, metabolic, and renal models, several limitations must be acknowledged in interpreting the cited studies. Many pre-clinical experiments employ small sample sizes, which restrict statistical power and limit the generalizability of the findings. Moreover, animal models do not fully replicate human disease complexity, for example, rodent spinal cord injury or MCAO stroke models cannot accurately mirror the chronic inflammatory, metabolic, and anatomical variations present in patients. Most studies also utilize short follow-up periods, providing limited insight into long-term safety, durability of functional recovery, and potential late-onset adverse effects such as ectopic differentiation or immune reactions. In clinical trials, many investigations remain in early phases (I/II), often without appropriate placebo controls or sufficiently powered randomized designs, making it difficult to draw firm conclusions about efficacy.

From a translational standpoint, several processing and manufacturing challenges remain unresolved. Beyond the commonly cited "variability in processing," the field is actively debating specific standardization needs, including:

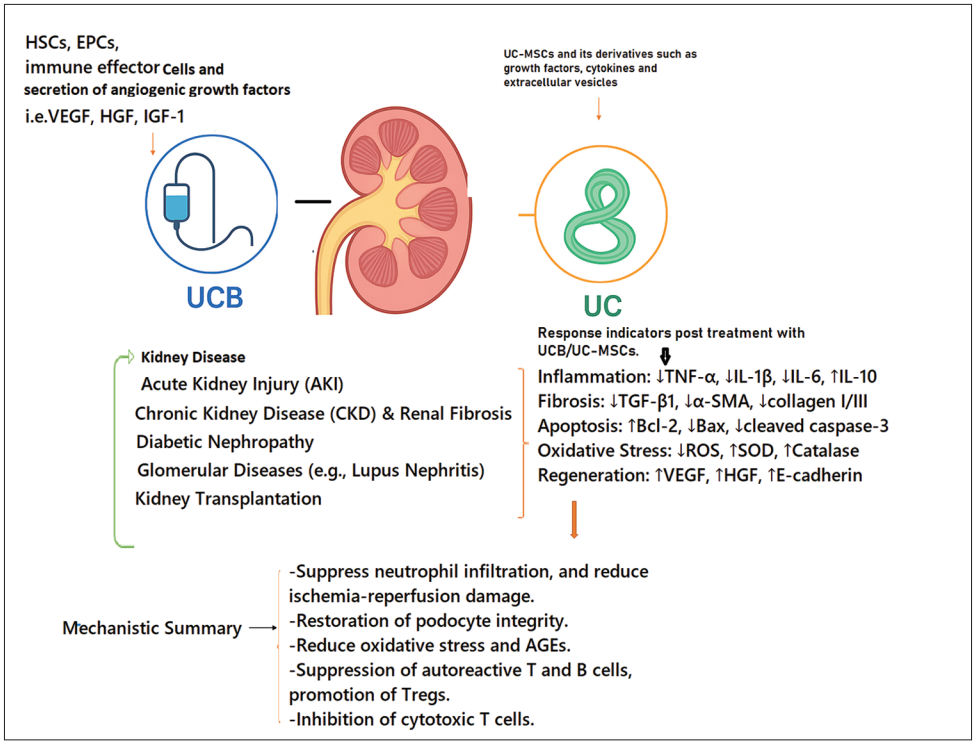

Fig. 10: Mechanistic overview for the regenerative effects of UCB and UC in nephrology applications

Table 7: Mechanistic roles in fertility and reproductive therapy

Mechanism	UC/UCB components involved	Fertility-relevant effects
Ovarian regeneration	UC-MSCs derived paracrine factors (VEGF, IGF-1, bFGF)	Restores folliculogenesis, increases ovarian reserve markers (AMH, AFC), repairs granulosa cells [64].
Endometrial repair	UC-MSCs, CB-derived EPCs	Promotes angiogenesis, reduces fibrosis, improves receptivity in thin endometrium [65].
Anti-Inflammatory and immunomodulatory	IL-10, TGF-β, HLA-G expression are secreted by several immune and stromal cell types	Suppresses excessive Th1/Th17, promotes Treg; reduces autoimmune-related infertility (e.g., premature ovarian insufficiency) [66].
Protection from chemotherapy/ radiotherapy damage	Secretion of antioxidant enzymes and exosomes from UC-MSCs	Reduces oxidative stress, prevents follicle apoptosis.
Support in assisted reproductive technology	UC-MSCs, CB plasma growth factors	Improves embryo implantation rates, reduces recurrent implantation failure risk.
Spermatogenic niche restoration	UC-MSCs, CB-derived HSCs	Supports Leydig/Sertoli cell repair, stimulates spermatogonial stem cell activity [67].

UCB: Umbilical cord blood, VEGF: Vascular endothelial growth factor, IGF-1: Insulin-like growth factor-1, EPCs: endothelial progenitor cells, TGF-β: Transforming growth factor-beta, IL: Interleukin, HLA-G: Human leukocyte antigen

Table 8: Mechanistic roles of UCB and UC in alleviating polycystic ovarian disease through several complementary biological pathways

Mechanism	UC/UCB components	Potential benefit in PCOD
Anti-inflammatory effect	IL-10, TGF-β, HLA-G	Suppresses ovarian inflammatory cytokines (TNF-α, IL-6), potentially improving follicular environment.
Reduction of oxidative stress	Antioxidant enzymes, exosomal miRNAs	Protects granulosa cells, improves oocyte quality.
Anti-fibrotic effect	MMP-2, MMP-9, HGF	Reduces ovarian stromal fibrosis, restoring normal architecture.
Endocrine regulation	IGF-1, VEGF	May normalize LH/FSH ratio, improve estrogen/progesterone balance.
Insulin sensitivity improvement (indirect)	Exosomal miRNAs targeting insulin pathways	Could help metabolic aspects of PCOS by modulating PI3K/Akt and AMPK signaling.
Folliculogenesis support	Exosomes and growth factors such as VEGF, bFGF	Promotes recruitment and maturation of healthy follicles.

TGF-β: Transforming growth factor-beta, IL: Interleukin, HLA-G: Human leukocyte antigen, TNF-α: Tumor necrosis factor-α, miRNA: microRNA, MMP: Matrix metalloproteinases, HGF: Hepatocyte growth factor, VEGF: Vascular endothelial growth factor, PCOS: Polycystic ovary syndrome, AMPK: AMP-activated protein kinase

- Adoption of xeno-free or chemically defined culture media to eliminate fetal bovine serum–related immunogenicity and batch variability.
- Establishment of minimum release criteria for UC-MSC products,

Table 9: Therapeutic potential of UCB and UC-derived cells in preclinical/clinical research

Study	Model/disease	Cell type	Administration	Outcomes	Reference
Wang *et al.* (2024)	SCI in rats	UC-MSCs	Transplantation into lesion area	Improved motor function (BBB scale), synapse formation, reduced inflammation, myelin repair	[73]
Xu *et al.* (2025)	Ischemic stroke (MCAO model in mice)	UC-MSCs	Intravenous	Decreased infarct volume, improved motor/cognitive performance, modulated apoptosis-related proteins, anti-inflammatory	[74]
Drabik *et al.* (2025)	Myocardial infarction (pigs)	WJ-MSCs	Local myocardial injection	Improved LVEF, reduced fibrosis, increased angiogenesis via VEGF/HGF	[75]
Wu *et al.* (2025)	Diabetic wound healing (mice)	Genetically modified UC-MSCs	Local injection to wound	Enhanced wound closure, M2 macrophage polarization, increased VEGF/TGF-β, ECM remodeling	[76]
Lv *et al.* (2025)	Kidney fibrosis (UUO in rats)	UC-MSCs	Intravenous	Reduced collagen deposition, improved renal function, inhibited TGF-β1/Smad3.	[77]
Ma *et al.* (2025)	SCI (Clinical trials)	UC-MSCs	Transplantation (clinical), Intravenous	Motor improvement (ASIA scale) and secretion of neurotrophic factors.	[78]
Huang *et al.* (2025)	Alzheimer's Disease (clinical)	UC-MSCs	Intravenous	Reduced TNF-α and IL-6, improved MMSE & ADAS-Cog, increased hippocampal volume, decreased amyloid-β	[79]
Tzng *et al.* (2024)	Myocardial infarction (porcine & human)	UC-MSC-derived exosomes	Direct myocardial injection	Improved LVEF, reduced scarring, increased VEGF/HGF, early functional recovery	[80]
Desai and Bhonde (2025)	Type 1 Diabetes (Clinical)	UC-MSCs	Intravenous	Improved HbA1c, fasting glucose, increased C-peptide, modulated inflammatory cytokines	[81]
Wolf *et al.* (2025)	Multiple Sclerosis (RRMS, Clinical)	UC-MSCs	Intravenous	Decreased lesion volume (MRI), improved EDSS scores, increased BDNF & NGF, T-cell modulation	[82]
Huang *et al.* (2025)	Acute Myeloid Leukemia (Clinical)	CD33-CAR-NK cells from UCB	Intravenous (after conditioning)	High remission, low relapse, no CRS/GVHD and sustained cytotoxic activity.	[83]

UCB: Umbilical cord blood, SCI: Spinal cord injury, LVEF: Left ventricular ejection fraction, HGF: Hepatocyte growth factor, VEGF: Vascular endothelial growth factor, TGF-β: Transforming growth factor-beta, ECM: Extracellular matrix, TNF-α: Tumor necrosis factor-α, IL: Interleukin
MRI: Magnetic resonance imaging, EDSS: Expanded disability status scale, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor

such as viability thresholds, identity markers (CD73, CD90, CD105), karyotype stability, and functional potency assays (e.g., immunosuppression capacity).
- It is crucial to standardize donor-related variables such as gestational age, maternal health, and the duration of umbilical cord processing after delivery.
- Harmonization of storage, cryopreservation, and thawing protocols, which significantly influence cell viability and therapeutic performance.
- The definition of optimal dosing, route of administration, and treatment frequency remains inconsistent across current studies and trials.

Addressing these limitations and moving toward internationally accepted manufacturing and clinical standards will be essential for ensuring reproducibility, safety, and eventual large-scale clinical translation of UC-MSC-based therapies.

CHALLENGES AND REGULATORY LIMITATIONS IN UMBILICAL CORD BLOOD/TISSUE

Clinical and technical barriers

Limited cell yield

A single umbilical cord contains a small number of stem cells, often insufficient for treatment without *ex vivo* expansion [84].

Variability in processing

Differences in isolation and culture protocols lead to inconsistent cell viability, differentiation potential, and therapeutic efficacy [85].

Regulatory and logistical hurdles

Strict regulatory frameworks and complex logistics (e.g., cryopreservation, storage, transport) delay clinical application and raise costs [86].

Ethical, legal, and social considerations

Informed consent

Ethical use depends on thorough parental consent, including clarity about storage policies and future applications [87].

Regulatory disparities

Diverse standards among agencies (e.g., Food and Drug Administration, European Medicines Agency, ISSCR) suggest that there must be global harmonization of stem cell policies [88].

Public awareness gaps

Persistent myths and lack of understanding hinder donor participation; education and transparency are critical for informed decision-making [89].

FUTURE RECOMMENDATION

Technological advancements

Many of the technological advancements described have direct applications in regenerative medicine, especially where biomaterials, scaffolds, and nano-engineered systems are required. Modern PU technologies such as 3D-printed polyurethane scaffolds, PU-based hydrogels, nanocomposite polyurethanes, and stimuli-responsive materials are increasingly used to mimic ECM, support cell adhesion, promote angiogenesis, and deliver therapeutic cells or bioactive molecules. Advanced polyurethane scaffolds can be combined with regenerative therapies, including mesenchymal stem cells (MSCs), growth factors, or tissue-repairing cytokines, to enhance cell survival, proliferation, and tissue integration. These biomaterials can be engineered for controlled release, allowing sustained delivery of growth factors or anti-inflammatory agents important for wound healing, diabetic ulcers, nerve regeneration, and cartilage repair [90].

Scaffold-based bioprinting with UC/UCB stem cells shows promise for applications in organ repair and wound healing. Gene-editing tools like CRISPR are being used to enhance stem cell functionality and therapeutic precision [91,92]. Hydrogels represent a versatile and promising class of biomaterials with increasing applications in modern therapeutics, particularly in regenerative medicine, wound healing, and controlled drug delivery, but further optimization and clinical validation are still needed [93].

Expansion and optimization

Ongoing efforts target the challenge of limited initial cell yield.

Innovations include hypoxic preconditioning and optimizing culture conditions to support large-scale cell proliferation while preserving therapeutic potency [94].

Therapeutic integration

Biomaterials (e.g., scaffolds, hydrogels, nanocarriers) and pharmacological agents are being combined with UC/UCB stem cells to improve cell retention, survival, and differentiation at the injury site [95]. Nanoparticle-based delivery systems can be directly linked to regenerative therapies because they enhance the stability, bioavailability, and targeted delivery of key regenerative molecules such as growth factors, cytokines, and antioxidants, all of which are essential for tissue repair in diabetes. By protecting these molecules from rapid degradation and releasing them in a controlled manner, nanoparticles amplify angiogenesis, reduce oxidative stress, and improve the overall healing microenvironment. In addition, nanoparticles can support stem cell and mononuclear cell therapies by improving cell survival, homing, and paracrine activity in damaged diabetic tissues. Together, this integration of nanotechnology with regenerative approaches offers a more efficient and sustained therapeutic strategy for promoting wound healing, β-cell protection, and tissue regeneration in diabetic patients. These combinatorial strategies are expected to significantly enhance regenerative outcomes [96].

CONCLUSION

Umbilical cord (UC) and UCB-derived stem cells represent a versatile, immune-privileged, and ethically favorable source for regenerative medicine, with therapeutic benefits driven by paracrine signaling, immunomodulation, angiogenesis, anti-apoptotic and anti-fibrotic effects, and direct differentiation. Their broad clinical applications span neurological, cardiovascular, hepatic, renal, musculoskeletal, reproductive, dermatological, gastroenterological, and oncological diseases, where they promote neuroprotection, tissue regeneration, immune regulation, vascular repair, and targeted cancer therapy. Despite encouraging preclinical and early clinical results, challenges such as low cell yield, variability in processing methods, heterogeneous outcomes, and regulatory barriers continue to limit translation into routine practice. Advances in 3D bioprinting, tissue engineering, gene editing, exosome-based delivery, and integration with biomaterials or pharmacological agents promise to enhance their efficacy. With standardized protocols, robust clinical validation, and harmonized regulatory frameworks, UC- and UCB-derived stem cells hold strong potential to emerge as a cornerstone of next-generation regenerative and personalized therapies.

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ETHICAL STATEMENT

Not Applicable.

CONFLICTS OF INTEREST STATEMENT

None.

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