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REVIEW

Sheep Umbilical Cord Mesenchymal Stem Cells: Biological Characteristics, Ethical Considerations, and Translational Applications

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ABSTRACT

Mesenchymal stem cells (MSCs) are widely used in regenerative medicine due to their self-renewal capacity, multilineage differentiation potential, and paracrine activity. Limitations associated with the sourcing and scalability of human MSCs have increased interest in xenogeneic alternatives, particularly sheep umbilical cord–derived MSCs (sUC-MSCs). These cells display high proliferative capacity, stable karyotypes, and a typical MSC immunophenotype (CD44, CD73, CD90, CD105), with low basal immunogenicity. sUC-MSCs exhibit osteogenic, chondrogenic, and adipogenic differentiation potential and secrete angiogenic and immunomodulatory factors, including VEGF, HGF, IGF-1, TGF-β, and IL-10. Owing to their biological similarities to human MSCs and accessibility from perinatal tissue, sUC-MSCs represent a suitable large-animal cell source for translational and preclinical research. Bioengineering strategies, including hydrogels, chitosan-based matrices, and peptide-functionalized scaffolds, further enhance their survival and delivery efficiency. Although challenges remain regarding immunogenicity and regulatory standardization, recent advances in omics profiling, gene editing, and extracellular vesicle–based delivery support the continued evaluation of sUC-MSCs as a scalable and ethically sustainable xenogeneic cell source for regenerative applications.

Keywords: Bioengineering applications, Immunomodulation, Mesenchymal stem cells, Paracrine signaling, Regenerative medicine, Sheep umbilical cord, Xenogenic stem cells

1. Introduction

Mesenchymal stem cells represent the building blocks of regenerative medicine owing to their exceptional self-renewal capacity, multilineage differentiation ability, and marked paracrine effects [1]. While initially isolated from bone marrow, MSCs are now being extensively studied from a wide variety of sources, including adipose tissue, dental pulp, and umbilical cord [2]. Their therapeutic importance is due to the ability of these cells to differentiate into osteogenic, chondrogenic, and adipocytic lineages and their potent immunomodulatory and trophic effects, which help in tissue repair [3]. Despite significant

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advances, issues of sourcing, scalability, and ethical concerns with human-derived MSCs have resulted in an increasing interest in exploring alternative cellular sources [4].

Recently, xenogenic MSCs, derived from non-human animals, have gained attention as promising candidates for preclinical models and possible therapeutic applications [5, 6]. The advantages of using these cells include being highly available, with fewer ethical issues compared to human embryonic tissues, and the possibility of developing scalable biobanking systems [7, 8]. Moreover, animal-derived MSCs provide an important basis for studying interspecies immunological interactions, testing regenerative strategies, and developing cell-based products for veterinary and human applications [9]. However, their use in clinical settings requires a deep understanding of their biological properties, safety profile, and translational barriers [10]. Within xenogenic sources, the sheep umbilical cord is considered an ethically sustainable and physiologically relevant reservoir of mesenchymal stem cells, representing an ideal model for translational regenerative studies.

Among xenogenic sources, the umbilical cord of sheep is one of the most promising for the derivation of MSCs [11]. sUC-MSCs show high proliferation rates, stable phenotypic characteristics, and great differentiation potential similar to those of human UC-MSCs [12]. Furthermore, sheep are physiologically and anatomically similar to humans to a considerable extent and thus represent a popular large-animal model in preclinical research in regenerative medicine (cf. Table 1) [13]. This combination is unique and confers a twofold role on sUC-MSCs: enabling rigorous preclinical testing and offering the prospect of a scalable medicinal product.

Xenogenic MSCs, besides their intrinsic capacity for regeneration, are being increasingly combined with biomaterial scaffolds, peptides, and advanced drug delivery systems to further enhance their viability, homing potential, and therapeutic outcomes [15]. MSCs generated from sheep have been explored for their applications in bone and cartilage regeneration [16], repairs of cardiovascular damage [17], and wound healing [18]. The developments in encapsulation technologies, such as chitosan-based scaffolds, hydrogels, and lyophilization, improve translational abilities due to overcoming problems with storage, transportation, and immunological recognition of the cells [19–22]. Integration of xenogenic MSCs with bioengineered carriers thus paves the way toward ready-to-use regenerative medicine systems.

Despite these breakthroughs, xenogenic MSCs are still poorly researched compared to their human-derived counterparts, with several crucial questions still open from the viewpoint of immunogenicity, zoonotic safety, and regulatory approval. The current review aims to provide an exhaustive analysis of the current status concerning research on xenogenic MSCs, focusing on MSCs derived from sheep umbilical cords. Emphasize their biological features, modes of action, preclinical and clinical uses, integration with biomaterials, and the translational hurdles that have to be overcome to realize their therapeutic promises. The present review consolidates current information on this developing area of research in regenerative medicine, connecting basic studies with commercial and therapeutic advances.

The objective of this narrative review is to synthesize current knowledge on sheep umbilical cord–derived mesenchymal stem cells (sUC-MSCs) by consolidating their biological characteristics, mechanisms of action, comparative position among xenogenic MSC sources, integration with biomaterials and bioengineering strategies, and their emerging translational relevance in both human and veterinary regenerative medicine.

This narrative review was prepared using a structured literature search conducted in PubMed, Scopus, Web of Science, and Google Scholar. Search terms included “sheep umbilical cord mesenchymal stem cells,” “sUC-MSCs,” “xenogeneic MSCs,” “ovine MSCs,” “MSC bioengineering,” and “regenerative medicine.” Eligible sources included peer-reviewed articles published between 2006 and 2025 that addressed the biological characteristics, translational applications, ethical considerations, or bioengineering strategies related to sUC-MSCs or comparable xenogeneic MSC models. Exclusion criteria included non-English publications, conference abstracts, and studies lacking primary MSC characterization. Additional references were identified through citation tracking of key articles.

Table 1. Comparative Physiological Parameters of Sheep and Humans [14].

Physiological Variables	Sheep	Human
Adult body weight (kg)	60–70	70–80
Lifespan (y)	10–12	70–80
Brain weight (kg)	0.13–0.14	1.3–1.4
Rectal temperature (°C)	38–39.5	36.7–37.5
Respiratory rate (breaths/min)	15–40	9–20
Heart rate (beat/min)	50–88	50–100
Maximum heart rate (beats/min)	260–280	140–150
Cardiac output (L/min)	1.5–13.2	4–8
Plasma volume (mL/kg)	37	43
Blood volume (mL/kg)	49	70
Haemoglobin (g/100 mL)	9–15	14–16

2. Sources of xenogenic mesenchymal stem cells

2.1. Umbilical cord–derived MSCs from animal sources

Umbilical cord (UC) tissue is one of the most promising sources of MSCs in both human and animal systems due to its non-invasive collection, high cellular yield, and significant proliferative capacity [23]. Xenogenic UC-MSCs have been successfully isolated in many species, including ovine, bovine, porcine, and equine models. Sheep UC-MSCs are particularly attractive because of their phenotypic similarity to human UC-MSCs and their capacity for long-lasting multilineage differentiation [24, 25]. Porcine UC-MSCs have been widely explored owing to the close anatomic and physiological similarities between pigs and humans, making them suitable translational models for cardiovascular and metabolic diseases [26]. Equine UC-MSCs are mainly explored in veterinary regenerative medicine, with a special focus on musculoskeletal repair, which underlines their double role in human pre-clinical studies and veterinary treatments [27]. Table 2 gives an overview in comparison of the UC-MSCs derived from different animal species, starting from their biological properties and differentiation potential, applications, and translational advantages/limitation.

2.2. Bone marrow–derived MSCs from animal models

Bone marrow (BM) represents the traditional and most extensively studied source of MSCs across a variety of animals. Initially identified in humans and rodents, bone marrow-derived mesenchymal stem cells (BM-MSCs) have since been successfully isolated from many xenogenic species, including sheep, goats, rabbits, pigs, and dogs [33]. These consistently show characteristic fibroblast-like morphology, plastic adherence, and expression of conventional MSC surface markers (CD44, CD73, CD90, CD105), while lacking hematopoietic lineage markers (CD34, CD45) [34]. Notably, cultured BM-MSCs also exhibit robust osteogenic and chondrogenic differentiation capabilities, making them particularly relevant in skeletal tissue engineering and orthopedic regenerative strategies [35].

In preclinical studies, bone marrow-derived mesenchymal stem cells from large animals, such as sheep and pigs, are indispensable for the pre-clinical testing of bone defect repair, cartilage regeneration, and spinal fusion approaches prior to clinical translation [36]. Ovine BM-MSCs have been extensively used in critical-sized defect models to test bone substitutes, scaffolds, and bioactive coatings, providing translational information more predictive than that

Table 2. Comparative overview of umbilical cord–derived MSCs from different animal species.

Species	Key Characteristics	Differentiation Potential	Applications/Uses	Advantages	Limitations	Reference
Sheep (sUC-MSCs)	High proliferation rate; stable karyotype; ISCT MSC markers (CD44, CD73, CD90, CD105 +)	Osteogenic, chondrogenic, adipogenic, neurogenic	Preclinical large-animal models; bone/cartilage regeneration; wound healing	Close physiological similarity to humans; ethically non-contentious; high yield; scalable biobanking	Limited clinical trials; potential immunogenicity in human use	[28]
Porcine (pUC-MSCs)	Phenotypically similar to human UC-MSCs; robust growth	Osteogenic, adipogenic, hepatic, cardiovascular lineages	Cardiovascular models, liver regeneration, xenotransplantation studies	Strong anatomical/physiological resemblance to humans; widely used in translational models	Risk of zoonotic pathogens (e.g., porcine endogenous retroviruses)	[29]
Bovine (bUC-MSCs)	Strong proliferative profile; consistent immunophenotype	Osteogenic, chondrogenic, adipogenic	Orthopedic defect models; veterinary tissue engineering	Large tissue availability; cost-effective source	Limited use in human translation; mainly veterinary	[30]
Equine (eUC-MSCs)	Stable phenotype; immunomodulatory capacity	Osteogenic, chondrogenic, tenogenic	Musculoskeletal repair in horses (ligament, tendon, cartilage)	High relevance for veterinary regenerative medicine	Species-specific, limited cross-translation to human therapy	[31]
Canine/Feline (c/fUC-MSCs)	Similar properties to human UC-MSCs; secrete bioactive factors	Multilineage (bone, cartilage, fat, neural)	Veterinary regenerative therapies (osteoarthritis, wound healing)	Companion animal therapies; translational veterinary insights	Not suitable for direct human therapeutic development	[32]

from rat studies due to their closer anatomical and biomechanical similarities to humans [37]. Porcine BM-MSCs are also commonly employed in models of cardiovascular and metabolic disorders due to their physiological similarity to humans [38]. These interspecies illustrate the importance of BM-MSCs in translating basic mechanistic studies to therapeutically relevant treatments [39]. Biologically, BM-MSCs are noted for their strong osteochondral lineage commitment, which has solidified their position as the gold standard cell type for the repair of musculoskeletal tissues. There are, however, certain limitations: bone marrow aspiration is an invasive procedure, yields decrease significantly with donor age, and age-related changes reduce their proliferative and differentiation potential during extended passages [40]. The above-mentioned drawbacks point to a growing preference for using perinatal tissues, such as the umbilical cord, for scaled applications, despite the continued relevance of BM-MSCs as a yardstick against which comparisons are made.

BM-MSCs have demonstrated substantial therapeutic benefit in human-relevant preclinical models and veterinary translations. Thus far, they have been applied in equines and canines for the treatment of tendon injuries, osteoarthritis, and ligament repair. In these instances, they efficiently modulated inflammation and enhanced tissue repair [41]. Due to their thorough characterization, consistent performance in large-animal models, and identified role in musculoskeletal healing, BM-MSCs have become a gold standard against which other sources of MSCs are evaluated [42]. Despite practical limitations, including invasive harvesting and decreased functionality with donor age, BM-MSCs continue to be a key contributor to xenogenic stem cell research and a basic reference in regenerative medicine.

2.3. Adipose tissue–derived MSCs

In recent times, adipose tissue has been recognized as a suitable and abundant source of mesenchymal stem cells (AD-MSCs) in sheep, pigs, horses, and dogs [43]. Compared to bone marrow, the procurement of adipose tissue is relatively less invasive, yields higher frequency of stem/progenitor cells, and provides a substantial stromal vascular fraction that can be rapidly processed for regenerative applications [44]. Xenogenic AD-MSCs consistently exhibit typical mesenchymal characteristics, adherence to plastic surfaces, and are capable of multilineage differentiation into adipogenic, chondrogenic, osteogenic, and, under specific conditions, neurogenic lineages. Their immunomodulatory properties are further enhanced by the secretion of bioactive molecules, such as IL-10, PGE2, and TGF-β, facilitating tissue repair through anti-inflammatory and paracrine mechanisms [45]. These characteristics have made AD-MSCs particularly important in both preclinical translational models and veterinary regenerative medicine.

In this regard, xenogenic AD-MSCs have found applications in a wide range of regenerative studies, including musculoskeletal, cardiovascular, and wound healing areas [46]. Equine and canine models have pointed out the efficacy of AD-MSCs during tendon repair and in osteoarthritis cases by reducing inflammation and restoring function. Porcine models have been useful in ischemia and myocardial injury studies [47]. Despite donor variability and species differences affecting their potency, accessibility, high yield, and strong regenerative profile place AD-MSCs among the leading xenogenic sources, complementary to bone marrow and umbilical cord MSCs in translational medicine.

2.4. Placenta and perinatal tissues

Perinatal tissues, including the placenta, amniotic membrane, and amniotic fluid, serve as significant sources of MSCs in xenogenic models, owing to their distinctive biological and ethical benefits [48]. These tissues are typically discarded after childbirth, rendering their collection non-invasive, morally permissible, and plentiful. MSCs sourced from placenta and associated tissues have significant proliferative ability, prolonged lifetime, and decreased senescence in comparison to adult-derived MSCs. Its have immunoprivileged characteristics, partially due to the prenatal environment, allowing them to avoid host immune monitoring and diminish the likelihood of rejection [49]. Moreover, perinatal MSCs have been documented to exhibit elevated expression of stemness-associated genes and feature elongated telomeres, facilitating prolonged proliferation and consistent differentiation capacity across several lineages [50].

In xenogenic contexts, MSCs have been isolated from placental and perinatal tissues in ovine [51], bovine [52], porcine [53], and equine [54] models, showing effectiveness in a wide range of regenerative applications, including neural injury, hepatic repair, cardiovascular regeneration, and wound healing [55]. For instance, ovine placental MSCs exert neuroprotective and angiogenic properties, while the use of bovine-derived perinatal MSCs has been explored for musculoskeletal repair. Their secretome is rich in bioactive molecules that include VEGF, HGF, and TGF-β, facilitating immunomodulation, angiogenesis, and extracellular matrix remodeling [56–60]. Collectively, these attributes establish xenogenic perinatal tissues as a sustainable and scalable cell

source and provide a robust platform for translationally oriented regenerative medicine, connecting preclinical research with potential clinical applications [61–66].

2.5. Comparative evaluation across species

A stringent interspecies comparison of MSCs underlines both conserved biological features and species-specific differences that impact on translational relevance [67–71]. Thus, across mammalian models, MSCs generally display fibroblast-like morphology, plastic adherence, and the expression of CD44, CD73, CD90, and CD105 in the absence of hematopoietic markers like CD34 and CD45 [72–74]. Despite such a shared phenotype, however, differences in proliferation rate, lineage commitment, and immunomodulatory efficacy reflect genomic and microenvironmental diversity across species and tissue origins. Perinatal sources-most notably umbilical cord and placental MSCs-exhibit consistently superior proliferation and delayed senescence when compared with adult-derived cells, whereas bone marrow and adipose sources have demonstrated stronger osteochondral differentiation with more limited expansion [75–78]. Comparative transcriptomic analyses further uncover species-dependent cytokine and growth-factor expression-including, for example, VEGF, IL-10, and TGF-β-that modulate paracrine performance and regenerative potential. Large-animal models, most notably ovine and porcine systems, offer physiologically relevant intermediates between small-animal and human studies, reinforcing sheep umbilical cord MSCs as a biologically stable and ethically favorable bridge toward clinical translation [79–82].

3. Sheep umbilical cord-derived MSCs

MSCs derived from sheep umbilical cords represent an important cell source due to their physiological coherence and translational relevance for regenerative medicine applications [83]. These cells were non-invasively derived from postnatal umbilical tissue and have significant proliferative capacity, genomic stability, and low immunogenicity; they thus constitute a sustainable and ethically acceptable alternative to human MSCs [84]. Their cellular activity, paracrine signaling, and immunomodulatory features share close similarities with human systems and thus are considered a critical model for preclinical testing and therapeutic development. Besides the basic stemness characteristics, sUC-MSCs possess dynamic molecular and functional properties that modulate their regenerative potential, including lineage differentiation and the secretion of bioactive trophic factors responsible for tissue repair and immune modulation [14, 28]. Understanding these biological pathways forms the basis for their improvement in complex treatment approaches, biomaterial interactions, and translational applications for human and veterinary medicine.

3.1. Biological and phenotypic characteristics of sUC-MSCs

sUC-MSCs show unique morphology, phenotype, and proliferative features that demarcate their biological entity and further support their regenerative capability. In culture, they display a characteristic spindle-shaped morphology with a strong tendency for adhesion to flexible surfaces and yield homogenous monolayers typified by uniformly elongated nuclei and filaments of well-organized actin [85]. These cells maintain structural integrity and genomic stability over multiple passages without any evidence of spontaneous transformation or chromosomal abnormalities, which is important for the qualifications of translation and clinical application [86]. sUC-MSCs display typical mesenchymal surface markers, such as CD29, CD44, CD73, CD90, and CD105, and lack hematopoietic and endothelial markers such as CD34, CD45, and CD31, according to the minimum criteria defined by the International Society for Cellular Therapy (ISCT) [87]. Their proliferative kinetics are outstanding, marked by a high population-doubling rate and optimal colony-forming efficiency indicative of good self-renewal ability and metabolic robustness [88]. At the molecular level, they maintain the expression of transcription factors typical of stemness, such as OCT4, SOX2, and NANOG, denoting partial retention of general characteristics without threatening lineage specificity. Diminished expression of major histocompatibility complex (MHC) class II molecules and the absence of costimulatory markers (CD80, CD86) give them partial immunological privilege, allowing for possible allogenic and xenogenic therapeutic uses [11]. All these properties taken together have established sUC-MSCs as physiologically stable, reproducible, and scalable cell entities and thus provide a reliable backbone for further studies on their differentiation behavior, secretome activity, and regenerative processes.

3.2. Differentiation and secretome profile of sUC-MSCs

sUC-MSCs have broad multilineage differentiation and secretory profile, both collectively defining their regenerative properties. Under appropriate inductive

conditions, they have efficiently differentiated into osteogenic, chondrogenic, and adipogenic lineages, producing calcium-mineralized nodules, cartilage-like matrices, and lipid-laden adipocytes, respectively, while also showing trans-lineage plasticity toward endothelial and neurogenic phenotypes [85]. This plasticity is made possible by the steady expression of lineage-specific transcription factors like RUNX2, SOX9, and PPAR-γ, which regulate structural and biochemical developments. Complementing their differentiation potential, sUC-MSCs predominantly exert their therapeutic effects via an active secretome rich in trophic factors, cytokines, and extracellular vesicles. Key secreted mediators like vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), and interleukin-10 (IL-10) promote angiogenesis, immunomodulation, and cellular survival in injury sites [89]. Their small-sized exosomes carry microRNAs and regulatory proteins that reduce inflammation, limit oxidative stress, and promote endogenous tissue repair. The reciprocity between differentiation plasticity and paracrine signaling provides the mechanistic basis for sUC-MSC-mediated regeneration and builds a framework for their study in therapeutic and bioengineering applications [85].

3.3. Therapeutic applications of sUC-MSCs

sUC-MSCs exert antitumor effects in melanoma models through reducing cell proliferation, migration, and survival due to the induction of autophagy and apoptosis, and TGF-β and NF-κB signaling modulation [83]. Meanwhile, advances in their manipulation specifically via telomerase gene (TERT) transfection have allowed for the generation of immortalized sUC-MSC lines maintaining differentiation potential and genomic stability over extensive passages, further improving scalable therapeutic applicability [84]. With the rarity of regenerative models of injury utilizing sUC-MSCs, the above findings emphasize its potential to alter pathological or normal microenvironments through the use of paracrine signaling and cell pathway modulation, thus giving a mechanistic basis for future studies in tissue repair.

The current research on sUC-MSCs ranges from basic studies on isolation to specific investigations into regeneration and modulation of diseases. Table 3 summarizes the main studies, their therapeutic objectives, and major findings that highlight the translational importance of sUC-MSCs.

3.4. Scalability and production advantages

sUC-MSCs have unique advantages regarding scalability and manufacturing, making them a suitable basis for translational and industrial applications in regenerative medicine [91]. The isolation of sUC-MSCs from postnatal umbilical tissue is an abundant and ethically amiable source; their high proliferative capacity and genomic stability allow for extended expansion without loss of stemness or differentiation capability [68, 90]. Recent improvements, including telomerase-mediated immortalization of sUC-MSCs, enhanced their longevity and batch consistency, supporting the creation of standardized cell banks for research, clinical evaluation, and biopharmaceutical manufacturing [68]. sUC-MSCs maintain a uniform immunophenotype over numerous passages and can be cryopreserved without functional impairment, which allows repeated manufacturing on a large scale according to GMP criteria. Due to their low immunogenicity and compatibility with serum-free cultivation techniques, sUC-MSCs represent a cost-effective and ethically acceptable tool for continuous cell supply, translating laboratory research into industrial bioprocess development and clinical application [14].

3.5. Dual role in human and veterinary regenerative medicine

sUC-MSCs have a distinct translational role at the interface of human and veterinary regenerative medicine. Their biological similarity to human MSCs in terms of immunophenotype and paracrine function makes them an excellent large-animal model for the validation of stem-cell therapies before clinical application, while their availability from livestock animals facilitates their direct therapeutic use in veterinary patients [92–94]. In preclinical settings, sUC-MSCs thus allow for the assessment of safety, biodistribution, and efficacy under physiological conditions that closely mirror human anatomy and immunology, enhancing the predictive power of translational research. Simultaneously, in veterinary medicine, these cells represent a practical and ethically acceptable treatment modality for musculoskeletal, dermal, and neurological injuries affecting companion and farm animals [95–97]. This dual usability represents a “One Health” paradigm, whereby advances made in animal models drive human medical progress, while veterinary application of MSC-based products informs and improves safety and efficacy. Taken together, this across-the-sectors

Table 3. Summary of published studies on sUC-MSCs and their therapeutic aims.

Main Focus / Experimental Model	Therapeutic or Experimental Aim	Key Findings	Reference
Isolation and characterization of ovine UC-MSCs	To establish a reliable protocol for isolating, expanding, and validating sUC-MSCs as a potential regenerative cell source	Confirmed fibroblast-like morphology, stable karyotype, and trilineage differentiation with canonical MSC marker expression	[14]
Biological characterization of sheep UC-MSCs	To assess morphological and phenotypic properties of sUC-MSCs for their suitability in regenerative applications	Demonstrated stable proliferation, typical MSC morphology, and consistent mesenchymal immunophenotype	[28]
Derivation of MSCs from Ovine Wharton's jelly	To validate Wharton's jelly as a non-invasive source of ovine MSCs for future regenerative therapies	Successfully isolated MSCs from umbilical Wharton's jelly with standard marker expression and multilineage potential	[90]
Immortalization of sUC-MSCs via TERT transfection	To generate stable, long-term expandable sUC-MSC lines suitable for research and therapeutic production	Created TERT-immortalized sUC-MSC lines maintaining differentiation capacity, karyotype stability, and safety	[85]
Anti-tumor effects of sheep UC-MSCs on melanoma cells	To assess whether sUC-MSCs or their conditioned media modulate tumor progression and inflammatory signaling	Inhibited melanoma proliferation and migration through autophagy and apoptosis induction and TGF-β/NF-κB modulation	[83]

approach places sUC-MSCs as both a physiologically diverse medicinal product and as a strategic link between basic research, clinical translation, and commercial biotechnological development.

4. Mechanisms of action of sUC-MSCs

The therapeutic activity of sUC-MSCs arises from an interconnected set of mechanisms including homing, intercellular signaling, immunomodulation, stromal niche modulation, and lineage differentiation which are conceptually summarized in Fig. 1. After systemic or local delivery, sUC-MSCs migrate toward injured tissues through chemokine–receptor interactions most prominently the CXCR4/SDF-1 axis, but also CCR2/CCL2 and CX3CR1/fractalkine networks which together guide directed trafficking and retention within inflammatory microenvironments [98, 99]. Once localized, sUC-MSCs engage in intercellular signaling via several conserved pathways. Paracrine activation of PI3K–Akt and ERK promotes cell survival and anti-apoptotic responses in host tissues, while Notch and Wnt/β-catenin pathways contribute to regulating progenitor cell fate and angiogenic remodeling. TGF-β/SMAD and NF-κB modulation underpin immunoregulatory activity by suppressing pro-inflammatory cascades and enhancing tissue repair programs [100, 101].

The differentiation microenvironment further shapes sUC-MSC behavior. ECM stiffness, mechanical loading, local cytokine gradients, and hypoxia-driven HIF-1α signaling collectively influence lineage commitment, enhancing osteochondral or adipogenic potential according to situational cues. These environmental inputs also modulate the expression of adhesion molecules, integrins, and matrix

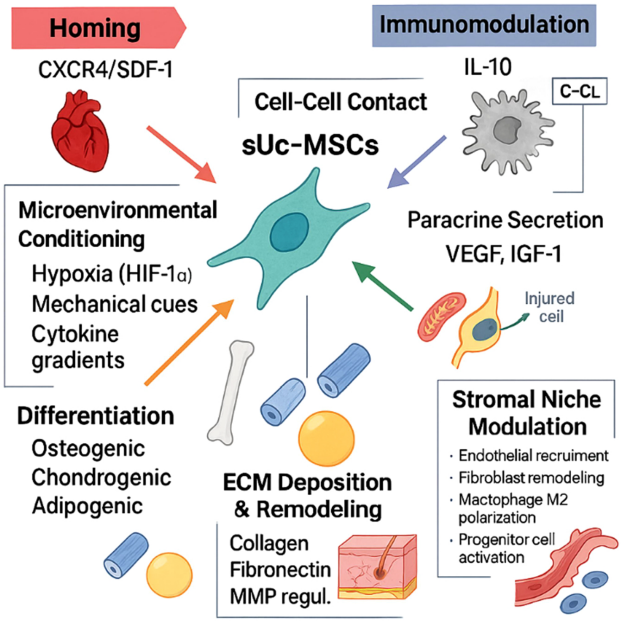

Fig. 1. Mechanisms of Action of sUC-MSCs, promote tissue repair through coordinated homing, immunomodulation, paracrine signaling, and multipotent differentiation, thereby supporting angiogenesis, microenvironmental conditioning, and stromal niche remodeling.

metalloproteinases, facilitating dynamic remodeling of injured tissues [102]. Through their secretome comprising VEGF, HGF, IGF-1, TGF-β, IL-10, prostaglandins, and extracellular vesicles enriched in microRNAs sUC-MSCs exert potent stromal niche modulation [103]. They recruit endothelial cells to promote neovascularization, attenuate oxidative stress, polarize macrophages toward an M2 reparative phenotype, inhibit neutrophil overactivation, and stimulate resident stem/progenitor cells [104]. Exosome-mediated transfer of regulatory RNAs

reprograms host cell survival pathways, enhances matrix deposition, and regulates fibroblast behavior to prevent excessive scarring. In parallel, sUC-MSCs retain intrinsic differentiation capacity into osteogenic, chondrogenic, and adipogenic lineages, enabling direct participation in structural tissue regeneration when microenvironmental conditions permit [105, 106].

Collectively, these coordinated mechanisms allow sUC-MSCs to construct a pro-regenerative milieu that integrates immune modulation, stromal remodeling, angiogenesis, and targeted differentiation forming the mechanistic foundation of their translational therapeutic potential.

5. Translational and bioengineering applications

The therapeutic relevance of sUC-MSCs extends beyond their intrinsic biological properties, demonstrating considerable value in both veterinary medicine and preclinical human research. Given their anatomical and physiological similarities to humans, sheep represent a robust large-animal model for studying MSC-based interventions prior to clinical translation.

5.1. Musculoskeletal and orthopedic repair

sUC-MSCs have successfully been employed in ovine models for bone defects, spinal injuries, and cartilage degeneration, integrating them into host tissues and enhancing osteochondral regeneration and overall structural/functional repair [107–109]. Their functionality within a load-bearing orthopedic environment further enhances the translational value of sheep as a preclinical platform, with predictive insight provided for human fracture healing, spinal fusion, and joint reconstruction therapies.

5.2. Dermal and soft-tissue regeneration

In veterinary medicine, sUC-MSCs offer an ethically available, non-invasive cell source for the management of chronic wounds and burns and complex dermal defects, in which their paracrine and immunomodulatory actions enhance angiogenesis, re-epithelialization, and matrix remodeling [110–113]. The parallel between these responses and human dermal repair strengthens the utility of sUC-MSCs in a One Health approach and supports the translational application to reconstructive and regenerative therapies across species.

5.3. Biomaterial-assisted delivery systems

Encapsulation of sUC-MSCs within biocompatible matrices, including chitosan, collagen, and hydrogel-based scaffolds, improves survival and mechanical protection, with sustained release of trophic factors, under conditions mimicking the native extracellular matrix [114]. Such engineered systems achieve higher efficiency in engraftment and local tissue integration, thus providing more predictable regenerative outcomes and offering versatile tools for specific orthopedic, cardiovascular, and dermal applications.

5.4. Cryopreservation, lyophilization, and shelf-stable formulations

The advances in serum-free culture, optimized cryopreservation, and lyophilization technologies have made long-term storage, reliable transport, and rapid clinical deployment of sUC-MSC products possible. These improvements help to address important logistical challenges that are critically associated with cell therapy distribution and support the generation of off-the-shelf regenerative formulations, thus making sUC-MSC-based interventions more accessible for both clinical and field environments [115–118].

5.5. Peptide-enhanced and nanostructured platforms

Coupling sUC-MSCs with bioactive peptides, nanofiber scaffolds, and nanostructured biomaterials enhances their adhesion, lineage differentiation, angiogenic signaling, and cytokine delivery. These precision-engineered constructs allow for controlled release of therapeutic factors, improved structural integration, and microenvironmental modulation tailored to specific tissue types, thus expanding the role of sUC-MSCs in advanced tissue engineering solutions [119, 120].

5.6. Toward clinically relevant delivery systems

The development of various innovations, including injectable hydrogels, exosome-loaded matrices, 3D-printed scaffolds, and bioreactor-based expansion systems, accelerates the translation of sUC-MSCs into standardized therapeutic formats (cf. Fig. 2) [121, 122]. Such innovation enables reproducible manufacturing, improved therapeutic consistency, and alignment with regulatory requirements; together, these features should favor the evolution of the sUC-MSC therapies toward scalable, clinically deployable regenerative medicine platforms.

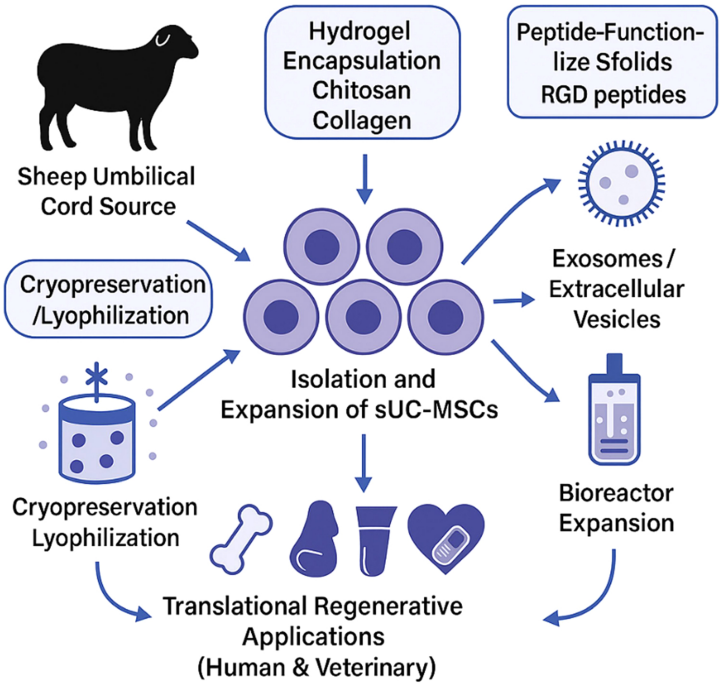

Fig. 2. Bioengineering and Translational Integration of sUC-MSCs.

6. Ethical and regulatory considerations

Although preclinical data highlight the therapeutic promise of sUC-MSCs, their responsible clinical translation requires rigorous control of biosafety, ethical sourcing, and xenogeneic regulatory compliance [123–125]. In contrast to human MSCs, sheep-derived cellular products carry species-specific zoonotic risks, particularly transmissible spongiform encephalopathies (TSEs) such as classical and atypical scrapie, for which prion infectivity has been detected in multiple ovine peripheral and even fetal tissues [126–128]. These hazards necessitate certified TSE-free flocks, traceability of donor herds, and alignment with guidelines on minimizing animal spongiform encephalopathy agents in human and veterinary medicinal products [129, 130]. From a regulatory standpoint, most xenogeneic cell-based products are regulated by the U.S. Food and Drug Administration (FDA) through the Center for Biologics Evaluation and Research (CBER) as biological products requiring Investigational New Drug (IND) authorization, under dedicated xenotransplantation and cellular/gene therapy guidances [131–133]. In Europe, sUC-MSC–based interventions would fall under the framework of advanced therapy medicinal products (ATMPs), supported by specific EMA reflections and the guideline on xenogeneic cell-based medicinal products, which mandate extensive preclinical biosafety testing and centralized authorization [134, 135]. In parallel, veterinary applications must conform to the World Organisation for Animal Health (WOAH, formerly OIE) Terrestrial Animal Health Code and standards for veterinary biologicals, which emphasize donor-animal health status, surveillance, and harmonized quality control for biological products used in international trade [136].

From an ethical and technological perspective, sUC-MSCs benefit from non-invasive sourcing as perinatal by-products of routine livestock reproduction, avoiding embryo destruction and alleviating many concerns associated with human perinatal tissues; nevertheless, their use must comply with animal-welfare regulations, transparent donor-herd management, and responsible communication regarding the biomedical use of agricultural species. The drive toward industrial scalability through telomerase-immortalized MSC lines, gene editing, and intensified bioreactor expansion introduces additional requirements for demonstrating genomic stability, absence of malignant transformation, and long-term biosafety, as highlighted in recent analyses of immortalized MSCs and telomere biology [137–139]. Parallel development of sUC-MSC–derived extracellular vesicle (EV)/exosome or other acellular products offers a route to lower-immunogenicity, more standardized formulations, but these candidates face their own translational hurdles, including stringent characterization of EV cargo, batch-to-batch potency

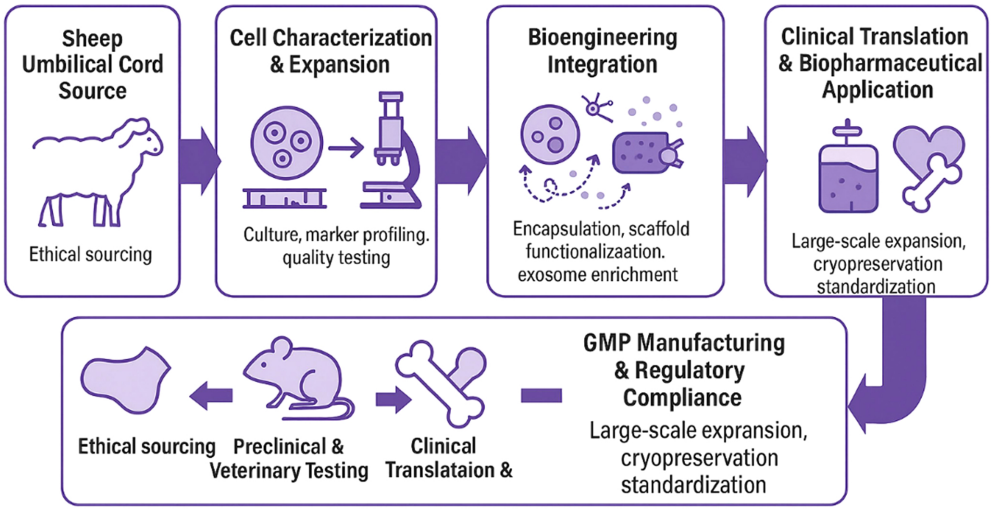

Fig. 3. Translational and Commercial Pathway of sUC-MSCs.

criteria, and harmonization of manufacturing and quality-control pipelines defined in current EV-focused regulatory and translational reviews [140–143]. Collectively, these species-specific biosafety issues, overlapping human–veterinary regulatory regimes, and technology-driven risk profiles delineate the main translational bottlenecks that must be resolved before sUC-MSC platforms can be widely implemented in clinical and veterinary practice.

7. Scientific challenges and future innovations

Notwithstanding significant advancements in xenogenic MSCs research, numerous scientific, regulatory, and translational challenges must still be overcome before their safe and effective clinical implementation. The primary drawback is the insufficient comprehension of interspecies immunogenicity and the long-term safety of xenogenic MSC engraftment, especially concerning possible zoonotic transmission, genomic instability, and immunological sensitization [144–146]. Standardization is a substantial obstacle; variations in isolation methodologies, culture environments, and characterization criteria among laboratories hinder reproducibility and regulatory endorsement. Ethical and biosafety issues associated with the use of animal-derived cells need the formulation of standardized worldwide guidelines that adhere to GMP and the criteria established by ISCT [147–149]. Future research should prioritize integrative multi-omics analysis, single-cell transcriptomics, and proteome mapping to clarify the molecular determinants of potency and immunomodulation in sUC-MSCs. Advancements in gene editing, namely CRISPR-Cas9-mediated humanization, with biomaterial engineering through peptide-functionalized scaffolds and exosome-mimetic delivery methods, provide promising opportunities to enhance therapeutic precision and reduce immunological risk [150, 151]. Concurrent initiatives should concentrate on creating acellular alternatives, such as sUC-MSC-derived extracellular vesicles and conditioned medium, to deliver standardized, cell-free formulations that reduce ethical and safety issues. The integration of cellular bioengineering, precision manufacturing, and regulatory advancements will establish the future of xenogenic MSC treatment (Fig. 3), establishing sUC-MSCs as a scalable and ethically sustainable foundation for regenerative medicine and translational biotechnology.

8. Conclusion

sUC-MSCs have emerged as a physiologically robust, ethically sustainable, and translationally pertinent cell source that connects preclinical research with therapeutic advancements in regenerative medicine. Their strong growth dynamics, genomic integrity, ability to differentiate into many lineages, and effective paracrine secretome synergistically support their therapeutic effectiveness in musculoskeletal, cardiovascular, dermal, and neuroregenerative models. Comparative investigations demonstrate that sUC-MSCs integrate the scalability and ethical viability of xenogenic systems with physiological and immunological traits that closely resemble human MSCs, thereby providing a strategic benefit for both veterinary and human translational research. Ongoing advancements in bioengineering, including hydrogel encapsulation, lyophilization, and

the incorporation of peptides or exosomes, are anticipated to enhance their viability, functioning, and delivery accuracy. Furthermore, the integration of omics-driven molecular profiling, telomerase-mediated immortalization, and AI-assisted manufacturing will expedite the advancement of sUC-MSC technologies from experimental frameworks to standardized, GMP-compliant therapeutic solutions. With the evolution of regulatory frameworks to support xenogenic and acellular stem-cell-derived therapies, sUC-MSCs are positioned to become fundamental to next-generation regenerative medicine, providing a safe, reproducible, and economically scalable solution for complex degenerative diseases in both human and veterinary health sectors.

Conflict of interest

The authors are affiliated with the Research and Development division of OXYZ Health & Wellness Academy, which provided funding for this study. The authors declare that they hold no personal financial interests, equity, patents, or commercial licensing rights related to the products discussed in this manuscript. The sponsor had no influence on the scientific content or conclusions of this work.

Ethical approval

Not applicable.

Data availability

Not applicable.

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Author contributions

All authors contributed equally to the conception and design of the study.

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