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COMPARATIVE EVALUATION OF MESENCHYMAL STEM CELLS DERIVED FROM BONE MARROW, ADIPOSE TISSUE, AND UMBILICAL CORD: IMPLICATIONS FOR IMMUNOMODULATORY THERAPIES

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ABSTRACT

Mesenchymal stem cells (MSCs) are promising options for treating autoimmune and inflammatory disorders like rheumatoid arthritis. This is due to their ability to modulate immune responses, regenerate tissues, and release signaling molecules. However, MSCs from different tissue sources show significant differences in their behavior, which affects their clinical use. This review compares MSCs derived from bone marrow, adipose tissue, and umbilical cord, focusing on their isolation characteristics, morphology and immunophenotype, proliferation and aging, differentiation potential, immune-modulating ability, and paracrine and secretory profiles. Bone marrow-derived MSCs are the traditional and well-studied source. They demonstrate strong osteogenic differentiation and immune-modulating effects, but their clinical use is limited by the invasive collection process, variation due to donor age, and early aging during lab expansion. Adipose-derived MSCs provide higher cell yields and are easier to isolate. They strong adipogenic differentiation and regenerative activity, but their immune-suppressing strength and paracrine consistency can differ based on the donor's metabolic state and inflammation levels. In contrast, umbilical cord-derived MSCs have better growth ability, delayed aging, stable appearance across passages, low immune response, and strong paracrine and immune-modulating characteristics. Overall, while all three MSC sources have therapeutic potential, umbilical cord-derived MSCs show better

biological and immune-related traits for use in immune-related diseases. This comparison underscores the importance of selecting the right source to improve MSC-based treatments.

KEYWORDS: Mesenchymal stem cells, Bone marrow-derived MSCs, Adipose-derived MSCs, umbilical cord-derived MSCs, immunomodulation, paracrine signaling.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-lasting autoimmune condition that mainly affects joints, connective tissues, muscles, and tendons. It is characterized by chronic inflammation of the synovial membrane, increasing damage to the joints, and eventual disability if not properly treated.[1] The disease greatly reduces quality of life and creates significant social and economic challenges worldwide.

Estimates suggest that about 0.5 to 1% of people globally have RA, with women affected two to three times more often than men. The incidence rises with age, especially after 50.[2]

The precise cause of RA is not fully understood. However, it involves a complicated relationship among genetic factors, environmental influences, and immune cells such as macrophages, leading them to release pro-inflammatory substances like tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These substances lead to ongoing inflammation in the synovial membrane, causing cartilage breakdown, bone erosion, and permanent joint deformity.[3]

While traditional treatments like glucocorticoids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs) have improved patient outcomes and slowed disease progression, they often come with significant side effects and long-term safety concerns.[4] Additionally, some patients do not respond to these treatments, highlighting the need for more effective and safer options.[5]

Mesenchymal stem cells (MSC) are multipotent stromal cells that can self-renew and tissue-engineering applications.[6] MSCs can be taken from different tissue sources, like bone marrow, adipose tissue, and perinatal tissues such as the umbilical cord. While adult tissues are common sources, obtaining these cells usually requires invasive procedures.[7] The biological features of MSCs from these tissues can also change based on factors like the donor’s age and health. Perinatal tissues, including umbilical cord blood, provide an alternative and non-invasive source. Studies indicate that MSCs from different origins have

similar morphological, phenotypic, and functional traits.[8] Even with the international society for cellular therapy (ISCT) setting minimal criteria for MSC characterization, there is still a lot of variability affects their ability to expand, their immune properties, and how they behave during ex vivo culture.[9]

Growing evidence also shows that the therapeutic effects of MSCs mainly happen through paracrine mechanisms. These involve secreting growth factors, cytokines, and immunomodulatory molecules rather than direct differentiation.[10] These findings underline the need to understand the differences among MSC populations based on their sources. This understanding can help inform their possible clinical uses. Due to their immunomodulatory and anti-inflammatory properties, MSCs have gained significant attention as a potential therapeutic strategy for autoimmune diseases such as rheumatoid arthritis.[11]

This review focuses on comparing mesenchymal stem cells derived from different tissue sources, highlighting their biological characteristics, therapeutic potential, and relevance in the management of rheumatoid arthritis.

ISOLATION AND CULTURE

Bone marrow derived MSCs

It is one of the most traditional and well-known sources of human mesenchymal stem cells (MSCs). The isolation process usually starts with collecting bone marrow aspirates from the iliac crest under sterile conditions. The aspirated sample is collected in anticoagulant-containing tubes. It then undergoes an initial centrifugation step to get the buffy coat, which is rich in mononuclear cells. These cells are isolated further using Ficoll-Paque density-gradient centrifugation according to standard protocols. The mononuclear cell fraction that appears at the interface is carefully collected and washed with phosphate-buffered saline to remove debris and plasma components. For culture, the isolated mononuclear cells are placed into tissue-culture-treated plates with Dulbecco's Modified Eagle Medium (DMEM) enriched with fetal bovine serum, antibiotics, and L-glutamine. The cultures are kept at 37℃ in a humidified 5% CO_2 incubator. A key feature of MSCs is their ability to stick to plastic surfaces. Therefore, after 48 hours, non-adherent cells are removed by changing the medium. The adherent cell population gradually develops into fibroblast- like, spindle-shaped colonies over the next few days, typically, cultures reach significant confluency within 7 to 12 days, after which the MSCs can be further expanded through passaging.[12]

Adipose tissue derived MSCs

Adipose- derived mesenchymal stem cells (AD-MSCs) are typically obtained from subcutaneous fat tissue. This tissue is most often collected during routine liposuction or surgical lipoaspirate procedures. It contains a stromal vascular fraction rich in multipotent MSCs. The adipose tissue is typically enzymatically digested using collagenase to release the stromal vascular fraction, followed by centrifugation. The isolated cells are then plated in culture flasks, where MSCs adhere to plastic and expand under standard culture conditions. This makes adipose tissue a practical and high-yield source for isolating stem cells in research and clinical studies. Once the adipose sample is collected, the MSC-containing fraction is separated and moved into standard culture conditions. Under standard incubator conditions, AD-MSCs grow quickly, maintain a stable fibroblast-like shape, and can be passaged multiple times for further applications. Since adipose tissue provides a large number of MSCs with strong growth potential, it is widely used in regenerative research. It serves as a reliable source for large-scale MSC culture.[13]

Umbilical cord derived MSCs

Wharton's jelly (WJ) is the soft connective tissue around the umbilical vessels. It is well-known as an ethical, plentiful, and non-invasive source of mesenchymal stem cells (MSCs). Researches usually isolate MSCs from WJ using either the explant method or enzymatic digestion. In the explant method, small pieces of WJ tissue are placed directly on culture dishes. This allows stromal cells to slowly migrate out of the tissue during incubation and form colonies of fibroblast-like cells. This method is straightforward and avoids using enzymes, which helps keep the cells alive. On the other hand, the enzymatic digestion method treats minced WJ tissue with enzymes that break down connective tissue. This process quickly releases stromal cells. After filtration and centrifugation, the cell pellet is resuspended and placed into culture flasks. In both methods, the isolated adherent cells are grown under standard culture conditions. Since the umbilical cord is usually discarded after birth, WJ-derived MSCs obtained through serial passaging provide a stable and uniform cell population. WJ-derived stem cells provide a practical and dependable source for research and regenerative use.[14]

MORPHOLOGY AND MARKERS

Bone marrow-derived MSCs

Human bone marrow- derived mesenchymal stem cells (BM-MSCs) show the typical shape seen in adult stromal stem cells. When they are first plated, the adhering cells including a mixed population of round and polygonal cells. Over time, these cells develop into a more uniform group that resembles fibroblasts. Mature BM-MSCs have an elongated, spindle-like shape with tapered ends and noticeable cytoplasmic extensions. This shape indicates their active movement and growth. These cells strongly attach to standard tissue- culture plastic surfaces and often form CFU-F (colony-forming unit-fibroblast), which shows their ability to grow from one cell. As they go through more passages, BM-MSCs keep a stable fibroblast-like shape, although small differences in cell size, nucleus shape, and cytoplasmic spreading may occur depending on the donor. These factors can affect how quickly they grow and their differentiation tendencies. Overall, their ability to stick to surfaces, form colonies, and maintain a stable spindle shape are clear signs of bone marrow-derived mesenchymal stem cells. In terms of immunophenotype, BM-MSCs meet the basic standards set by the International Society for Cellular Therapy (ISCT). They consistently show key mesenchymal markers like CD73, CD90, and CD105. These markers confirm their stromal origin and relate to their cell adhesion, immune regulation, and ability to differentiate into multiple cell types. On the other hand, BM-MSCs do not express hematopoietic and leukocyte markers such as CD34, CD45, CD14, and HLA-DR, confirming that there are no blood or immune cells contaminating the culture. Depending on the donor and how the cells are isolated, some subpopulations may show additional markers like CD146 and CD271. These subsets are linked to differences in their ability to form bone or cartilage. Together, their spindle-shaped morphology, strong adherence to surfaces, colony-forming capability, and specific marker expression profile establish the identity, purity, and functional potential of human bone marrow- derived MSCs.[15]

Adipose tissue derived MSCs

Adipose- derived mesenchymal stem cells (AD-MSCs) have a clear pattern in their shape and traits that helps with their identification and characterization. When freshly isolated, these cells usually appear as a mixed group. However, after they stick to the culture plastic, they gradually take on a typical spindle shape similar to fibroblasts, which is common for mesenchymal stromal cells. In the early passages, AD-MSCs grow quickly and display a uniform, elongated structure with prominent nuclei and a clear outline in the cytoplasm. As subculturing continues, the cells may become wider and less elongated. They can show signs

of early aging, including increased granularity in the cytoplasm or less ability to grow, reflecting the natural aging of MSCs in the lab. In addition to these visual features, AD-MSCs have a unique immunophenotypic profile that meets standards for mesenchymal stem cells. They strongly express important surface markers such as CD29, CD44, CD73, CD90, CD105, and HLA-ABC, confirming their identity as stromal cells with multipotent abilities. At the same time, they do not show markers for blood or immune cells, such as CD14, CD19, CD45, and HLA-DR. CD34 may be transiently expressed in early passages of AD-MSCs but is typically lost during subsequent culture expansion. This ensures that the cultured cells do not contain unwanted blood- derived or immune cell types. This combination or morphological and immunophenotypic assessment offers a strong and reliable method for maintaining consistency in research studies, preclinical evaluations, and clinical applications.[16]

Umbilical cord- derived MSCs

It is shows the typical shape expected from primitive stromal cells. When taken from Wharton's jelly, the initial cells growth looks like small, rounded or semi-spindle-shaped cells. Over time, these cells change into a uniform fibroblast- like appearance. As they multiply, UC-MSCs become elongated and spindle- shaped, featuring prominent cytoplasmic extensions with tapered ends. During their growth, the cells stick firmly to plastic surfaces and often form swirling patterns as they near confluence a common trait of mesenchymal cells that are actively dividing. Importantly, this fibroblastic shape stays consistant from early to mid passages, indicating that UC-MSCs retain their structure and growth behavior without significant changes. Their ability to form colonies and their relatively quick doubling time highlight the growth advantage of MSCs from neonatal tissue compared to those from adults. The immunophenotypic profile of UC-MSCs clearly supports their identity as mesenchymal cells. Flow cytometry analysis consistently show high levels of the key mesenchymal markers CD44, CD90, and CD105. The international society for cellular therapy (ISCT) recognizes these as crucial positive markers for MSC classification. These markers indicate the cells ability to adhere, their commitment to stromal lineage, and their role in tissue repair. At the same time, UC-MSCs show little to no expression of markers found in hematopoietic and immune cells, such as CD34 and CD45, confirming they are free from blood-derived or immune lineage contamination. This combination of positive and negative markers, along with stable gene expression across passages and the capacity for tri-lineage differentiation, supports a characteristic phenotypic profile of UC-MSCs. Together with their unique shape

and growth characteristics, these markers confirm UC-MSCs as a trustworthy and stable source of mesenchymal stem cells for research and therapeutic uses.[17]

PROLIFERATION AND SENESENCE

Mesenchymal stem cells (MSCs) from different tissue sources show significant differences in how they grow and their tendency to age. These factors affect their use in therapy and regeneration. Bone-marrow-derived MSCs (BM-MSCs) usually have limited growth potential. As they go through more culture passages, their growth slows down, mainly because of telomere shortening related to the donor's age and decreased telomerase activity. These cells tend to exhibit earlier senescence compared with MSCs from other sources, as seen by higher levels of p16^INK4a, p21, and p53 expression, more SA-β-gal positivity, and a strong senescence-associated secretory phenotype (SASP). Adipose-derived MSCs (AD-MSCs), on the other hand, show better growth and a greater ability to expand. This is due to their higher initial yield and stable metabolism. However, their aging characteristics are intermediate between BM-MSCs and UC-MSCs. Oxidative stress-related aging may be accelerated in AD-MSCs derived from donors with obesity or metabolic disorders. Among the commonly studied sources, umbilical-cord-derived MSCs (UC-MSCs) generally show superior proliferative capacity. They have rapid population doubling, high colony-forming efficiency, and a significantly delayed onset of aging. Their neonatal origin gives them longer telomeres, less DNA damage, low levels of aging markers, and minimal SASP activity. This makes them very suitable for long-term culture and large-scale production. Overall, evidence shows that UC-MSCs have the best growth and the lowest aging issues, AD-MSCs have moderate growth and aging profiles, while BM-MSCs are the most likely to experience aging from culture passages.[18]

DIFFERENTIATION POTENTIAL

Comparative analysis of mesenchymal stem cells derived from bone marrow, adipose tissue, and umbilical cord blood show that their differentiation abilities vary across different sources. While all three MSC populations can differentiate into osteogenic, adipogenic, and chondrogenic cells under the right conditions, the extent of this commitment differs significantly. Bone marrow MSCs tend to favor osteogenic development. They demonstrate high alkaline phosphatese activity, significant calcium-containing mineral deposition, and increased levels of osteogenic transcription factors like RUNX2 and osteocalcin. These cells also create well-structured chondrogenic pellets rich in proteoglycan, indicating strong

cartilage-forming potential. It is also important to note that the differentiation capacity of BM-MSCs declines with donor age and prolonged in-vitro expansion, which may limit their regenerative potential in clinical applications. In contrast, adipose-derived MSCs have a more pronounced response to adipogenic markers like PPARγ and FABP4, their osteogenic and chondogenic differentiation potential is generally lower under standard induction conditions compared to BM-MSCs, but can be enhanced using optimized induction protocols. Umbilical cord-derived MSCs generally show relatively lower osteogenic and adipogenic differentiation efficiency under standard induction conditions, likely due to their more primitive and less lineage-committed state. However, they show relatively better chondrogenic activity, forming matrix-rich cartilage-like structures when stimulated with TGF-β. Overall, these findings highlight that MSCs from different tissue sources have inherent biases, and recognizing these differences is important for choosing the right MSC type for specific regenerative or therapeutic uses.[19]

IMMUNOMODULATION

Immunosuppression

Mesenchymal stem cells (MSCs) have a strong immunosuppressive profile, which is important for managing rheumatoid arthritis, were chronic immune overactivation damages joints. MSCs come from different sources like bone marrow, fat tissue, and umbilical cord. They consistency suppress harmful immune responses through several coordinated methods. MSCs inhibit the growth and activation of effecter T-cells, especially the Th1 and Th17 subsets that play a key role in EA progression. At the same time, they promote the development of regulatory T-cells, which helps restore immune balance.[20]

MSCs also reduce key pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-2, and IFN-γ, leading to a significant decrease in synovial inflammation. Additionally, they increase the release of strong anti-inflammatory agents like IL-10, TGF-β, PGE2, and IDO. This creates a tolerogenic environment that limits immune cell infiltration into the joints. Furthermore, MSCs lower the maturation of antigen- presenting cells and decrease the expression of co-stimulatory molecules, which effectively reduces immune activation in the synovium. They also influence inflammatory signaling pathways like NF-κB, MAPK, and JAK/STAT, preventing the escalation of inflammatory responses. Overall, these processes confirm MSCs as effective immunosuppressive and immunoregulatory agents that can reduce the autoimmune mechanisms behind rheumatoid arthritis.[21]

Anti-inflammatory cytokine secretion

Mesenchymal stem cells have strong anti-inflammatory effects mainly through the release of soluble signals. Key cytokines like IL-10 and TGF-β reduce the production of pro-inflammatory factors such as TNF-α, IL-β, and IL-6. They also help expand regulatory T cells. Additionally, MSC-derived signals like PGE2, IDO, and HGF affect inflammatory pathways like NF-κB and JAK/STAT. This reduces immune cell activation and tissue damage in rheumatoid arthritis. Overall, these cytokine effects support the broader immune-suppressing roles of MSCs in managing inflammation.[22]

Interaction of MSCs with immune cells

Mesenchymal stem cells interact dynamically with both innate and adaptive immune cells. They play a role in regulating the immune responses in inflammatory and autoimmune diseases, including rheumatoid arthritis, through paracrine signaling and direct cell contact.

Interaction with T cells: MSCs suppress the activation and growth of $CD4^+$ and $CD8^+$ T lymphocytes. They also change T-cell polarization by reducing pro-inflammatory Th1 and Th17 responses while promoting the growth of regulatory T cells (Tregs). These effects happen through soluble immunomodulatory factors and contact-dependent mechanisms, leading to less cytokine-driven synovial inflammation and a restoration of immune tolerance in RA.[23]

Interaction with B cells: MSCs influence B-cells responses by inhibiting their activation, preventing their differentiation into antibody-secreting plasma cells, and stopping the formation of memory B cells. This regulation reduces the production of autoantibodies and decreases antigen presentation, both of which contribute to the development and progression of rheumatoid arthritis.[24]

Interaction with Natural killer (NK) cells: MSCs decrease NK-cell cytotoxicity and the release of inflammatory cytokines by down regulating activating surface receptors. This helps limit excessive immune-mediated tissue damage and supports an anti-inflammatory environment in inflamed joints.[25]

Allogeneic compatibility and immunogenicity of MSC sources

Mesenchymal stem cells usually have low immunogenicity. They show minimal expression of major histocompatibility complex class II molecules and co-stimulatory markers like CD80, CD86, and CD40. This allows their use in allogeneic therapies. However, the level of immune tolerance differs based on tissue sources. Bone marrow-derived MSCs have moderate allogenic compatibility and low HLA-DR expression. Their immunogenic profile can change depending on donor age, inflammation, and prolonged in vitro growth. Adipose-derived MSCs have similar immunological characteristics to bone marrow MSCs, but differences among donors and their metabolic state can influence their immune response. In comparison, umbilical cord-derived MSCs show better allogeneic compatibility because of their neonatal origin. They consistently have low levels of immunogenic markers and produce more immunoregulatory factors like indoleamine 2, 3-dioxygenase and HLA-G. Overall, while all MSC sources are low in immunogenicity, umbilical cord-derived MSCs are often viewed as highly suitable for off-the-shelf allogeneic use. Adult tissue-derived MSCs may need careful donor selection and culture adjustment.[26]

PARACRINE AND SECRETORY PROFILE OF MSCs

Mesenchymal stem cells mainly perform their therapeutic functions through paracrine signaling, rather than direct differentiation. Their secretory set, which includes cytokines, chemokines, immunomodulatory mediators, and growth factors, plays a vital role in resolving inflammation, reprogramming immune cells, forming new blood vessels, and repairing tissue. Thus, comparing the paracrine and secretory profiles of adipose-derived MSCs (AD-MSCs), bone marrow-derived MSCs (BM-MSCs), and umbilical cord or Wharton's jelly MSCs (UC/WJ-MSCs) is key to finding the most effective therapeutic source.

Bone Marrow-Derived MSCs

BM-MSCs are the most studied cell type and show a well-defined but age-dependent paracrine output. These cells secrete moderate amounts of IL-6, IL-10, TGF-β, and SDF-1α, which aid in immune modulation and repair. However, their basic levels of strong tolerogenic mediators like IDO1 and HLA-G5 are lower than in other sources. Chemokine secretion, which includes CXCL9, CXCL10, and CXCL11, occurs but is not easily induced without inflammatory priming. Additionally, the decline in donor BM-MSCs due to aging reduces the consistency and strength of their paracrine signaling. While BM-MSCs still produce regenerative factors like VEGF and HGF, their immunosuppressive abilities are relatively moderate compared to UC-MSCs.[27]

Adipose-derived MSCs

AD-MSCs are plentiful and easy to isolate. They have a strong secretory profile with high levels of IL-6, pro-survival factors, and angiogenic mediators. Their chemokine secretion is similar to that of UC-MCSs, yet their immunoregulatory molecules, especially HLA-G5 and IDO1, are status and inflammatory priming conditions, which might support Th17 responses in certain environments. While AD-MSCs are great for tissue repair and forming new blood vessels, their pure immunosuppressive power is generally less than that of UC-MSCs.[28]

Umbilical Cord/Wharton's Jelly MSCs

UC/WJ-MSCs consistently show the strongest paracrine and immunomodulatory profile among all MSC sources. They naturally produce high levels of IL-6, SDF-1α, and growth factors while keeping low immunogenicity. Notably, when stimulated by inflammation (e.g., IFN-y), UC-MSCs significantly "license" themselves, dramatically increasing key immunosuppressive genes like IDO1 and HLA-G5. Chemokines that recruit T cells, including CXCL9, CXCL10 and CXCL11, are strongly upregulated, enhancing UC-MSC's ability to attract and suppress effector T cells. Adhesion molecules such as ICAM-1 and VCAM-1 are strongly induced, supporting effective cell contact and immunoregulation. Importantly, growth factors (VEGF, HGF, TGF-β) remain stable during inflammation, which shows that the functionality of UC-MSCs is preserved in challenging immune conditions.[29]

Comparative Interpretation

In summary, UC/WJ-MSCs display a relatively superior and dynamic paracrine profile, particularly in immunosuppressive and anti-inflammatory signaling. BM-MSCs show stable secretory behavior, but it is sensitive to age. AD-MSCs provide good support for growth but have weaker tolerogenic effects. The higher inducibility of immunoregulatory mediators in UC-MSCs positions them as the most promising MSC source for immune-related disorders, inflammatory diseases, and regenerative therapies where strong paracrine activity is essential.[30]

CLINICAL APILICATION

Among the commonly investigated mesenchymal stem cell (MSC) sources, bone marrow (BM-MSCs), and umbilical cord-derived MSCs (UC-MSCs), each has distinct biological advantages. However, their stability for clinical use varies significantly. BM-MSCs are the classical source and the most studied, with well-established differentiation potential and

decades of clinical experience. Still, their limited yield, invasive collection procedure, and a drop in potency based on donor age limit large-scale therapeutic use. AD-MSCs provide a much higher cell yield, rapid growth capacity, and minimally invasive harvesting, making them appealing for regenerative applications, particularly in musculoskeletal and wound-healing therapies. However, their immunomodulatry ability seems slightly lower than that of UC-MSCs in comparative studies. UC-MSCs, which come from perinatal tissue, often the best clinical profile: they display strong growth, effective immunosuppression, lower immune response. These qualities have led to their increasing use in early for inflammatory, neurological, and metabolic disorders.[31]

Overall, while BM- and AD-MSCs remain important in clinical settings, UC-MSCs currently show the most balanced mix of biological strength, scalability, and safety, making them the most promising source for future clinical use.

CONCLUSION

Rheumatoid arthritis is a chronic autoimmune disease that needs different treatment options beyond standard drug therapies. Mesenchymal stem cells (MSCs) are getting more attention because of their ability to modulate the immune system and reduce inflammation. However, their effectiveness can vary based on where they come from. Among bone marrow-derived, adipose-derived, and umbilical cord-derived MSCs, umbilical cord MSCs have a better ability to grow, lower risk of causing immune reactions, and stronger effects in suppressing the immune system. They can be collected without surgery and in an ethical way. Given these benefits, umbilical cord-derived MSCs seem to be the best option for MSC-based therapy in rheumatoid arthritis. Still, more well-designed clinical studies are needed to set standardized protocols and ensure long-term safety and effectiveness.

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