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Review Article

Innovative Cell Therapies: Leveraging Stem Cells from Body Fluids

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Abstract

Stem cell therapy holds great promise for the treatment of a multitude of pathologies by promoting tissue regeneration and repair. Traditionally, bone marrow and adipose derived stem cells have been the primary source of stem cells for clinical applications. However, these methods have limitations, including invasiveness and low cell yield. This review explores body fluids as an alternative, readily accessible source of stem cells. We discuss various body fluid-derived stem cells, including stem cells from amniotic fluid, peripheral blood, cord blood, menstrual fluid, urine, synovial fluid, breast milk, and cerebrospinal fluid and highlight their unique characteristics and advantages for cell therapy. Overall, this review suggests that body fluids offer a promising and accessible alternative to bone marrow for stem cell therapy, and continued research needs to further investigate their potential use in therapeutic applications requiring stem cells.

Key words: BODY fluids-derived stem cells; stem cell therapy; regeneration; personalized medicine

Introduction

The field of regenerative medicine strives to develop innovative treatment techniques to restore function in compromised tissue and organ systems. This can be accomplished by harnessing the healing potential of innate mechanisms in the human body. Widely embraced approaches to renew physiological function include tissue engineering, extracellular vesicles (EVs), and cellular therapeutics[1, 2]. In all three of these modalities, stem cells play a crucial role through self-renewal, differentiation into specialized cell types, and the production of restorative secretomes for immunomodulation and trophic effects[3-5]. Bone marrow and adipose tissues have long been the gold standard sources for stem cell collection[6, 7]. However, harvesting stem cells from these tissues poses challenges, such as necessitating invasive procedures and potentially yielding a limited number of stem cells[8, 9]. As a result, researchers have begun investigating alternative reservoirs that are more easily accessible and may offer enhanced therapeutic promise.

Bone marrow collection, while effective, can be invasive and cause discomfort for the donor. In addition, the differentiation potential, and the number of stem cells in bone marrow naturally declines with age[10]. Collecting adipose stem cells (ASCs) also poses similar challenges. In addition, the location and technique chosen to harvest ASCs can affect cell viability and physiological function[11]. Fortunately, a new frontier is emerging: the utilization of body fluids as a readily accessible alternative[12]. The human body contains a complex network of fluids that plays a vital role in maintaining homeostasis by performing tasks like transporting nutrients, regulating temperature, and lubricating tissues. Ultimately, these abundant fluids could serve as a source of stem cells requiring minimally invasive or non-invasive harvesting methods, rendering them a more patient-friendly and obtainable approach.

This review explores the potential of various body fluids, such as umbilical cord blood, amniotic fluid, urine, breast milk, menstrual blood,

peripheral blood, and synovial fluid, as a source of stem cells. These "body fluid-derived stem cells" (BFSCs) exhibit unique properties and hold promise for regenerative medicine applications. We will investigate the characteristics of BFSCs found in different fluids, discuss isolation techniques, and examine their potential for treating a range of conditions. Finally, we will address the ongoing challenges and future directions in harnessing the power of BFSCs for clinical use.

Classifying stem cells

There are four main ways to classify different types of stem cells.

***Potency*:** This refers to a stem cell's ability to differentiate into various cell types[13, 14] 1). Totipotent stem cells: The most versatile cells, able to differentiate into all cell types of an organism, including each primary germ cell layer and extra-embryonic tissues such as the placenta (only present in very early embryo stages). 2). Pluripotent stem cells: Can differentiate into any fetal or adult cell type. However, they are unable to form extra-embryonic tissues and organize into an embryo independently. Examples include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). 3). Multipotent stem cells: Can differentiate into a limited number of closely related cell types within a germinal layer or lineage. Examples include bone marrow stem cells and mesenchymal stem cells. 4). Oligopotent stem cells: Even more limited differentiation potential than multipotent cells, typically differentiating into just a few specific cell types (e.g., lymphoid or myeloid progenitor cells). 5). Unipotent stem cells: The most specialized, only able to differentiate into one specific cell lineage. Yet, they still maintain self-renewal capabilities unlike non-stem cells. (e.g., skin epithelial stem cells).

***Development Stage*:** This focuses on when in an organism's development the stem cells arise: 1). Embryonic stem cells (ESCs): During the formation of an embryo, a blastocyst is formed containing an inner cell mass (ICM) that gives rise to all structures of the embryo. This occurs five days after fertilization of the egg and includes embryonic stem cells derived from this ICM[15, 16]. These pluripotent cells can differentiate into any somatic cell lineage[17]. 2). Fetal stem cells: After 9 weeks of gestation, the structures developed by the embryo commence further maturation and growth. The developing organism is subsequently classified as a fetus. From this point until birth, harvested stem cells are referred to as fetal stem cells (FSCs). These cells can be harvested from fetal organs and extra-embryonic tissues, such as the liver and placenta, respectively[18, 19]. 3). Perinatal stem cells: This term is used to describe stem cells obtained from tissue surrounding the fetus like umbilical cord blood or amniotic fluid[20, 21]. Unlike FSCs, perinatal stem cells can include maternally derived stem cells[19]. 4). Adult stem cells: Found in various tissues throughout the body after birth. The location of these cells is widely distributed throughout the body and they generally differentiate into the type of tissue or fluid cellular components they inhabit[22]. 5). induced pluripotent stem cells (iPSCs): Artificially created in the lab by reprogramming adult cells to de-differentiate into an embryonic-like state[23].

***Origin*:** This classifies stem cells depending on their source within the body

Tissue-derived stem cells: Reside within tissue niches and play a role in maintaining and repairing those tissues. Tissue niches are specific microenvironments within solid tissues where stem cells reside. These niches provide essential support and signaling molecules that regulate stem cell behavior, including proliferation, differentiation, and self-renewal. This tissue niche as a specialized "home" for stem cells, where they receive the necessary cues to maintain their unique properties, (e.g., bone marrow stem cells[24], hair follicle stem cells[25].

Body fluid-derived stem cells: Extracted from fluids containing cells that initially migrate from their solid tissue niches. This phenomenon is not fully understood in many cases, but it is believed to be influenced by various factors, including a) developmental processes: during embryonic development and growth, stem cells may be released into body fluids to reach new locations where they contribute to anti-inflammation or tissue repairing if needed, (such as amniotic fluid stem cells)[26]. b) physiological conditions: certain physiological states, such as aging or pregnancy, may influence the migration of stem cells into body fluids to replace the aged cells or maintain the integration of tissue (i.e., urine-derived stem cells[12]); c) injury or damage: tissue damage can trigger the release of stem cells from their niches to aid in inhibiting inflammation and repair processes (i.e., synovial fluid-derived stem cells)[27].

In summary, BFSCs are a unique population of stem cells that have migrated from their original solid tissue niches into body fluids. While the exact mechanisms underlying this migration process are still being elucidated, these cells possess the potential for regeneration and repair, making them an exciting area of research for developing new therapeutic approaches.

Cell Types: This classification focuses on the specific lineages or tissues that the stem cells can differentiate into. 1). Epithelial stem cells: Found in the skin[28], lining of organs, and surfaces that serve as protective barrier. They can differentiate into various epithelial cell types during the wound healing process like epidermal stem cells[29]. 2). Mesenchymal stem cells (MSCs): Located in connective tissues like bone marrow, fat, and muscle. These cells have been extensively researched due to their ability to influence the surrounding microenvironment through immunomodulation, regenerative properties, and supportive roles for other cell types[30]. 3). Hematopoietic stem cells: Found in bone marrow. They can differentiate into all types of blood cells (red blood cells, white blood cells, platelets)[31]. 4). Neural stem cells (NSCs): They have the potential to differentiate into new neurons and glial cells. These cells can be harvested and isolated from the central nervous system or pluripotent stem cells can be selectively induced to differentiate into NSCs[32].

By considering all four of these classification methods, scientists can gain a deeper understanding of the unique properties of different stem cell types. This knowledge is crucial for exploring their potential applications in regenerative medicine and treatment of various diseases.

Classify based on:	Description	Examples
Potency	Ability of a stem cell to give rise to various cell types	• Totipotent: differentiate into all cell types of an organism (only present in the fertilized egg or zygote). • Pluripotent: differentiate into almost any cell type found in the body (excluding those for fetal development). • Multipotent: differentiate into a limited number of closely related cell types. • Oligopotent: differentiate into just a few specific cell types. • * Unipotent: only differentiate into one specific cell type.
Development Stage	When the stem cells arise during an organism's development	• ESCs: derived from the inner cell mass of an early-stage embryo. • FSCs: isolated after 9 weeks of gestation from the fetus or extra-embryonic tissues. • iPSCs: artificially created in the lab by reprogramming adult cells to an embryonic-like state.

		• Perinatal stem cells: found in tissues associated with pregnancy, obtained immediately after the baby is born, such as: umbilical cord blood, umbilical cord tissue, placenta and amniotic fluid. • Adult stem cells: Found in various tissues throughout the body after birth.
Cell Types	Focuses on the specific lineages or tissues that the stem cells can differentiate into.	• Epithelial stem cells: located in the skin, lining of organs, etc. differentiate into various epithelial cell types. • MSCs: located in connective tissues. Can differentiate into bone, cartilage, fat, muscle and endothelial cells. • HSCs: Found in bone marrow. differentiate into all types of blood cells. • Neurogenic stem cells: reside in specific regions of the central nervous system. Can differentiate into new neurons and glial cells.
Origin	Source of the stem cells within the body.	• TSCs: reside within specific tissues (bone marrow, fat, muscle, liver, kidney, skin, and hair folic. • BFSCs: extracted from fluids containing cells that migrated from their tissue niches (amniotic fluid, urine, breast milk, menstrual blood, peripheral blood, umbilical cord blood, cerebrospinal fluid, salivary gland fluid and synovial fluid).
Abbreviations: BFSCs: Body fluid-derived stem cells; ESCs: Embryonic stem cells; FSCs: Fetal Stem cells; HSCs: Hematopoietic stem cells; iPSCs: Induced pluripotent stem cells; MSCs: Mesenchymal stem cells; TSCs: Tissue-derived stem cells		

Table 1. Classification of stem cells

Body fluid stem cells

These stem cells are from different sources: such as amniotic fluid, peripheral blood, umbilical cord blood, menstrual fluid, urine, synovial fluid, cerebrospinal fluid (CSF) and breastmilk (**Table 1**). The key characteristic is that these fluids circulate throughout various bodily systems. Thus, most known body fluid-derived stem cells are either within fluids (like PBSCs in blood) or present in readily extracted fluids (like AFSCs in amniotic fluid). In contrast, stem cells present in areas such as bone marrow, dental pulp, and adipose tissue require invasive procedures to access. Therefore, despite their therapeutic potential they are not considered "body fluid-derived stem cells" due to their location and required methods of extraction.

The susceptibility of pathogen contamination can greatly affect the therapeutic potential of body fluid derived stem cells[33]. Despite having a potential source of stem cells, the minimally and non-invasive harvest of stem cells from fluids with prolonged exposure to the external environment, like secretions from mucous membranes, do not have the same therapeutic potential compared to sterile body fluids for cell-based therapy.

Unsterile body fluids where stem cells are not as widely available for therapeutic application due to potential contamination by pathogens: mucus, saliva, tears, sweat, and vaginal fluid.

Body fluids where stem cells can be obtained and potentially used therapeutically due to the fluids' sterility: amniotic fluid, peripheral blood, umbilical cord blood, menstrual fluid, urine, synovial fluid, cerebral spinal fluid (CSF), and breastmilk

Several body fluids harbor populations of stem cells with distinct properties and advantages over bone marrow and adipose derived stem cells. Here, we explore some of the most promising candidates:

A. Fetal Sources:

1. *Amniotic fluid-derived stem cells (AFSCs):*

This fluid surrounding a developing fetus contains a unique population of amniotic fluid stem cells (AFSCs). AFSCs exhibit multilineage differentiation potential (ability to become various cell types) and immunomodulatory properties[19], making them attractive candidates for treating various diseases, including neurological disorders and inflammation-related diseases [34, 35].

AFSCs exhibit a remarkable ability to differentiate into cell types representing the three germ layers (ectoderm, mesoderm, endoderm)[36], which give rise to various organs and tissues: 1). Ectoderm: AFSCs can become cells of the nervous system (neurons, glial cells) and skin (epithelial cells). 2). Mesoderm: They can differentiate into bone, cartilage, muscle, fat, and cells of the blood and circulatory systems. 3). Endoderm: AFSCs show potential to form cells of the lungs, liver, pancreas, and gastrointestinal tract.

AFSCs are a heterogeneous population of cells that come from the fetus and the amniotic membrane[37]. These cells can come from the developing embryo's three germ layers, the amnion, the skin, the respiratory system, the intestinal tract, and the urinary tract. They are thought to be mostly cells that have been shed from the epithelium and digestive and urinary tracts of the fetus .The origin of this multi-lineage potential likely stems from the fact that the amniotic fluid contains cells shed from different organs or tissues of the developing fetus.

While AFSCs demonstrate promising differentiation capabilities in vitro, translating this potential into effective in vivo therapies remains an active area of research. The specific mechanisms underlying their differentiation towards diverse cell types are still under investigation. The heterogeneity within the AFSC population, as discussed earlier, presents both challenges and opportunities. Understanding and potentially isolating specific subpopulations with desired characteristics could further enhance their therapeutic potential.

2. *Umbilical cord blood-derived stem cells (UCBSCs):*

Cord blood, which is collected form the umbilical cord after it is cut from the newborn, contains hematopoietic stem cells that can further differentiate into mature blood cells. These cells are primarily used in allogenic hematopoietic blood cell transfusions for treating a wide range of diseases like leukemias, lymphomas, aplastic anemia, thalassemia, and diabetes[38]. Additionally, the hematopoietic stem cells isolated from cord blood are relatively immune incompetent compared to hematopoietic stem cells isolated from bone marrow and peripheral blood. Therefore, this characteristic allows them to tolerate a higher disparity in human leukocyte antigen (HLA) matching and significantly reduces the probability of developing graft vs host disease during an allogenic transplant[39].

MSCs have also been isolated from umbilical cord blood, which makes it a potential therapeutic alternative to bone marrow MSCs in regenerative medicine and particularly tissue engineering. Of note, MSCs originating from cord blood demonstrated a higher proliferative potential and preserved differentiation capacity when compared to MSCs from the bone marrow[40].

B. Adult Sources:

1. Peripheral Blood-derived stem cells (PBSCs):

Hematopoietic stem cells (HSCs) from peripheral blood are less concentrated than UCBSCs but offer a more feasible collection method through apheresis after growth factor injection[41-43]. They've been used to treat various conditions like leukemia, lymphoma, and multiple myeloma through both autologous and allogenic hematopoietic stem cells transplants. HSCs, characterized by the CD34 surface marker, are the most used subtype of PBSCs in the clinical setting. Other populations of PBSCs have been discovered, but their expression patterns and characteristics are not as explicitly defined[44]. Ultimately, continued research on these additional subtypes could lead to a wider range of therapeutic applications for PBSCs.

2. *Menstrual blood-derived stem cells (MenSCs)*:

MenSCs express markers that have been previously identified to be specific to mesenchymal stem cells[45]. This expression pattern, along with their anti-inflammatory and regenerative properties, makes them a promising option for cell-based therapies[46]. These MSCs have been shown to differentiate into numerous cell types and offer an additional non-invasive alternative to MSCs harvested from the bone marrow. Their potential in treating gynecological disorders, wound healing, and neurological diseases is being explored.

3. *Urine-derived stem cells (USCs):*

Present in small quantities in voided urine, these cells offer a non-invasive collection method and likely originate from the kidney mesoderm. Furthermore, they show similarities to mesenchymal stem cells through their proliferative, migratory, and differentiation capacities[47]. Research is ongoing to explore their potential in regenerative medicine, cell therapy, and drug discovery[48, 49].

4. *Synovial fluid-derived stem cells (SFSCs):*

Residing in joint synovial fluid, SFSCs contribute to joint health. Their ability to differentiate into cartilage cells makes them promising candidates for osteoarthritis treatment[33]. In addition, their anti-inflammatory properties offer potential benefits for joint-related inflammatory conditions.

5. *Breast milk-derived stem cells (BMSCs):*

Present in breast milk, these cells show potential for differentiating into various cell types, including mammary epithelial cells, adipocytes, and neurons. Their potential applications in regenerative medicine and infant health are under investigation[50].

6. *Cerebrospinal fluid-derived neural stem cells:*

Despite the inability to produce stem cells itself, CSF is near the subventricular zone which participates in neurogenesis and the production of NSCs[51]. This body fluid, produced by the choroid plexus, has been shown to promote proliferation, survival, and neuronal differentiation of NSCs through its microenvironment and cell signaling[51, 52] . Additionally, in diseases like multiple sclerosis, NSCs try to repair damage but may be negatively affected by the disease environment[53]. This study found that cerebrospinal fluid from MS patients can hinder the growth and function of these stem cells, suggesting that the etiology of neurologic diseases could interfere with the brain's natural repair process involving CSF.

It is imperative to acknowledge that the research surrounding many of these stem cell types remains in its preliminary stages. The full spectrum of their therapeutic potential and safety necessitates comprehensive exploration. To harness the complete capabilities of BFSCs for clinical application, continued investigation and optimization are indispensable. Furthermore, the unique nature of each source of BFSCs demands meticulous refinement of parameters such as dosage, administration route, and treatment frequency. Preclinical evaluation in large animal models is crucial to assess safety, efficacy, and potential long-term consequences prior to human trials. Specific areas requiring concentrated effort include: a) dosage optimization: precise determination of the optimal dosage is essential to maximize therapeutic efficacy while mitigating adverse events; b) route of administration: Identification of the most effective delivery method (e.g., intravenous, intramuscular, or localized injection) is critical for achieving optimal outcomes; c) treatment frequency: Establishing the optimal treatment regimen to sustain therapeutic benefits is a priority; d) preclinical evaluation: Rigorous testing in large animal models is indispensable to assess safety, efficacy, and potential long-term implications. Despite these ongoing challenges, the promising characteristics of BFSCs offer a compelling avenue for future medical advancements.

Summary of body fluid-derived stem cells key characteristics:

Body fluid-derived stem cells (BFSCs) offer a significant advantage in regenerative medicine due to their unique properties and ease of access. Isolated from various bodily fluids through non-invasive or minimally invasive methods[54], BFSCs are a readily available source compared to traditional therapeutic sources of stem cells obtained from tissues like bone marrow. These stem cells share characteristics with mesenchymal stem cells (MSCs) found in bone marrow[12]. They can also possess the ability to self-renew and differentiate into various cell types like bone, cartilage, muscle, and nerve cells.

In addition, BFSCs exhibit immunomodulatory properties, making them potentially suitable for treating autoimmune diseases Immunomodulatory properties play a crucial role in tissue regeneration by influencing the body's immune response to promote healing and repair. These properties facilitate a balanced immune response that reduces inflammation, enhances tissue repair, prevents rejection, and promotes angiogenesis, all of which are critical for effective tissue regeneration. This combination of advantages – non-invasive collection, abundant source, immunomodulatory properties, and regenerative potential – positions BFSCs for exciting applications in: 1) Regenerative medicine: Treating conditions like skin wounds[55, 56] bone injuries43, [57-59] and kidney diseases49, [60, 61].2). Cell therapy: Targeting various disorders, including neurological diseases[62-64] and diabetes[65, 66]. 3). Drug discovery and development: Utilizing BFSCs for disease modeling and drug screening[67, 68]. However, body fluid research is still in its early stages, and more clinical trials are needed to evaluate their full potential and safety for therapeutic use. Ultimately, the non-invasive nature of their collection and promising therapeutic potential makes them a fascinating area of ongoing research with significant potential for future clinical applications.

In summary, extracellular bodily fluids such as urine, blood, breast milk, menstrual fluid, umbilical cord blood, and other specific fluids like amniotic fluid and CSF are emerging areas of exploration for potential stem cell sources. These sources offer some advantages, including non-invasive or minimally invasive collection and potentially unique stem cell populations. However, it's important to note that existing research primarily focuses on identifying and characterizing potential stem cell populations within these fluids. While their applications in disease modeling, drug testing, and therapeutics hold great promise, these areas are still in the exploratory phase. Continued research is needed to

understand the properties, isolation techniques, expansion methods, and potential applications of these stem cells. Therefore, the potential of body fluids as a future source of stem cells is intriguing. It is a promising avenue for further research for therapeutic applications requiring a reliable source of stem cells.

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