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Adult telomerase positive stem cells: Compare and contrast biobanking with other proposed endogenous adult stem cells involved in regeneration and repair of damaged tissues

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Abstract

Biobanking is the process whereby biological samples, e.g., blood, DNA, cells, tissues, and/or organs, from multiple individuals are stored for later use, such as future research or clinical use. In contrast to a simple freezer collection, a biobank usually maintains information for each sample, such as gender, ethnicity, lifestyle choices, clinical choices, and sometimes genomic data. Common categories of biobanks include sperm banks, umbilical cord banks, stem cell banks, tumor banks, clinical biobanks, etc. Biospecimens are collected with informed consent under approved standard operating procedures (SOPs) to minimize variability between samples, e.g., time of harvest, processing delay, temperature during transport, special tubes, special reagents, etc., and clinical notes are included so later analyses can if these variable affected outcomes. After collection, samples are transported promptly to processing facility where subsequent handling follows strict SOPs for downstream use. Processing is documented with chain of custody, time stamps, methods, for quality control (QC) records. Storage conditions are chosen based on specimen type, required analyses, anticipated duration of storage, and stability, balancing cost and logistics. Cell samples are processed into appropriate aliquots to reduce ice crystal formation during freeze-thaw procedures and frozen. Typical conditions include low temperature (-80°C), vitrification (-150°C), and liquid nitrogen (-196°C). The hypothesis being tested is that the same biobanking procedures are used for all adult cells involved in regeneration and repair of damaged tissues. This study will compare and contrast biobanking procedures of proposed endogenous adult cells involved in regeneration and repair of damaged tissues.

Keywords: Biobanking; aTPSCs; MSCs; VSELs; MUSE; MIAMI; MAPCs

1. Introduction

Biobanking is the process whereby biological samples, e.g., blood, DNA, cells, tissues, and/or organs, from multiple individuals are stored for later use, such as future research or clinical use. In contrast to a simple freezer collection, a biobank usually maintains information for each sample, such as gender, ethnicity, lifestyle choices, clinical choices, and sometimes genomic data. Common categories of biobanks include sperm banks, umbilical cord banks, stem cell banks, tumor banks, clinical biobanks, etc. [1-7].

Biospecimens are collected with informed consent under approved standard operating procedures (SOPs) to minimize variability between samples, e.g., time of harvest, processing delay, temperature during transport, special tubes, special reagents, etc., and clinical notes are included so later analyses can if these variable affected outcome [1,8]. After collection, samples are transported promptly to processing facility where subsequent handling follows strict SOPs for downstream use. Processing is documented with chain of custody, time stamps, methods, for quality control (QC)

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records [8]. Storage conditions are chosen based on specimen type, required analyses, anticipated duration of storage, and stability, balancing cost and logistics [8]. Cell samples are processed into appropriate aliquots to reduce ice crystal formation during freeze-thaw procedures and frozen. Typical conditions include low temperature (-80oC), vitrification (-150oC), and liquid nitrogen (-196oC).

Multiple endogenous adult cells have been postulated to be involved in the regeneration and repair of damaged tissues. The aforementioned cells include mesenchymal stem cells (MSCs), very small embryonic-like stem cells (VSELs), multilineage-differentiating stress-enduring cells (MUSE), marrow-isolated adult multilineage inducible cells (MIAMI), multipotent adult progenitor cells (MAPCs), and adult telomerase positive stem cells (aTPSCs).

Mesenchymal stem cells are a tripotent adult progenitor stromal cells that can self-renew up to 70 population doublings from birth (humans) and differentiate into mesodermal lineage cells, such as fat, cartilage, and bone. They are found in many tissues, including bone marrow, adipose tissue, umbilical cord, and interstitial connective tissues. The tripotent progenitor MSC contributes to connective tissue homeostasis. The minimal criteria defining human MSCs is their adherence to bare plastic, express CD90, CD105, CD117, CD123, CD166, and MHC-Class-I cell surface markers. MSC is also an acronym for medicinal secretory cells which express CD73, CD90, and CD105 cell surface markers [9-18].

Very small embryonic-like stem cells (VSELs) were initially described as tiny (3-5 microns in mice and 5-7 microns in humans) non-hematopoietic cells in bone marrow that expressed pluripotency markers, e.g., Nanog and Oct-3/4, and could generate cells from all three germ layer lineages in vitro. They are typically defined as lineage negative, CD45 negative, and CD34+, CD133+, and CXCR4+. Experimental work suggests that VSELs can give rise to hematopoietic, mesenchymal, endothelial, and organ-specific cells in vitro and can contribute to repair of myocardium, bone, vasculature, liver, and lung. VSELs circulate at very low levels in peripheral blood, but increase in number following trauma, burns, stroke, myocardial infarction, G-CSF mobilization, inflammatory bowel disease, and some cancers. This suggests that VSELs may be involved in endogenous repair processes [19-24].

Multilineage-differentiating stress-enduring cells (MUSE) were first reported in 2010as stress-tolerant cells in human bone marrow-derived mesenchymal stromal cells and dermal fibroblasts. They were identified with SSEA-3 cell surface marker with pluripotency-marker expression and trilineage differentiation at the single cell level. They are described as a rare endogenous pluripotent stem cell present in peripheral blood, and interstitial connective tissues that can self-renew and generate cells from all three germ layer lineages. The show SSEA-3+/CD105+cell surface markers and express Oct-3/4, SOX2, and Nanog transcription factors, while lacking spontaneous teratoma formation. MUSE cells can survive prolonged serum deprivation, hypoxia, and other harsh conditions. After systemic delivery MUSE cells can home to damaged tissues and then spontaneously differentiate into tissue-compatible cell types. MUSE cells have low telomerase activity and controlled proliferation. Compared to iPSCs and ESCs, MUSE cells exhibit lower proliferation potential, do not from teratomas, and do not need reprogramming to prevent teratoma formation. Pre-clinical animal studies MUSE cells have been shown to improve structure and function in models of spinal cord injury, stroke, liver and kidney injury, myocardial infarction, lung damage, and skin disorders. Clinical studies using allogeneic MUSE cells (without HLA matching) for acute myocardial infarction, cervical spinal cord injury, amyotrophic lateral sclerosis (ALS), COVID-19-related adult respiratory distress syndrome (ARDS), epidermolysis bulbosa, and subacute ischemic stroke [25-33].

Marrow-isolated adult multilineage inducible cells (MIAMI) are a rare subpopulation of human bone-marrow-derived mesenchymal stromal cells (MSCs). They were isolated under low oxygen, serum-free conditions. MIAMI cells express several embryonic stem cell markers in vitro, e.g., Oct-4a, Rex1, Sox2, Nanog, SSEA-4, and telomerase reverse transcriptase activity and are capable of pluripotent induced differentiation. In preclinical studies, MIAMI cells were studied for neuroprotection, ischemic limb repair, and other degenerative conditions. MIAMI cells are CD34 and CD45 negative, but do express CD29, CD44, and CD90 cell surface markers [34,35].

Multipotent adult progenitor cells (MAPCs) are a rare population of 9-12-micron adult progenitor cells originally isolated from bone marrow that can self-renew. They can differentiate into multiple cells/tissues, e.g., mesodermal (fat, cartilage, bone, muscle, hematopoietic, endothelial), endodermal cells (liver, pancreas), and ectodermal (epithelial, neural) lineages under appropriate culture conditions, as well as having immunomodulatory properties. They express low levels of MHC Class-I cell surface self-recognition markers. They were described in the early 2000's as a distinct population from the tripotent MSC, having broader differentiation potential and different growth requirements, e.g., low serum, EGF (inductive, epidermal growth factor), PDGF (proliferative, platelet-derived growth factor), and cultured at 5% CO_2, 5% O_2, and 90% N_2. MAPCs are being studied in both pre-clinical and clinical for a range of conditions: ischemic injury (e.g., stroke, myocardial infarction), tissue regeneration (e.g., bone, cartilage, liver), and autoimmune and inflammatory diseases (e.g., graft-versus-host disease, multiple sclerosis) via immunomodulation. Because MAPCs can

be used allogeneically, they offer the potential for off-the-shelf, rather than pluripotent stem cells, such as ESCs and/or iPSCs, without being tumorigenic. MAPCs are multipotent rather than pluripotent, so they cannot generate as many cell types as iPSCs or ESCs. MAPCs are not hematopoietic. They can support hematopoiesis but do not form hematopoietic cells [36-40].

Adult telomerase positive stem cells (aTPSCs) were originally discovered in 1975 while studying complete limb regeneration if adult terrestrial salamanders. It was proposed that aTPSCs are a rare endogenous stem cell population consisting of totipotent stem cells and (>2-8-micron) pluripotent stem cells that can be harvested directly for tissue repair without genetic manipulation. Totipotent and pluripotent stem cells are located in any tissue or organ with an interstitial connective tissue component. Totipotent stem cells are 0.1-2-microns in size, display CEA-CAM-1+ and CD66e+ cell surface markers; express telomerase, Bcl-2, Nanog, Nanos, and CXCR4 genes. Their default state is of a dormant quiescent cell existing within interstitial connective tissue niches under hypoxic conditions. Once activated they have an unlimited proliferation potential, but are not tumorigenic. They will form any somatic cell of the body, the nucleus pulposus of the intervertebral disc (the only functional adult derivative of the notochord), gender-specific germ cells, and placental tissues, thus being equivalent in differentiation potential as 4-cell stage blastomeres. There are three categories of pluripotent stem cells, based on size, cell surface phenotypic markers, and expressed genes, e.g., halo-like stem cells (HLSCs), corona-like stem cells (CLSCs), and pluripotent stem cells (PSCs). Their default state is of a dormant quiescent cell existing within interstitial connective tissue niches under hypoxic conditions. Once activated, while they have an unlimited proliferation potential, they are not tumorigenic. They will form all somatic cells of the body. Genomically-labeled pluripotent stem cell clone (Scl-40β) was utilized in induced pre-clinical animal models of disease, e.g., Parkinson's disease, myocardial infarction, pulmonary fibrosis, and type-1 diabetes. Both autologous and (gender-matched, ABO-blood group matched) allogeneic TSCs and PSCs have been used in 18 IRB-approved clinical studies for neurodegenerative, cardiovascular, pulmonary, autoimmune, kidney, systemic, and orthopedic morbidities. Cumulative results demonstrated a 100% safety record and 86% efficacy for reversing signs and symptoms in the disorders [41-60].

The hypothesis being tested is that the same biobanking procedures are used for AL proposed adult cells involved in regeneration and repair of damaged tissues. This study will compare and contrast biobanking procedures of proposed endogenous adult cells involved in regeneration and repair of damaged tissues..

2. MATERIALS AND METHODS

Supplies

- Polypropylene cryovials
- Freezing Medium
  - Avian: Eagle's MEM, 1% antibiotic/antimycotic, 10% Horse SerumS7, pH 7.4
  - Mammalian: OptiMEM + GlutaMax, 10% Heat Inactivated Serum, antibiotic/antimycotic, pH 7.4
- Dimethyl Sulfoxide (DMSO), Ultra-Pure
- Mr. Frosty, Isopropyl alcohol-controlled rate freezer
- Isopropyl Alcohol

Equipment

- 4^0C Refrigeration
- -80^0C Refrigeration
- Liquid Nitrogen Dewer
- 37^0C water bath
- 37^0C glass bead bath
- Centrifuge
- Fluorescent Activated Cell Sorter (FACS)
- Flow Cytometer
- Hemocytometer
- Brightfield Microscope

3. Results

Table 1 Biobanking of MSCs, VSELs, MUSE, MIAMI, MAPCs, and aTPSCs

Attributes	**MSCs Tripotent**	**VSEL**	**MUSE**	**MIAMI**	**MAPCs**	**aTPSC TSCs**	**aTPSC PSCs**
Size, microns	15-30	Mouse 3-5 Human 5-7	10-15	12-18	10-15	0.1-2.0	6-8
Cells tested	Clone derived from a single cell and Popula-ions of cells	Popula-tions of cells	Popula-tions of cells	Popula-tions of cells	Popula-tions of cells	Clones derived from a single cell and Popula-tions of cells	Clone derived from a single cell and Popula-tions of cells
Time in storage at 4C	24 hours	6-12 hours	4-6 hours	Short term	6-12 hours	>40 days	>20 days
Freezing Medium	Species-Specific Plating Medium	DMEM or alpha-MEM	DMEM or alpha-MEM	DMEM or alpha-MEM	DMEM or alpha-MEM + 20-30% Serum	Species-Specific Plating Medium	Species-Specific Plating Medium
Number of cells in suspension for freezing	10^3 to 10^7	10^6	10^6 to 10^7	1-2 x 10^6	1-2 x 10^6	10^3 to 10^12	10^3 to 10^9
Cryovial composition	Polypro-pylene	???	???	???	???	Polypro-pylene	Polypro-pylene
Cryoprotectant	DMSO	DMSO	DMSO	DMSO	DMSO	DMSO	DMSO
Purity of DMSO	Ultra-pure 100%	8-10%	5-10%	5-10%	5-10%	Ultra-pure 100%	Ultra-pure 100%
Adding cell suspension prior to DMSO	Yes	No	No	No	No	Yes	Yes
Amount added to cryovial	10%	10%	5-10%	5-10%	5-10%	7.5%	7.5%
Mixing DMSO to Cell Suspension	Cap cryovial and slowly invert cryovial 5-6 times	DMSO added to freezing medium before the cells	DMSO added to freezing medium before the cells	DMSO added to freezing medium before the cells	DMSO added to freezing medium before the cells	Cap cryovial and slowly invert cryovial 5-6 times	Cap cryovial and slowly invert cryovial 5-6 times
Allotted Time to process cryovials prior to freezing	3-3.5 minutes	10-20 min at 4^{o}C	10-15 min at 4^{o}C	10-15 min at 4^{o}C	10-15 min at 4^{o}C	3-3.5 minutes	3-3.5 minutes

Freezing Apparatus	Liquid Nitrogen Dewer	Liquid Nitrogen Dewer	1° per minute down to -80C, then into liquid N2	1° per minute down to -80C, then into liquid N2	1° per minute down to -80C, then into liquid N2	1° per minute down to -80C	1° per minute down to -80C
Freezing & Storage Temperature	-196°C	-196°C	-80oC, then -196oC	-80oC, then -196oC	-80oC, then -196oC	-80°C	-80°C
Degree Drop in Temperature	Flash Freeze -196°C/ sec	Flash Freeze -196°C/ sec	1° per minute down to -80C, then into liquid N2	1° per minute down to -80C, then into liquid N2	1° per minute down to -80C, then into liquid N2	Slow Freeze 1°C/min	Slow Freeze 1°C/min
Time in Storage	20+ years	10-15 years	Several decades	10-20 years	Several decades	20+ years	20+ years
Thaw Apparatus	Water or Glass Bead Bath	Water Bath	Water bath	Water bath	Water bath	Water or Glass Bead Bath	Water or Glass Bead Bath
Thaw Temperature	37°C	37°C	37°C	37°C	37°C	37°C	37°C
Remove cryovial contents to plating medium	1:14 ratio contents to plating medium, invert to mix	1:10 ratio contents to plating medium	1:5 to 1:10	1:5 to 1:10	1:5 to 1:10	1:14 ratio contents to plating medium, invert to mix	1:14 ratio contents to plating medium, invert to mix
Time Frame to Dilute DMSO	1.5-2 min	<30 min	10-20 min	<30 min	10-20 min	1.5-2 min	1.5-2 min
Centrifuge	1,000 RCF 15 min	200-300 RCF	200-300 RCF	200-300 RCF 5 min	200-300 RCF 5 min	2,000 RCF 15 min	1,500 RCF 15 min
Remove Supernatant	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reconstitute Cell Pellet in Plating Medium	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Count Recovered Viable Cells	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer	FACS, Flow Cytometer or Hemo-cytometer
% Recovery = # Viable Cells Recovered /# Cells Frozen x 100	Optimum > 95%	Not defined	70-90%	70-90%	70-90%	Optimum 98-99%	Optimum 98-99%

4. Discussion

Initially, clones of aTPSCs and MSCs derived by repetitive single cell clonogenic analysis [61], were optimized for cryopreservation characteristics, e.g., purity of the dimethyl sulfoxide (DMSO), freezing medium, number of cells in suspension, composition of cryovials, adding cell suspension to cryovials before adding DMSO, purity of DMSO, percentage of DMSO added to cryovial, time period from adding DMSO to freezing cells, freezing and storage temperature(s) of cells, temperature for thawing cells, time period for diluting DMSO, removal of DMSO from cells, and overall processing time in the presence of liquid ultra-pure DMSO [62]. As shown (Table 1), clearly there are similarities and differences between the two populations of cells, comparing column 2 to columns 6 and 7. We then tested isolated populations of MSCs, TSCs, and PSCs from avians, mice, rats, and humans, derived as previously described [41,44,51,54,57,63], and found no difference between individual clones of rat MSCs (Rt-MSC), TSCs (Scl-4β, Scl-9β, Scl-44β), and PSCs (Scl-40β), and their respective isolated populations of cells from avians, mice, rats, and humans. In these studies, a decrease in optimum number of viable cells recovered is inversely related to the processing time that the cells are in contact with liquid ultra-pure DMSO. As the processing time in DMSO increases, the number of viable cells decrease. We discovered that 5 min is about the maximum time that the cells can be in the presence of liquid ultra-pure DMSO before cell death occurs. Therefore, it is far better to process small batches of cryovials for cryopreservation at a time rather than a single large batch of cryovials. The literature was then reviewed for other proposed adult stem cells, e.g., VSELs, MUSE, MIAMI, and MAPCs, for the above cryopreservation characteristics (Table 1). Literature consensus was that VSELs, MUSE, MIAMI, and MAPCs are within the family of MSCs, and therefore can be processed utilizing the same procedures, and thus engendering similar results.

5. Conclusion

The hypothesis tested was that the same biobanking procedures are used for ALL proposed adult cells involved in regeneration and repair of damaged tissues. Clearly, that was not the case. While there are similarities and differences with respect to cryopreservation procedures between MSCs, VSELs, MUSE, MIAMI, and MAPCs, the aTPSCs procedures are decidedly different. What is interesting to note is that if the aTPSC procedures were used with MSCs, there was a higher recovery of viable cells from cryopreservation, than if the standardized procedures for MSCs, VSELs, MUSE, MIAMI, and MAPCs were utilized instead.

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