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Salvage of Cadaver Stem Cells (CSCs) as a Routine Procedure: History or Future for Regenerative Medicine

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Abstract

We present a review in the different capacities and features of Cadaver Stem Cells (CSCs). CSCs could be an innovative and interesting option in the near future for Regenerative Medicine and Transplantation procedures. This provocative topic has not been fully addressed before. The isolation of viable and functional CSCs from humans up to many days post mortem is possible today. There is a real chance to obtain culture and expand viable stem cells for cell therapy from the plentiful source of cadaver donors. Therefore, it seems that it will be possible to routinely obtain CSCs from almost any human cadaver organ or tissue as desired. This could open a new universe of strategies and research in order to find out their real potential as a routine therapeutic procedure for many diseases.

Keywords: Cadaver stem cells; Donor; Regenerative medicine

Introduction

Due to the shortage of donors, many patients waiting for transplantation will not ever receive the needed organ at all. For some diseases, cell transplantation could be a possible alternative, but donor cells are usually currently procured from living donors, and thus the supply is also severely limited [1]. There is a real chance to isolate culture and expand viable stem cells for cell therapy from the plentiful source of cadaver donors [2]. Organ and tissue from this origin is a widely utilized and an obvious strategy for transplantation to treat heart, kidney, lung, liver, eye, bone, skin disease, among others [3-9]. But there is a reasonable possibility also to isolate in the near future, stem cells from these same cadaveric organs and tissues that could give new therapeutics options for many patients with severe lesions and diseases [10-12]. The number of hematopoietic stem cells (HSC) transplantations utilizing marrow, peripheral and cord blood cells has increased these last years also the demand on a wider access to the different sources of human HSC. Cadaveric donors were pointed out in several publications more than 50 years ago, as a potential source of hematopoietic cells for transplantation purposes [13]. With the increasing use of cadaver donors for multiple organ harvests, it should be asked why bone marrow and may be its stem cells, specially Mesenchymal Stem Cells (MSCs), can not be routinely salvaged from cadaver donors for regenerative medicine procedures [14]. In this way, and in order to match the new demands of Regenerative Medicine, collections of stem cells including those like MSCs from the post-mortem body, could be easily obtained from this source and preserved and/or expanded for these purposes [15]. In this way, it is reasonable to expect that very soon, there will be studies to improve on the isolation procedures of different types of cadaver stem cells [10]. Therefore, it seems that it will be possible to routinely obtain stem cells of this kind from almost any human organ or tissue as desired [3,16-22]. The procurement of different stem cell types from other sources beside living donors is a true possibility that needs to be explored [23]. This could open a new universe of strategies and research in order to find out the real potential of cadaver donor stem cell therapy as a routine procedure. The central idea would be, if postmortem tissue could be a suitable source for the separation of stem cells to later be cultured-expanded and used in regenerative medicine interventions for functional replacement of diseased organs and tissues [13,24-26]. In this way, stem cells from cadaver donors could offer the medical community some interesting advantages over those from living ones [2]. We present here a novel review on the history and future of what we have called Cadaver Stem Cells (CSCs), and addressed for the first time their potential utility in regenerative medicine and Transplantation procedures. This provocative topic has not ever been fully discussed before.

Bone Marrow and Other Cadaver Sites for the Obtention of Viable CSCs

Many sites of cadaver donors could be suitable for CSCs obtention. The heparinized cadaveric multiple organ donors are an important source of organs and tissues for transplant therapies. Since these donors are heparinized before an organ donation, blood in their bone marrow cavities remains liquid and can be easily aspirated. By aspirating bone marrow it is possible to aspirate easily large numbers of marrow cells from pelvic bones. Cadaveric marrow remains liquid and not infected if the aspiration is performed within 2 hours after the heart, liver, and kidneys are removed. Harvested cells are viable (96%) and grow hematopoietic colonies in vitro [27]. The fact that before the donation these cadaveric multiple organ donors are always phenotyped for HLA antigens and evaluated for the presence of any potential blood transmitted diseases (HIV, HBV, CMV, etc.) makes this source of cells safe and has an important economic aspect [10,27]. Unfortunately, all these donors stem cells are usually wasted at this moment. This could be an efficient and rapid method for extracting not only hematopoietic progenitors but also other kind of pluripotent cells like MSCs. The obtention of large amounts of human bone marrow from human cadavers at the time of "sterile" autopsy during routine organ and tissue procurement procedures for transplantation, has been hampered for years by several factors like: difficulty in obtaining the marrow with the need of extensive procedures required to get substantial yields by multiple aspirations, difficulty in matching for HLA antigens, since only about one in 10,000 recipients would be compatible with a given donor; the high cost of preparing and storing marrow in liquid nitrogen

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and the need for nonstandard equipment especially designed to accomplish, under sterile conditions, extraction of the cellular marrow from the bone, homogenization of the marrow clumps and separation of the marrow fat, between many others [10,23,25,28-30]. The first preliminary studies in this direction were done in the early 50´s [13]. Bone marrow was obtained from bones within 14 hours of death from patients aged 17 to 75 years [10,25]. Marrow cell viability from cadaver donors indicated that these cells should be harvested immediately, thus necessitating an on-call group of technicians who would isolate cells at night [10]. Preliminary observations started in 1959 shown that one or two billion nucleated cells could be obtained from a fetus bone marrow, done by the usual rib removed at surgery or an aspiration biopsy of the ilium [13]. *Also, subjects dying of blood loss, vascular accident, coronary-artery disease or other non-septic and non-neoplastic conditions were thought to be suitable also for these techniques, provided no more than approximately four hours have elapsed since death occurred, although an interval of one or two hours was preferable* [13]. In 1978 some studies strongly suggested that human pluripotent hemopoietic stem cells could survive in cadaveric marrows [26], and the presence of pluripotent hemopoietic stem cells and their proliferative capability in 12-hours post-mortem was observed in murine bone marrow [31]. All these findings demonstrated the persistence of hemopoietic stem cells in cadaveric marrows, showing the cadaver to be a potentially abundant source of these cells [10,14]. Soon, it was also demonstrated that high yields of nucleated marrow cells could be best obtained from adult cadaver sources and that the opportunity to procure cadaver bone marrow could be enormously expanded if the source of marrow was obtained at the time of a routine postmortem examination, without requiring the prosector to carry out any new, special or further procedures. Also it was noticed that the risk of blood contamination increased per hour post-mortem. In donors with multiple traumas, the risk of blood contamination with organisms of high virulence was greater, but smaller in donors with preceding organ procurement. For this reason the postmortem time before bone marrow procurement was suggested to be kept to a minimum [23,28,30]. The methods for bone marrow obtention and processing were thought to be simplified as much as possible by the use of easily available and economical equipment [24]. The number of nucleated cells obtained from 1 ml of bone marrow was significantly higher in vertebrae than in the sternum or ribs. Viability of cells was not significantly affected by storage temperature or duration of storage (6–72 h). When analyzing the number of colony-forming units (CFU-GM, BFU-E and CFUGEMM) it was found no significant differences between cadaveric bone marrow and bone marrow aspirates from living donors. In this way bone marrow from cadaveric donors could be harvested and procured with a high degree of viability and good function [11]. With an appropriate technique of harvesting and procurement, it was feasible to recover enough stem cells for transplantation. Bone marrow was harvested from vertebral bodies, sternum body and ribs. In three cases, sternal samples were taken before perfusion of organs with UW solution. Cadaveric vertebral bodies (VB) have long been proposed as a suitable source of bone marrow (BM) for transplantation (BMT), but they have rarely been used for this purpose [10]. In 1995 VB BM was infused immediately following whole organ transplantation to augment donor cell chimerism. Transplantation of any organ resulted in the migration of bone marrow-derived leukocytes from the donor into the recipient, where they have been shown to persist indefinitely. This phenomenon of tolerance was augmented in 18 patients by infusing donor bone marrow cells at the time of whole organ transplantation. The thoracolumbar vertebral column (VC) was harvested from 24 cadaveric organ donors, yielding an average of 9 VB per donor. The marrow obtained was subsequently infused peri-operatively into 18 ABO-matched recipients undergoing whole organ transplantation [21]. A point of practical value was that the loss of cells during the first 36 h was not a crucial problem and the start of procurement could be postponed until the day after the donor operation. Between 1 and $4x10^6$ CD34 cells are sufficient for engraftment using unrelated peripheral blood progenitor cells. Only a few CD34 cells were lost during cryopreservation. Thus, 6.2×10^8 CD34 cells would be enough for two adult recipients with 70 kg body weight, giving $4x10^6$ CD34+ cells/kg. An interesting question arises when comparing cadaveric donors (CD) bone marrow with bone marrow aspirated from living donors (LD). All these studies did not saw any differences in viability of the cells after the procurement. The fact that the fraction of CD34+ cells was smaller in the LD marrow than in the CD marrow probably indicates that aspirated marrow is diluted with peripheral blood. When quality, as measured by colony-forming units, of CD marrow is compared with bone marrow aspirated from LD, they saw a tendency towards lower amounts in the cadaveric marrow, but the difference was not significant. As regards of costs, the method for harvesting and procurement of cadaveric bone marrow was relatively simple and fast, when used together with organ retrieval [11,12]. In 1986 a 12 year old male with acute lymphocytic leukemia received donor bone marrow from his histocompatible father whose marrow was harvested 40 minutes postmortem after he suffered a myocardial infarction. The marrow was stored in liquid nitrogen for 17 days prior to infusion into the recipient. Trypan blue viability was greater than 99% for the fresh marrow. Progenitor cell assays revealed that 20% of the CFU-MIX, 16% of the BFU-E, 10% of the CFU-E, and 17% of the CFU-GM were spared during the cryopreservation period. Post-transplantation, the recipient had a leukocyte count greater than $>10^3/\mu L$ by day 26. Southern blotting analysis documented the donor origin of the peripheral blood mononuclear cells and granulocytes isolated 46 days post-transplantation. Unfortunately, the patient died of complications related to graft-v-host disease 67 days following transplantation. This case demonstrated the feasibility of cadaveric marrow as a source of donor cells and was the first reported case of documented leukocyte engraftment in a recipient of cadaveric marrow [32]. In 2003, a Poland group described an optimization of isolation of early hematopoietic cells from heparinized cadaveric organ donors, considering that heparinized cadaveric organ donors are a potential source of hematopoietic cells for transplantation purposes. They resuspended the bone marrow in RPMI or Iscove's medium supplemented with heparin or ACD. Bags with harvested marrow contained 20% atmosphere air during short-term storage/transportation. Finally, they also noticed that cells survived short-term storage better if the collected marrow was not depleted of erythrocytes [33]. Vertebral bone marrow is a rich and easily accessible source of hematopoietic and MSCs that has been used to promote chimerism and transplantation tolerance in connection with cadaveric organ transplantation [34]. In 2012, Gorantla et al. developed and validated a procedure to isolate viable bone marrow cells from the vertebrae of cadaveric organ donors for composite organ grafting. They performed six pre-clinical full-scale separations to adapt vertebral BM preparations to a good manufacturing practice (GMP) environment. Larger lumbar vertebrae yielded about 1.6 times the cells of thoracic vertebrae. The average product yielded $5.2 \pm 1.2 \times 10^{10}$ total cells, $6.2 \pm 2.2 \times 10^8$ of which was CD45+, CD34+. This procedure could be used to prepare clinical-grade cells suitable for use in human allotransplantation [35]. In general, all organs submitted for transplantation such as the kidney, liver, heart and also tissues like the cornea, the middle ear ossicles, or even fat, muscle, bone and skin between many others, when removed postmortem and reused for allografting are alived. In an animal model complete and therapeutic liver repopulation could be achieved with hepatocytes derived up to 27 hours post-mortem. Cadaveric liver cells

had a repopulation capacity similar to freshly isolated hepatocytes. These data provided evidence that non-heart-beating donors could be a suitable source of hepatocytes for much longer time periods than previously thought possible [36]. It has also been shown previously that split-thickness skin grafts could be allografted up to 3 weeks after death if stored at 4°C [37], a fact that supports the idea that not only adult differentiated cells survive in the inner mileu of these organs and tissues but also probably stem cells [16]. Human induced pluripotent stem cells (iPSCs) have become also an intriguing approach for neurological disease modeling, because neural lineage-specific cell types that retain the donors' complex genetics can be established in vitro. iPSCs generated from a skin biopsy collected post-mortem during the rapid autopsy of a 75-year-old male, whole body donor, defined as an unaffected neurological control by both clinical and histopathological criteria. Statistical analysis also demonstrated that fibroblast proliferation was significantly affected by biopsy site, but not donor age (within an elderly cohort). These results provided evidence that autopsy donor-derived fibroblasts can be successfully reprogrammed into iPSCs, and may provide an advantageous approach for generating iPSC-based neurological disease models [20]. Post-mortem human brain tissue represents a vast potential source of neural progenitor cells for use in basic research as well as therapeutic applications [38]. More recently, stem and progenitor cells have been isolated from postmortem brain, spinal cord, and the retina [18,19,39]. It has been observed an increase in sphere numbers from organ of Corti and spiral ganglion after 6 h and 1 day post-mortem respectively and it is speculated that hypoxia, acidosis, or lack of nutrients and other postmortem-related factors may contribute to a stimulation or positive selection of stem cells over other cells in dying tissue [16]. Neural stem cells can be isolated from deceased early postnatal and adult rats with varying post-mortem intervals. Neurospheres can be obtained from the forebrain tissue, including the lateral ventricle in the early postnatal rats, and from the striatal wall of lateral ventricle, including the subventricular zone (SVZ) in adult rats. The number of neurospheres obtained in primary cultures from early postnatal animals was much larger than that from the adult rats. The adult mammalian central nervous system harbors a population of multipotent stem/progenitor cells that can be induced to grow as proliferative neurospheres in vitro. Neural progenitor cells (NPC) from postmortem adult human retina can also differentiate into multiple neural components. Then, the retina may constitutively replace neurons, photoreceptors, and glia. As the only part of the central nervous system directly visible in vivo, by non-invasive means, the retina may offer a unique and accessible opportunity to study the role of NPC in neurodegenerative and CNS diseases in humans [19]. Retinal progenitor cells from post-mortem human tissue yielded viable cultures that grew to confluence repeatedly, although not beyond 3 months. Viable progenitor cells can be cultured from the post-mortem retina of premature infants and exhibit a gene expression profile consistent with immature neuroepithelial cells [9]. Inner ear stem cells, have been isolated, and may be useful in cell replacement therapies for hearing loss, after protracted post-mortem intervals. Neonatal murine inner ear tissues, including vestibular and cochlear sensory epithelia, display remarkably robust cellular survival, even 10 days post-mortem. No difference was detected in the proliferation and differentiation potential between stem cells isolated directly after death and up to 5 days post-mortem. At longer post-mortem intervals, the potency of sphere-derived cells to spontaneously differentiate into mature cell types diminishes prior to the cells losing their potential for self-renewal. Three week old mice also displayed sphere forming stem cells in all inner ear tissues investigated up to 5 days post-mortem. All these results demonstrated that post-mortem murine inner ear tissue is suited for isolation of stem cells [16]. Neural precursor cells (NPCs) capable of resisting to a prolonged ischemic insult as this may occur at the site of traumatic and ischemic CNS injuries have also been isolated. These results suggest that PM-NPCs can be obtained from animal cadavers even several hours after death and their self-renewable capability is comparable to normal neural precursors [40].

Surviving Times of CSCs

Generally, it appears that many stem cells survive for hours or even days after death [23,30,41], but no study thus far has systematically and quantitatively investigated the postmortem time course of the decrease in stem cell numbers and the specific potential of stem cells isolated at different postmortem time intervals. Then, accessibility to stem cells from healthy or diseased individuals, and the maintenance of their potency are challenging issues for stem cell biology [23]. The isolation of viable and functional skeletal myogenic cells from humans up to 17 days, and mice up to 14 days post mortem, much longer beyond previous reports has been recently described. There are needs of more studies that should be done in the future to determine the reasonable time limits for harvesting special human stem cells in the post-mortem interval. There have been many early publications about the cells surviving times in the preparations of cadaveric bone marrow (CBM) specimens. Almost all this research, looks like it has been forgotten or unnoticed by the scientific community for decades. In 1966 Fedorov published on the problem of the viability and time of preparation of CBM [23,30]. In 1968 Kovalenko in the preparation, freezing and transplantation of CBM [42]. Also, in the same year Khakimov described a method of prolonged preservation of CBM by the freezing method [43]. In 1979 Liu et al. described Hemopoietic activities of cryopreserved murine fresh and post-mortem bone marrow cells [44], and in 1980 the same author published on the "cryopreservation of human CBM cells"[41]. Bone marrow cells harvested and stored at 4°C for 7 days did not display either a significant increase in programmed cell death. However, prolonged storage resulted in lower ROS production, indirectly giving evidence of activation of intracellular signaling proteins [29]. Recent studies have shown that CBM cells could be stored up to seven days without an increase in apoptosis and that three days of storage does not affect the CD34+ fraction of the cells. The bone marrow could be harvested in case of a sudden death, phenotyped and transplanted immediately or stored for later use [12]. Neurosphere-generating cells can be isolated from adult mouse spinal cord and forebrain subependymal zone after postmortem intervals of up to 140 h, when kept at 4°C, and up to 30 h when kept at room temperature. Although there is an inverse relationship between postmortem interval and the number of neurospheres generated, neurospheres derived under these conditions are proliferative and can give rise to both neurons and glia [18]. Also, there was not a significant difference in the population of neurospheres between the living and the deceased animals at least within 2 days after death. A few neurospheres were still obtainable at 6 days after death in early postnatal animals, but almost no neurospheres were obtained at 5 days after death in the adult rats [17].

Influence of Different Factors on CSCs Viability and Regenerative Capacities

Muscle stem cells are enriched in post mortem tissue, suggesting a selective survival advantage compared with other cell types. Transplantation of mouse muscle and hematopoietic stem cells regenerated tissues robustly. Cellular quiescence contributes to this cell viability where cells adopt a reversible dormant state characterized by reduced metabolic activity, a prolonged lag phase before the first cell division, elevated levels of reactive oxygen species and a transcriptional

status less primed for commitment [29]. Finally, severe hypoxia, or anoxia is critical for maintaining stem cell viability and regenerative capacity. Thus, these cells provide a useful resource for studying stem cell biology [7]. It is also possible to create culture conditions that permit the survival and full engraftment potential of muscle and HSCs for remarkably longer periods post mortem than previously described, providing a source of stem cells for use in studying stem cell biology [30]. Muscle stem cells have a remarkable ability to survive for extended periods post mortem, in both humans and mice. Significantly, post-mortem skeletal muscle and HSCs maintain their functional properties in vitro and after transplantation, or after prolonged storage in anoxia [7]. It was generally thought that stem cells lose their potential and utility for experimental and clinical purposes within 24-48 h post mortem in the necrotic environment of the cadaver [29]. But the lack of oxygen, nutrients, or the presence of extensive necrosis seems to trigger a cellular response in stem cells that make them adopt a deeper state of quiescence or dormancy. Whether these dormant cells are subsequently enriched in post-mortem muscles awaits further experimentation. The resistance to severe hypoxia, which has been observed in cadavers and in vitro could be considered either as an intrinsic characteristic of a subpopulation of stem cells, or a general mechanism of all stem cells, which have developed the capacity to reduce their metabolic activity and adopt a more stem cell state under extreme conditions of stress [7,45].

Some Other Advantages of CSCs

An interesting and possible alternative that could find out a solution by the use of CSCs, would be that one observed when a stem cell from a selected niche location is needed. This is generally seen when a very special therapy for a very specific diseased site, like the ear, the brain or potentially many other ones, should be given to a patient. In this situation, maybe, unique "niche stem cells" could offer the only possible solution [3,4]. Human embryonic stem cells could also be such a source but are subjected to ethical criticism. Stem cells isolated from the human inner ear or the brain from cadaver donors, on the other hand, could serve as a source without ethical constraints [16,19]. In this scenario another possibility could come from the use of human tissue removed during infrequent surgeries [46], but surgically removed tissue is usually taken from patients with diseased organs. In this way stem cells from healthy "niches" of cadaver donors could be the only answer for these circumstances [16]. Another benefit offered by exploring new sources for human stem cell obtention, like those from cadaver donors, could come from the speculation that hypoxia, acidosis, or lack of nutrients and other postmortem related factors as it was said, may contribute to a stimulation or positive selection of the more robust efficient stem cell over others from tissues of living donors [22]. This stem cell activation may be the result of an effort to repair local tissue damage and further studies should be done in this direction to demonstrate if this is really true [16]. There is also a relatively large evidence and many preliminary results that show that it is possible to isolate from postmortem human subjects stem cells not only from neonatal, but also from older ones [16]. This evidence permits to speculate that stem cells obtained from cadaver donors of any age will be a feasible and generalized procedure to be done in the near future. Finally, in a pioneering study that involved 18 kidney transplants, where the unmatched, living unrelated donors gave not only the kidneys to the selected patients but also their stem cells to be infused, induction of tolerance was obtained in the HLA disparate kidney transplantation recipients with durable chimerism. In this way, it is envisioned that in the next decade we will probably find in cadaver donors not only the needed organs and tissues for transplantation but also the "key cells" (CSCs) to finally defeat rejection without pharmacological immune-supression [47-49].

Conclusions

Beside the fact that this topic has not ever been fully addressed before as a whole very important chapter, CSCs will be soon the center of a deep discussion in Regenerative Medicine and Transplantation. Maybe also, they could be a scientific revolution in these fields. As far as we know, we have been the first ones in the world, to use Cadaveric Bone Marrow Mesenchymal Stem Cells in a human clinical trial, to treat large severe burns [50]. We really see feasibility and a great potential for the routine salvage and therapeutic use of CSCs for regenerative medicine and transplantation procedures. In order to accomplish this, further studies should be done. If this comes to be true it might surely change significantly the way we see today the possible sources of stem cell obtention and uses; finally considering CSCs as very important tools for cell therapies, regenerative medicine and transplantation.

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