World Journal of Stem Cells

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DOI: 10.4252/wjsc.v7.i7.1010

World J Stem Cells 2015 August 26; 7(7): 1010-1021
ISSN 1948-0210 (online)
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REVIEW

Allogenic banking of dental pulp stem cells for innovative therapeutics

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Conflict-of-interest statement: The authors declare that they have no conflict of interests.

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Received: October 13, 2014
Peer-review started: October 14, 2014
First decision: January 8, 2015
Revised: June 8, 2015
Accepted: June 18, 2015
Article in press: June 19, 2015
Published online: August 26, 2015

Abstract

Medical research in regenerative medicine and cell-based therapy has brought encouraging perspectives for the use of stem cells in clinical trials. Multiple types of stem cells, from progenitors to pluripotent stem cells, have been investigated. Among these, dental pulp stem cells (DPSCs) are mesenchymal multipotent cells coming from the dental pulp, which is the soft tissue within teeth. They represent an interesting adult stem cell source because they are recovered in large amount in dental pulps with non-invasive techniques compared to other adult stem cell sources. DPSCs can be obtained from discarded teeth, especially wisdom teeth extracted for orthodontic reasons. To shift from promising pre-clinical results to therapeutic applications to human, DPSCs must be prepared in clinical grade lots and transformed into advanced therapy medicinal products (ATMP). As the production of patient-specific stem cells is costly and time-consuming, allogenic biobanking of clinical grade human leukocyte antigen (HLA)-typed DPSC lines provides efficient innovative therapeutic products. DPSC biobanks represent industrial and therapeutic innovations by using discarded biological tissues (dental pulps) as a source of mesenchymal stem cells to produce and store, in good manufacturing practice (GMP) conditions, DPSC therapeutic batches. In this review, we discuss about the challenges to transfer biological samples from a donor to HLA-typed DPSC therapeutic lots, following regulations, GMP guidelines and ethical principles. We also present some clinical applications, for which there is no efficient therapeutics so far, but that DPSCs-based ATMP could potentially treat.

Key words: Adult stem cells; Multipotent stem cells; Cell-based therapy; Cell tissue bank

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Core tip: To achieve clinical applications, stem cell-based therapy must shift from lab experimentation to clinical grade stem cells. We present here the development of advanced therapy medicinal products (ATMP) by the banking of dental pulp stem cells (DPSCs) for allogenic use. The dental pulp represents an efficient tool for industrial applications due to its accessibility after wisdom teeth extraction for orthodontic purpose. DPSC therapeutic batches can be produced in good manufacturing practice condition after human leukocyte antigen typing and stored in allogenic biobanks. We propose some clinical applications, for which there is no efficient therapeutics so far, but that DPSCs-based ATMP could potentially treat.

Collart-Dutilleul PY, Chaubron F, De Vos J, Cuisinier FJ. Allogenic banking of dental pulp stem cells for innovative therapeutics. *World J Stem Cells* 2015; 7(7): 1010-1021 Available from: URL: http://www.wjgnet.com/1948-0210/full/v7/i7/1010.htm DOI: http://dx.doi.org/10.4252/wjsc.v7.i7.1010

INTRODUCTION

Adult organisms contain postnatal somatic stem cells that are involved in symmetrical and asymmetrical cell divisions, allowing stem cell compartment maintenance and cell differentiation[1]. Thus, adult stem cells provide replacement and repair cells for normal turnover or injured tissues[2]. As these stem cells are able to renew particular tissues, they have motivated research on how to apply them in the clinic. Because of their self-renewal and ability to regenerate tissue, stem cells could provide long-lasting clinical benefits to recipients. Among these potentially beneficial cells, mesenchymal stromal cells are spindle-shaped, plastic-adherent cells isolated from bone marrow, adipose tissue, dental pulp and many other tissue sources[3,4]. They are also called mesenchymal stem cells (MSCs) in reference to their significant self-renewing properties and ability to form skeletal and connective tissue, and are suggested to be responsible for the normal turnover and maintenance of adult mesenchymal tissues[2,5]. MSCs are now the focus of intensive efforts in order to elucidate their nature and properties, and to develop cell-based therapies with real clinical applications[6]. Moreover, MSCs provide promising therapeutic benefits as they primarily mediate positive effects through paracrine mechanisms independent of cell differentiation[7]. Many preclinical and clinical trials have been completed and the major hurdles are now cell engraftment and survival, stem cell fate control, and donor-patient compatibility for allogenic applications. Several current efforts are directed at promoting the registration and banking of stem cell lines and providing associated data[8,9]. Banking MSCs, with shared materials and data, is an important step for the efficient progress of stem cell research and clinical translation. Emphasis on clinical applications is increasing, with an aim of establishing clinical grade, human leukocyte antigen (HLA)-matched banks for clinical translation[10].

DENTAL PULP STEM CELLS

Teeth are formed of two main parts, the crown and the root, that can be defined by anatomic criteria. They are linked by the periodontal ligament to the supporting alveolar bone, which is composed of both compact and trabecular bone. The dental crown consists of enamel, dentin, and dental pulp tissue. During tooth growth and development, ameloblasts form enamel and odontoblasts generate primary dentin. After tooth eruption, ameloblasts disappear from the surface of the enamel; consequently, enamel formation ceases to occur naturally *in vivo*. In contrast, odontoblasts, along the inner surface of the dentin inside the pulp chamber, continue to deposit dentin matrix to form secondary dentin throughout life. In addition to secondary dentin, odontoblasts can form tertiary (reparative) dentin in response to several stimuli, such as mechanical, chemical, and/or bacterial stimulation. Even when odontoblasts have been damaged, the reparative dentin can be formed in the dental pulp to protect against further disruption of the pulp tissue. This reparative dentinogenesis has been thought to be mediated by newly generated odontoblasts arising from dental pulp tissue. These findings led to the speculation that odontogenic progenitor cells or stem cells may exist in dental pulp tissue[11]. The first type of dental stem cell was subsequently isolated from the human pulp tissue and given the name dental pulp stem cells (DPSCs)[12]. Dental pulp is a soft connective tissue entrapped within the dental crown, and divided into four layers. The external layer is made up of odontoblasts producing dentin; the second layer is poor in cells and rich in collagen fibers; and the third layer contains progenitor cells and undifferentiated cells, some of which are considered stem cells. From this layer, undifferentiated cells migrate to various districts where they can differentiate under different stimuli and make new differentiated cells and tissues. The innermost layer is the core of the pulp and comprises the vascular area and nerves[13]. Dental pulp is an interesting source of adult stem cells because of the large amount of cells present and the non-invasiveness of the isolation methods compared to other adult tissue sources[13-15]. MSCs defined as dental stem cells can be obtained from human permanent and primary teeth, human wisdom teeth[12], human exfoliated deciduous teeth[16], apical papilla[17], the periodontal ligament[18,19] and the dental follicle[20,21].

Dental pulp tissue from human third molar, exfoliated deciduous or supernumerary teeth represent an easily accessible source for harvesting MSCs as these teeth are often discarded.

Stem cells that reside in dental pulp (DPSCs) have been described as a population of MSCs, as they match the definition given by the Mesenchymal and Tissue

Stem Cell Committee of the International Society for Cellular Therapy[3]: DPSC are plastic-adherent when maintained in standard culture conditions; they express some specific surface molecules such as CD105, CD73, CD90 and lack expression of CD45, CD34, CD14, CD19 and HLA-DR surface molecules; and they have the ability to differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*[11,12,18,22-24]. Moreover, DPSCs can differentiate into a large array of cells and tissues[25-28] and a comparison of their multipotency with Bone Marrow Stem Cells has demonstrated that proliferation, availability, and cell number of DPSCs were greater than for bone marrow MSCs[24,29].

In addition, DPSCs were also found to undergo myogenic and neurogenic differentiation capacities *in vitro*, expressing respective gene markers and exhibiting neuron-like cell morphologies. The plasticity and multipotential capability of DPSCs can be explained by the fact that dental pulp is made of both ectodermic and mesenchymal components, and contains neural crest-derived cells[13]. Concerning cell surface molecules, the persistence of negative results for CD45 demonstrates that these cells are not derived from a hematopoietic source, although they are of mesenchymal origin[25]. Like all MSCs, DPSCs are also heterogeneous and the various markers may be expressed differently by subpopulations of these stem cells[24]. A selected subpopulation of $CD34^+/CD45^-$ DPSCs, which represented roughly 10% of dental pulp cells, has also been described. These cells displayed an increased capacity of self-expanding and differentiating in pre-osteoblasts, and were able to self-maintain and renew for long time[17]. Although MSCs were originally described as CD34 negative, it seems that this subpopulation of DPSCs expresses the CD34 cell surface antigen in the manner reserved for the most primitive stromal stem cells (other than hematopoietic) that was gradually lost after the differentiation of lineage committed progenitors[30].

DPSCS BIOBANKING

The term "biobank" describes various facilities that store biological samples, from small tissue collections to wide repositories featuring a variety of tissues and biological sample types[31,32].

Storage and collection of biological material might be accompanied by various medical and epidemiological data that are used for current research and for potential future works[33]. Biobanking has been defined as a structured resource for genetic and medical research and their therapeutic applications. It includes human biological material and extensive associated information[34,35].

Several types of biobanks can be distinguished, according to the purpose and target: case control, clinical trial, tissue, biomolecular resource center, stem cells[36]. Stem cell biobanks have received much attention as a new biologic resource for both research and clinical applications, leading to the development of stem cell banks around the world[37]. Stem cells of dental origin represent a promising source of new stem cells as, in western countries, 80% of teenagers and/or young adults have their wisdom teeth extracted. Furthermore, dental pulp is naturally protected within the pulp chamber, the inner cavity of the tooth, in a sterile environment. Pulp from one wisdom tooth generally contains between 200000 and 300000 DPSCs[38]. Studies have indicated that DPSC isolation was feasible for 5 d after tooth extraction[39]. Efficient results were obtained by cryopreserving second-passage DPSC cultures, but could also be achieved by isolating and cryopreserving entire pulp tissues, with digestion and culture performed post-thaw[40]. Such minimal processing may be of interest for the banking of samples for which there are no immediate plans for expansion and use. Furthermore, cell recovery could be achieved by mechanical disruption with a single-use device, in accordance with the GMP (European Good Manufacturing Practices) standard. Dental pulp and DPSC recovery is represented in Figure 1.

Immunologic considerations: Allogenic use and immunomodulation

Immune mechanisms confer immediate protection against foreign organisms (innate immunity) and specific immune responses to neutralize pathogens (adaptive immunity). The immune system recognizes tissue compatibility and can raise an effective immune response against pathogens or incompatible allogenic tissues. Tissue compatibility or incompatibility is determined from allelic similarities or disparities at genetic loci that encode the major histocompatibility complex (MHC) antigens, also called the HLA system. The HLA system encodes two major classes of highly polymorphic cell surface glycoproteins: HLA class Ⅰ molecules are expressed on all nucleated cells and HLA class Ⅱ molecules are expressed on antigen-presenting cells, thymic epithelial cells, and B lymphocytes. These immunological principles, which apply to organ or tissue transplantation, can be extended to transplantation of DPSCs or DPSC-derived tissue, especially for HLA class Ⅰ molecules (HLA-A, HLA-B and HLA-C)[41]. Thus, a major clinical challenge to DPSC banking will be to overcome the immunological barriers to the transplantation of DPSC-derived tissues in order to prevent rejection[42,43]. Ensuring HLA compatibility is certainly the most interesting method of minimizing the risk of rejection. Embryonic stem cells have been shown to express very low levels of HLA class I proteins, with a moderate increase during differentiation[44]. Regarding MSCs, HLA expression remains unclear, but they have been extensively studied for their immunomodulatory properties[45-49]. Indeed, MSCs exert a profound inhibitory effect on T cell proliferation *in vitro* and *in vivo*, with similar effects on B cells, dendritic cells and natural killer cells[50]. Moreover, T-cell inhibition is not restricted by HLA type, and immunosuppressive effects are

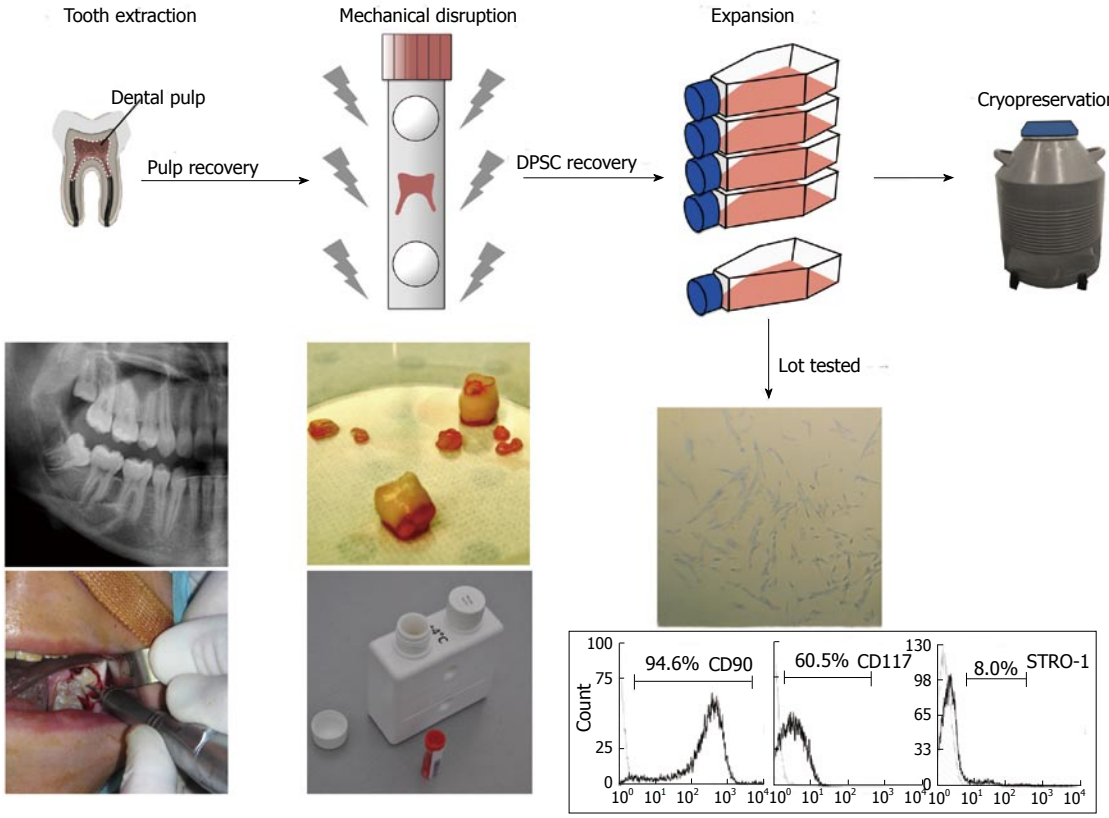

Figure 1 Dental Pulp tissue and dental pulp stem cell recovery. Wisdom teeth are extracted in aseptic conditions and transferred to the cell bank in a sterile transport tube. The teeth are then cracked opened and the pulps are mechanically disrupted in a tissue grinder/homogenizer. The cell suspensions obtained are screened for expression of stemness markers by flow cytometry, before storage in liquid nitrogen. DPSC: Dental pulp stem cell.

mediated through soluble factors and the generation of regulatory cells[47,51]. These findings suggest that MSCs can induce peripheral tolerance, enhancing their potential for therapeutic applications[45,48]. A higher immunosuppression of T-cell alloreactivity has also been demonstrated in DPSCs in comparison with bone marrow stem cells[52]. These properties distinguish DPSCs as one of the most accessible cell sources for cell-based therapy in regenerative medicine and inflammation-related diseases[46].

To overcome rejection and use DPSCs in transplantation medicine, the formation of a histocompatibility bank is an attractive option, where DPSCs are stored after HLA isotyping. Ideally, considering the large numbers of wisdom teeth extracted from genetically diverse populations, adequate levels of isotype matching with patients may be achieved. The establishment of an HLA-organized DPSC allogenic bank could be sufficient to provide stem cells for a large number of patients. The concept of haplobanking with HLA homozygous cell lines would also limit the number of HLA mismatches[53]. Several studies have been conducted to determine the number of donors needed to cover the population of a country. These findings are dependent on ethnic disparities of the population and the type of stem cells considered. The creation of a bank containing highly selected homozygous lines is an attractive approach to HLA matching. Selected homozygous lines can provide HLA matches for a wide percentage of populations. Estimates of the number of homozygous cell lines needed have mainly been established considering embryonic stem cells, for the main proteins HLA-A, HLA-B and HLA-DR. Data from cadaveric organ donors, cord blood bank or *in vitro* fertilization-derived embryos led to the estimate that approximately 150-190 human embryonic stem cell lines with various HLA genotypes, or a collection of 10-30 homozygous lines for the common HLA types, would be sufficient to provide HLA-matches for a wide part of the population in the United Kingdom[54], Japan[55,56], the United States[57] or China[58]. Because of the low incidence (1.5%) of HLA-homozygous individuals in the normal population[54], a systematic collection of discarded wisdom teeth would be of prime interest. The determination of the HLA types of 100 DPSC lines from teeth collected in Japan revealed 2 homozygous lines for all the 3 considered HLA loci. These 2 homozygous lines therefore have the potential to cover approximately 20% of the Japanese population with a perfect match[59].

Methods and good manufacturing practices

The production and marketing of stem cell-based therapy faces imperative steps, including product characterization, safety testing and clinical trials design. At both national and international levels, numerous standards and regulations must be followed in order

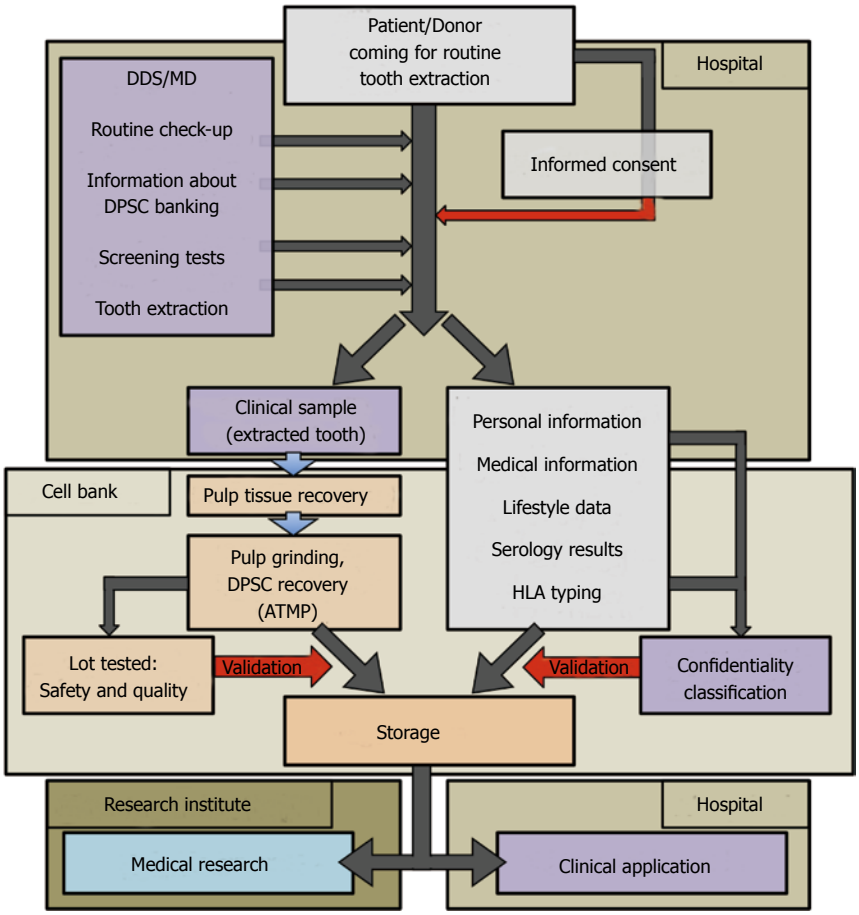

Figure 2 Process flowchart for current Good Manufacturing Practices manufacturing of dental pulp stem cell lots/therapeutic products. The chart is divided into 4 areas: Hospital for tooth recovery, Cell Bank, Research Institute and Hospital for clinical applications: (1) Hospital: direct contact between patients and authorized medical staff, such as Medical Doctor (MD) or Doctor of Dental Surgery (DDS). Clinical sample and donor's personal data are recovered; (2) Cell Bank: current Good Manufacturing Practices manufacturing of Advanced Therapy Medicinal Products (ATMP) from the biological samples (dental pulps). All data concerning the donors are anonymous; (3) Research Institute: dental pulp stem cell (DPSC) lots are used for animal experiments to develop new therapeutics; and (4) Hospital: clinical grade DPSC lots are used for therapeutics. Red arrows represent critical parameters related to each step of processing (informed consent, quality, safety, confidentiality). HLA: Human leukocyte antigen.

to translate DPSCs into clinical products. There are variations in these international and national guidelines, and in the regulations that are applied to the collection and storage of human tissue, personal data and medical records[32]. The Food and Drug Administration, in the United States, and the European Medicines Agency (EMA), in Europe, are responsible for creating and enforcing these regulations. In Europe, stem cells for clinical therapies are classified under advanced therapy medicinal products (ATMP) unless they are minimally manipulated and intended for homologous use[60]. A Committee for advanced therapies (CAT) has even been created to evaluate cell production marketing by assessing the quality, safety and efficacy of ATMPs, in accordance with the regulatory framework. EMA regulation defines the current Good Manufacturing Practices (cGMP) guidelines to manufacture ATMPs[61]. Even though clinical grade production of DPSCs needs to be implemented, DPSCs can be isolated, stored, and eventually expanded by applying rational modifications to the commonly used methods[15,62], in order to continue complying with good manufacturing practices[63] from the donor (patient having his/her tooth extracted, in aseptic condition) to the storage tank. The critical step of enzymatic pulp tissue digestion can be replaced by mechanical disruption in single use devices, such as a tissue grinder/homogenizer. Fetal bovine serum usually required for *in vitro* expansion can be replaced by human serum supplements derived from peripheral blood serum, peripheral blood plasma, or platelet lysate[64]. Moreover, genetic stability has been demonstrated for DPSCs for up to 9 cell passages[65,66].

Legal and practical issues (consent, confidentiality, commercialization)

Translation of DPSC research into clinical applications relies on abundant *in vitro* and *in vivo* preclinical data. However, when it comes to potential therapeutic applications, some barriers can appear, due to restrictions specified in the consent document used for the collection of biological materials, questions about ownership of the collected DPSCs, and the confidentiality of the information associated with the cell lines[10]. The constitution of an allogenic DPSC bank contains

procedures to ensure anonymity, although authorized parties can access some clinically relevant information.

The rights of donors and the interests of researchers are protected by incorporating relevant government legislation (ethical committee review) and procedures (*e.g.*, anonymity and consent). It is crucial to explain the use and transfer of cells and data at the time of informed consent, especially highlighting features that distinguish collection for research from collection for a biobank[67]. The whole process, from the patient coming for tooth extraction to storage of DPSC lots, is presented in Figure 2.

Allogenic DPSC biobanking brings together a multitude of data on individuals, including health and lifestyle. Thus, the way the informed consent is obtained should reflect the personal information used for medical research, taking into account that the patient was originally coming for a routine tooth extraction. As informed consent is derived from the standard that every donor has the right to self-determination, the patient must be informed about the nature of biobanking, the procedures in which the tooth he has donated might be involved, and the expected outcome of the research[36,68]. The physical and intellectual property of biological samples collected must be clearly established and explained[69].

INNOVATIVE THERAPEUTICS

Upon discovery of stem cells in the dental pulp, DPSCs demonstrated their ability to regenerate a complex consisting of a mineralized matrix of odontoblasts and connective tissue containing blood vessels similar to that observed in normal human tooth[12]. Since then, the use range of potential medical applications based on DPSCs include the repair and regeneration of bone[13,70], the central nervous system[27,71,72], liver tissue[73], heart tissue[74], eyes[75], muscles[76,77], and salivary gland cells[78,79]. Overall, it holds great potential in the field of regenerative medicine and tissue engineering[13,23] alone or combined with various biomaterials[80-84]. Some have proposed that DPSCs may have greater potential than the current MSC gold standard, the bone marrow-derived MSC[29].

Allogenic banking of DPSCs could boost industrial and therapeutic innovations by providing tools for unsolved medical problems, including the production of advanced therapy medicinal products (ATMP). We present here some clinical applications, for which there is no efficient therapeutics so far, but that DPSCs-based ATMP could potentially treat.

Spinal cord injuries

Chronic medullary lesion, a result of spinal cord trauma, is characterized by neurologic deficiency without evolution. Six months after trauma, these lesions are considered chronic, with no chance of improvement. According to the Christopher Reeves foundation, these spinal cord lesions affect 1.2 million persons in the United States and 300000 persons in Europe. Numerous preclinical studies have been conducted to graft stem cells of various origins into injured spinal cords, such as neural stem cells[85], embryonic stem cells[86-88], with encouraging results[89]. DPSCs, due to their embryologic origin, express some markers of both mesenchymal and neuroectodermic origin[12,16]. Indeed, DPSCs originate from migrating cranial neural crest cells. During embryonic development, these neural crest cells differentiate into a wide variety of cell types, including neurons of the peripheral nervous system[27]. MSCs have been thought to be usable in the treatment of spinal cord injuries, and adult human DPSCs could provide an ideal source of stem cells for therapeutic applications in such neurological pathologies[90]. The efficiency of DPSCs in improving neural regeneration has been shown *in vitro*[72,73,91] and *in vivo* after spinal cord injury[92-94]. These preclinical data enhance the therapeutic potential of intrathecally administrated HLA-typed DPSC lots in treatment of nerve tissue injuries.

Sjögren's syndrome

Sjögren's syndrome is an autoimmune pathology affecting 0.2% to 3% of the general population[95]. It is a chronic inflammation of the salivary and lacrimal glands, characterized by lymphocytic infiltration of the exocrine glands with a polyclonal B cell activation[96]. Although the pathogenesis of primary Sjögren's syndrome remains unclear, T cells and B cells have been shown to be involved. Pharmacological treatments have limited efficiency, with only the capacity to temporarily ameliorate symptoms, and with no modification of the overall course of the disease[97]. Given the lack of disease-modifying drugs, treatment options are now focused on biotherapies[98]. As detailed above, immunomodulatory properties of MSCs have been demonstrated *in vitro* and *in vivo*, suggesting a therapeutic potential for autoimmune disease treatments[47], especially through anti-inflammatory cytokines production and T regulatory cells promotion[99]. These immunomodulatory properties have also been demonstrated for DPSCs, identifying them as a cell source for cell-based therapy of immune and inflammation-related diseases[47]. Intravenous injection and local injection of DPSC lots into salivary glands represents a potential novel immunotherapeutic tool for autoimmune Sjögren's syndrome.

Irradiated salivary glands

Cancers that originate from the aerodigestive epithelium, including carcinomas of the head and neck, are the leading causes of cancer-related mortality worldwide, accounting for about 2 million deaths and 500000 new cancers diagnosed annually[100,101]. Treatment involves chemotherapy, radiotherapy, and surgery. Radiation-induced salivary hypofunction is one of the major developments that affect survivors. Even though radiotherapy is focused on the cancerous area, radiations often affect salivary glands, causing severe hyposialia and oral dryness after orofacial cancer

treatment; hyposalivation underlying xerostomia after radiotherapy is still a major problem in the treatment of head and neck cancer. To date, the only treatment for this oral dryness is the use of artificial saliva to supply salivary glands, a treatment with limited efficiency. Salivary stem cell (salisphere) transplantation has been shown to functionally restore salivary gland efficiency after radiation-induced impairment of salivary gland function and consequential xerostomia[79]. Furthermore, it was demonstrated that DPSCs used as a cell source for the treatment of salivary gland hypofunction could partially revert this hypofunction[80]. Thus, stem cell-based therapy has great potential in prevention or treatment of radiation-induced hyposalivation[102]. New therapeutic strategies are now being considered using stem cells injected intravenously or directly into salivary glands to allow salivary gland cell reactivation[103-106].

Acute periodontitis

Periodontal diseases are highly prevalent diseases that can affect up to 90% of the population worldwide. They have various forms, from gingivitis, the mildest form caused by dental plaque, to periodontitis, which induces the loss of connective tissue and bone support, and causes tooth loss in adults[107]. Acute periodontitis is an inflammatory disease of the periodontium triggered by the host's immune response and resulting in the progressive loss of gingival tissue, periodontal ligament and supporting alveolar bone[108]. Actual therapeutics consist of the control of bacterial infection and the stabilization of tissue loss. Regenerative treatment using bone grafts, gingiva grafts, and growth factors offer interesting possibilities, but only in specific indications[109-111], and with unpredictable results[112]. In this context, topical application of stem cells in periodontal lesions appeared to be a promising strategy to regenerate periodontium[113]. *In vitro* studies demonstrated the ability of DPSCs to differentiate into osteoblast and cementoblast lineage, and to participate in periodontal ligament and cementum regeneration[114,115]. *In vivo* experiments enhanced the therapeutic potential of dental stem cell grafting to regenerate periodontal tissues[116-118]. Allogenic transplantation could enhance periodontal tissue repair and limit local inflammation through MSC immunomodulation[108,119].

Endodontic regeneration

Dental pulp, the soft connective tissue described above, is the tissue entrapped within the teeth, in which are recovered DPSCs. In case of dental decay, this tissue can be infected and become necrotic, because it is encased in a thick dentin wall, and consists of a microcirculatory system originating from a very small opening at the apex of the root. This anatomical configuration limits the development vascular supply during pulp regeneration. Endodontic treatment, when needed, includes the removal of vital and necrotic tissues from the root canal system, along with infected root dentine. It aims to prepare the canal space to facilitate disinfection by irrigants and medicaments. Prevention of reinfection is then achieved through the provision of a fluid-tight root canal filling and a coronal restoration[120]. The potential possibility of regeneration of pulp tissue by cell therapy is a promising approach for the future treatment of pulpitis or peri-apical disease assuring longevity of teeth and improved quality of life. It has been demonstrated that transplantation of DPSC was capable of inducing complete pulp regeneration in a root canal after pulpectomy[121]. Thus, the use of DPSC, combined with a supporting scaffold, could be used to treat and heal infected root canals, providing an interesting alternative to the actual inert fillings used in endodontics. Root canals anatomy limits the use of rigid scaffold systems in pulp regeneration: scaffolds for pulp regeneration should be injectable, with fibrous structures that ideally mimic the extracellular matrix of the pulp tissue and support stem cells growth.

Induced pluripotent stem generation from DPSC

Pluripotent stem cells can be induced from fibroblasts by retroviral introduction of Oct3/4, Sox2, c-Myc and Klf4[122]. These induced pluripotent stem (iPS) cells are similar to embryonic stem cells in morphology, proliferation and differentiation capacities[123]. They proliferate extensively and differentiate into virtually any desired cell type, providing an unlimited source of replacement cells for human therapy[124]. It has been shown that DPSCs could be also reprogrammed into iPS cells, with a higher efficiency rate than dermal fibroblasts. DPSCs-derived iPS cells were indistinguishable from human embryonic stem cells, highlighting the potential of DPSCs as an alternative source for generating iPS cells[125,126]. Many reprogrammed cell lines could easily be established from DPSCs obtained from young patients with a low risk of bacterial contamination and genetic modification, as extracted wisdom teeth are generally aseptically obtained from the mandible and are protected from ultraviolet and other damage by surrounding hard tissues. It was shown that iPS cells could be efficiently generated from DPSCs using the conventional 4 reprogramming factors (Oct3/4, Sox2, c-Myc and Klf4)[59,125,126], as well as using only 3 factors (Oct3/4, Sox2 and Klf4)[59], or even using only 2 non-oncogenic factors (Oct4 and Sox2)[30]. Interestingly, the efficiency rate of reprogramming was related to the donor's age, with higher rate for younger patients with wisdom teeth still under maturation[59].

With respect to safety, it would be ideal not to use retrovirus vectors for transient expression of the reprogramming genes. DPSCs are assumed to offer high efficiency of iPS cell generation even with the use of non-integrating vectors such as Sendai viruses or modified mRNA. Clinical use of iPS in regenerative medicine is very promising. However, time-efficiency and financial considerations argue in favor of the use of allogenic rather than autologous iPS lines. Similarly to DPSCs, biobanking of iPS lines would be a reasonable

strategy. In this setting, DPSC banking could be of great help to establish iPS cell banks with a sufficient repertoire of HLA types, since the establishment of clinical-grade iPS cell lines from individual patients would require much time and incur a high cost[59].

From DPSC to successful therapy: Limitations and issues

The notion of stem cells as postnatal units of organ or tissue regeneration allows imagining therapies such as tissue engineering. A stem cell that could be expanded and modified *ex vivo,* and transplanted *in vivo* encourages attempts to treat severe or lethal diseases. However, even when the use of stem cells could replace the lost cells, it does not guarantee that the regenerated cells could circumvent the cell death caused by the disease. And replacing lost cells, even with cells expressing several specific cell markers, is far from a successful therapy with fully functional cells. Indeed, clinically successful translation of stem cell science into medicine has been conducted following a simple framework in which organ-specific stem cells were used for organ-specific diseases[6]. The roles of DPSC, and MSCs in general, as niche cells, tissue organizers and skeletal or neural progenitors open opportunities and pose challenges. The molecular mechanisms by which stem cells become functional are still largely unknown. Its comprehension and identification may involve new methods that go far beyond the empirical injection of poorly characterized cultured cell strains[6]. Such methods may involve modeling of disease mechanisms, identification of cell-derived bioactive factors and their use as drugs (including factors mediating the interactions with endothelial and hematopoietic cells), definition of targeted specific disease mechanisms and organ-specific strategies to deliver DPSC to a site of interest[127].

CONCLUSION

DPSC-based therapy is now entering into a new stage of development, shifting from initial *in vitro* and *in vivo* studies to optimization of therapeutic products for clinical applications. As for other MSC, there are still many challenges concerning stem cell potency, age-related and disease-related tissue impairment, and production of clinical grade stem cells lots. The strategies presented in this review emphasize the potential of DPSC to be used for innovative clinical trials based on rational DPSC therapy, following GMP conditions.

Indeed, dental pulp is a remarkable site of stem cells, and the collection of stem cells from dental pulp is a non-invasive practice that can be performed after routine wisdom teeth extraction. DPSC can be recovered in GMP conditions and cryopreserved for long periods, after HLA typing. However, in the perspective of therapeutic use, optimization and better methods are still necessary for DPSC isolation, expansion and banking.

Although producing and storing patient-specific stem cells could resolve immunological problems, this procedure would be costly, laborious, and time-consuming. Allogenic DPSC banking containing clinical grade stem cell lines offers an alternative and provides stem cell lines from which it will be possible to choose a HLA match for the patient to be treated. There are variations in national and international regulations for the collection and storage of human tissue, but ethical principles related to biobanks always include safety, informed consent and confidentiality. The recovery of DPSC doesn't involve any invasive procedure as they come from already extracted teeth. Thus, the main concerns are: (1) for the donor, clear explanations about the banking project and confidentiality of all personal and medical data; and (2) for the patient, safety of DPSC lots produced in accordance to guidelines. To date, despite promising preclinical data, clinical trials using DPSCs have not been widely reported. Allogenic biobanks represent a new strategy that aims to develop the clinical applications of the DPSC potential, involving both researchers and clinicians.

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