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Review Article

Dental Pulpal Stem Cells: An Unfathomable Gem of Tooth

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Abstract

Teeth are the most natural, noninvasive source of stem cells which are easy, convenient, and affordable to collect, hold promises in therapeutic applications. Stem cells of the pulp appear to hold the key to various cell-based therapies in regenerative medicine, but most of the possibilities are in experimental stages and many procedures are undergoing standardization and validation.

Keywords: Stem cells, pulp, totipotent, pluripotent, SHED, regenerative.

INTRODUCTION

Human body is a complex structure that consists of a number of organ systems working together for the sustenance of life.

It performs a variety of functions essential for its survival and healthy existence which is made possible by the ability of the tissues to undergo renewal or regeneration. The renewal or regeneration of tissues is possible due to the presence of a unique set of unspecialized cells called the stem cells. The different types of stem cells are classified based on their capacity for differentiation, which include [1].

Totipotent cells: Stem cells capable of generating an entire organism; this property is exhibited by embryonic stem cells.

Pluripotent stem cells: Found in embryonic, foetal and to some extent, in adult tissues; they can potentially differentiate into cells of ectodermal, mesodermal, and endodermal origin (germ layers).

Multipotent stem cells: These differentiate into cells of different lineages, usually derived from the same germ layer.

Induced pluripotent cells: These are created by retroviral transcription of genes like Oct4, Nanog, Sox2, Klf4, and c-myc from multipotent stem cells or adult somatic cells; these cells have properties similar to that of pluripotent cells.

Somatic Cell Nuclear Transfer

This is a cloning technique where an adult somatic cell nucleus is introduced into a de-nucleated ovum; this ovum then divides to form the entire organism. This procedure could be used to generate human stem cell lines for therapeutic purposes (therapeutic cloning).

Stem cells are also classified based on the tissue of originas hematopoietic stem cells, umbilical cord blood and stem cells from the dental pulp. Stem cells from the dental pulp exhibit predominantly mesenchymal stem cell (MSC) properties [1].

Teeth are the most natural, non-invasive source of stem cells. Dental stem cells, which are easy, convenient and affordable to collect, hold promises for a range of potential therapeutic application [2]. Dental pulp stem cells (DPSC) from permanent teeth were first isolated by Gronthos *et al.*, and later Muira *et al.*, isolated stem cells from exfoliated human deciduous teeth (SHED).There are other sources of dental stem cells like apical papilla, periodontal ligament, and the dental follicle but DPSC/ SHED have a distinct advantage owing to their volume, ease of access, and their ‘immature’ nature, which give them a vast gamut of differentiation [3, 4]. Recent findings and scientific research articles support the use of MSC autologous within teeth and other accessible tissue harvested from oral cavity without immunorejection [3].

Dental stem cells are novel targets for research as the stem cell populations in the pulp may be the most viable alternative to umbilical cord blood cryopreservation. Many studies focusing on gene expression patterns of umbilical cord and dental pulp containing mesenchymal stem cells showed similar gene expressions but they clearly diverged in the differentiation capacity [4]. Moreover few schools of thought suggest MSC derived from dental pulp are more committed to the osteoblastic and odontogenic lineages than MSC of umbilical cord [5]. Furthermore studies on dental pulp may also provide molecular and biological insights into the developmental mechanisms involved in angiogenic and odontogenic processes. The advantages of SHED include [1-4].

- Provides an autologous transplant for life
- Retrieving the pulp is simple and painless procedure
- SHED cells are complementary to stem cells from the cord blood
- Useful for close relatives of the donor.
- Not subjected to the same ethical concerns as embryonic stem cells
- A high percentage of stem cells are present in pulp tissue
- Dental stem cells have also demonstrated compatibility and attachment to various biomaterials.
- Dental stem cells are capable of differentiating or transforming into varied cell types such as bone, dentin, cartilage, fat, nerve, and muscle [5].

The concept of regeneration has significantly advanced after the discovery of stem cells but still the practice of dental pulpal stem cell preservation or usage is yet to be explored .Still in our state not a hand full of dental professionals are practising or advocating the same. Surprisingly many studies have shown that the most regenerative potentials are for those primary teeth and orthodontic extractions which are discarded as a medical surplus now. Many studies researched extensively have shown that these pulpal stem cells have found to contain chondrocytes, osteoblasts, adipocytes and mesenchymal stem cells which hold enormous potential in targeted therapy by minimising the risk of rejection [5-8]. Adipocytes have been successfully used to repair damaged heart muscles5. Few data also suggest indicating its use in spine, orthopaedic conditions, crohn's disease etc8. Chondrocytes on a wider scale used to grow bone and cartilage for transplant and to a lesser extent to grow intact teeth in animal models. Mesenchyme stem cells have successfully used in repair of spinal injury .It may also have the potential to use in neuronal degenerative disorders like Alzheimers and Parkinson's disease. The most recent achievement of these stem cells in the field of dentistry is a new way to battle tooth loss. These stem cells can be better utilized for patients and to a certain extent to their immediate family and blood relatives. Researchers have so far succeeded in making specific dental tissues or tooth like structures in animal models but trails are on-going for the regeneration of functional tooth in humans [8]. United States have made stem cell research as one of the pillars of their health programmes and it is likely that the next innovation in stem cell is the availability of regenerative dental kits ,which enables the dentist the ability to deliver stem cell therapy as a routine dental procedure.

Stem Cell Banks

Dental stem cells are a valuable source of stem cells and are found in teeth with healthy pulp. These teeth could be deciduous teeth, wisdom teeth and other permanent teeth. Presently, these teeth are being discarded as medical waste. A stem cell bank allows an individual the opportunity to preserve their biomaterial for innumerable therapies and can be considered as a biological assurance. The banking of umbilical cord as a source of stem cells, have been encouraged for the past few decades. Dental stem cell banking is complementary to umbilical cord blood banking. Dental stem cells consist of mesenchymal variety of stem cells [9]. The advantage dental stem cells give is possibility of a larger collection. Instead of a 15-20 minute window post-delivery in case of umbilical cord blood banking, dental stem cells can be acquired from milk tooth or wisdom tooth [10]. This increases the opportunity of collection. If one tooth is rejected, the next tooth can be considered for banking. The collection of stem cells from bone-marrow presents multiple collection frequency options but the procedure is invasive and quite painful [10]. On the other hand, dental stem cells can be collected between 6-12 years for children and from adults by extracting their third molars. According to researchers the right time to recover baby teeth with stem cells is before the teeth become very loose. It is necessary for these stem cell banks to be licensed and patented. The patent gives the technology for extraction, multiplication and banking of the dental stem cells. Deciduous teeth especially the canines are the best sources and 12 deciduous teeth are sufficient and for the adults a minimum of 2 molars during the extraction of the third molars. Once collected, the dental stem cells should arrive at the storage facility within 16 hours, much ahead of the 72- hour deadline.

In India stem cell banks are present, and even some of these banks do not only freeze cord stem cells but also dental stem cells of baby teeth [13]. This can be done easily when a child's anterior milk tooth is shedding, the tooth is extracted by the dentist and preserved in a special kit provided from the stem cell bank company who then in their turn transfer the tooth to their special labs to harvest the dental stem cells and store them in their bank for each child confidentially until they are needed later for the child himself or a member of his family [13]. Cryopreservation or banking of stem cells maintains the viability of these cells indefinitely. During cryopreservation, the cells are put to nap through a process called vitrification, in which the tissue is placed in liquid nitrogen at a temperature of

–196 degrees Celsius. The cryo¬preservation process stops all cellular metabolism involving both cell growth and cell death. The cells preserved today can be applied to future regenerative therapies [14, 15]. There are many parents who did not have the opportunity to bank their children's cord blood. This allows these parents another chance to bank their children's accessible and valuable stem cells when they are undergoing a routine dental procedure. The obstacles in dental stem cell preservation are mainly thought in the preservation cost, lack of awareness, ethical issues and insufficient knowledge among the dental professionals. Moreover umbilical cord preservation has more popularized, though both meet similar outcomes. Dental stem cell banking can do wonders in the field of dental and medical research. Stem cell banking can be popularized by effective cost reduction measures.

Dental Pulpal Stem-Cell Biology in Oral Cancer

Cancer is a Greek word Karkinos meaning crab, denoting how carcinoma extends its claws like crab into adjacent tissues [15]. The global burden of cancer continue to increase over centuries as childhood mortality and death from infectious disease decline and people live longer. During 2007, it was estimated that there will be more than 12 million new cancer cases worldwide [16]. The risk of being diagnosed with cancer increase with age. Longer people live, the more likely it is for a specific mutation to occur in their genome, leading to genetic alterations that may lead to malignant phenotype [17]. Most patients with oral cancers or potentially malignant oral mucosal lesion are asymptomatic at the time of diagnosis. Oral Squamous cell carcinoma (OSCC) is the most common malignancy to affect the human oral cavity. Oral squamous cell carcinoma is a multistep process in which multiple genetic events occur that alter the normal functions of oncogenes and tumour suppressor genes (TSG). This can result in increased production of growth factors or numbers of cell surface receptors, enhanced intracellular messenger signalling, and or increased production of transcription factors. Genetic alterations are known to occur during carcinogenesis including point mutations, amplifications, rearrangements and deletions [17]. Oral cancers are usually preceded by clinically evident Potentially Malignant Disorders (PMD) which shows dysplastic changes on histopathological evaluation. Oral squamous cell carcinoma may usually occur from precursor lesions. Most patients with oral cancers or potentially malignant oral mucosal lesion are asymptomatic at the time of diagnosis. If the precursor lesion is diagnosed, scrutinized and managed before malignant progression, it increases the survival rates, and decreases the morbidity associated with treatment of oral cancer [18]. Despite of recentadvances in the treatment of oral squamous cell carcinoma, the mortality rate remains high [18]. Cancer is mainly treated using surgical resection, fractionated radiotherapy, and chemotherapy. However, treatment-related side effects, off-target effects, and drug resistance limit the efficacies of many therapeutic options. Furthermore, metastatic cancer cells usually cannot be eliminated by traditional therapies, and recurrence is extremely likely. Therefore, researchers are working to develop new, effective therapies with low or no toxicity in normal cells.

Recently hematopoietic stem cells and umbilical cord stem cells are being used in the treatment of leukaemia and lymphomas [1]. Stem cells have unique properties, such as migration toward cancer cells, secretion of bioactive factors, and immunosuppression, which promote tumour targeting and evade obstacles currently impeding gene therapy strategies. Preclinical stem cell-based strategies show great promise for use in targeted anti-cancer therapy applications. Nevertheless, there remain scientific concerns regarding the use of stem cell therapies, and further studies are needed to validate preclinical findings [19]. Stem cells, most commonly mesenchymal and neural stem cells, can be modified via multiple mechanisms for potential use in cancer therapies. Common modifications include the therapeutic enzyme/prodrug system, and nanoparticle or oncolytic virus delivery at the tumour site. Stem cells can also be applied in immunotherapy, cancer stem cell-targeted therapy, and anticancer drug screening applications [20]. Few studies have emerged on focussing novel technologies which aim in engineering T lymphocytes to selectively recognize cancer specific markers on transformed cells thus facilitating the elimination of tumour cells without harming normal cells [3]. MSC also have intense immunomodulatory properties and can supress Tcell proliferation through secretion of factors such as transforming growth factor β, hepatic growth factors, prostaglandin E2 and interleukin -10. Stem cell technologies may open new doors for cancer therapy [21]. Stem cells migrate to solid tumours and micro metastatic lesions, facilitating site-specific anti-tumour agent delivery. Stem cells can be engineered to stably express a variety of antitumor agents, overcoming the short half-lives of conventional chemotherapeutic agents. However, conquering stem cell therapy limitations will require additional research to better illuminate relationships between normal and cancer stem cells. A better understanding of fundamental stem cell mechanisms will improve stem cell-based regenerative medicine and anti-cancer strategies, and is imperative for more widespread clinical utilization of stem cell-based therapies. However, while using stem cells to treat human cancers appears theoretically feasible, challenges such as treatment durability and tumeriogenesis necessitate further to be explored improve therapeutic performance and applicability [21].

CONCLUSION

Stem cells of the pulp appear to hold the key to various cell-based therapies in regenerative medicine, but most of the possibilities are in experimental stages and many procedures are undergoing standardization and validation. With the rising involvement of DPSC in regenerative medicine, other concerns that need to be addressed simultaneously include long-term cost effective preservation, in-vitro expansion and its potentialin cancer therapy. Long-term preservation of SHED cells or DPSC is becoming a popular consideration similar to the banking of umbilical cord blood. It may still be necessary to explore the long-term (>15 years) effect of cryopreservation on the post-thaw yield of DPSC/ SHED. Lack of awareness of recent updates is also a pitfall in the dental stem cell research. Alarmingly a recent epidemiological study conducted among dental professionals in Karnataka revealed that almost 84% of their study samples were unaware about the guidelines related to stem cell given by Indian council of Medical Research (ICMR) [20]. So this necessitates the need of spreading cognizance among both dental specialists and at the communal level by conducting CDE programmes, conferences, or seminars which in turn facilitate to enhance the knowledge. It is high time to explore about DPSC on a wider angle for the betterment of humanity, rather keeping it as a "an enigmatic nugget of tooth".

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