Review Article

ID: JCDR/2012/2985:1855

Stem Cell Therapy: A Newhope for Dentist

K. SARASWATHI GOPAL, ARATHY MANOHAR LANKUPALLI

ABSTRACT

While the regeneration of a lost tissue is known to mankind for several years, it is only in the recent past that research on regenerative medicine/dentistry has gained momentum and eluded the dramatic yet scientific advancements in the field of molecular biology. The growing understanding of biological concepts in the regeneration of oral/dental tissues coupled with experiments on stem cells is likely to result in a paradigm shift in the therapeutic armamentarium of dental and oral diseases culminating in an intense search for "biological solutions to biological problems." Stem cells have been successfully isolated from variety of human tissues including orofacial tissues. Initial evidence from pioneering studies has documented the likely breakthrough that stem cells offer for various life-threatening diseases that have so far defeated modern medical care. The evidence gathered so far has propelled many elegant studies exploring the role of stem cells and their manifold dental applications. This review takes you on a sojourn of the origin of stem cells, their properties, characteristics, current research, and their potential applications. It also focuses on the various challenges and barriers that we have to surmount before translating laboratory results to successful clinical applications heralding the dawn of moderan dentistry.

Key Words: Dental pulp stem cell (DPSC), regeneration, scaffolds, stem cells, Periodontal regeneration, Repair and regeneration of bone in craniofacial defects, Whole tooth regeneration, Regeneration of damaged coronal dentin and pulp

INTRODUCTION

The sojourn of science has unraveled and understood that the secret of life lies in the "DNA," thanks to Sir James Watson and Crick for their epoch making a historic discovery. In our endeavor to demystify the DNA, we have realized that scientific discoveries in cellular, developmental, and molecular biology have truly revolutionized our collective understanding of the biological processes that could greatly impact and dramatically change our lives in the future.

In the new millennium, where biology and biotechnology have replaced chemistry, we are exploring "biological solutions to biological problems." Owing to the extraordinary advances taking place in the field of cellular and molecular biology, we are on the verge of a paradigm shift, evolving from offering simple mechanical care to consider biological solutions to health promotion, risk assessment, diagnosis, treatment, and even prognosis.

Although stem cell technology is just emerging, the regeneration of body parts is hardly a new concept. The regenerative capability of a living creature was recorded as early as 330 BC, when Aristotle observed that a lizard could grow back the lost tip of its tail. Since then, there have been slow but steady attempts at understanding the regenerative capabilities of human being and it is only in the last decade that we have seen an information explosion in the area of stem cell research. Stem cells are likely to revolutionize the entire health care delivery. The time is certainly ripe for all of us to familiarize ourselves with the following: what are stem cells, their characteristics, their potential applications, current research translating to therapy, and possible barriers of its application from the bench to the bedside/chair.

What are Stem Cells and their Characteristics? They are unspecialized cells with an extraordinary ability to self-renew, capable of differentiating into one or more specialized cell types playing a crucial role in homeostasis and tissue repair. When called into action following an injury, a stem cell self-renews - undergoes cell division and gives rise to one daughter stem cell and one progenitor cell. A progenitor cell is an intermediate cell type formed before it achieves a fully differentiated state. It is regarded as committed to differentiating along a particular cellular developmental pathway of stem cells:

Stem cell → Stem cell + Progenitor cell → Differentiated cell

Based on their origin, stem cells are categorized either as embryonic stem cells (ESCs) or as postnatal stem cells/ somatic stem cells/adult stem cells (ASCs).

Characteristics

1. Totipotency: generate all types of cells including germ cells (ESCs).
2. Pluripotency: generate all types of cells except cells of the embryonic membrane.
3. Multipotency: differentiate into more than one mature cell (MSC).
4. Self-renewal: divide without differentiation and create everlasting supply.
5. Plasticity: MSCs have plasticity and can undergo differentiation. The trigger for plasticity is stress or tissue injury which upregulates the stem cells and releases chemoattractants and growth factors.

Among the types of differentiation are:

1. Direct differentiation: a specific type of cell in a special niche developed in a multistep unidirectional pathway (e.g., MSCs differentiating into osteoblasts/fibroblasts).

2. Transdifferentiation: direct conversion of one cell type to another different cell type (e.g., blood cells into brain cells and vice versa).
3. Dedifferentiation: a unipotent stem cell becoming a multipotent one.
4. Cell fusion: a stem cell fusing with a somatic cell resulting in another lineage (e.g., ESCs fuse in vitro with HSCs and neuronal cells).

Embryonic stem cells

Embryonic stem cells (ESCs) are derived from embryos that are 2-11 days old called blastocysts. They are best grown from supernumerary embryos obtained from in vitro fertilization centers. They are totipotent - cells virtually capable of differentiating into any type of cell including the germ cell. ESCs are considered immortal as they can be propagated and maintained in an undifferentiated state indefinitely. These stem cells have the highest potential to regenerate and repair diseased tissue and organs in the body. However, the therapeutic benefit of ESCs is bogged by a controversy owing to the belief that the process of extraction of stem cells from an embryo destroys the embryo itself and some view this as taking life, thereby, raising moral and ethical concerns [1,2]. Further, it is difficult to control the growth and differentiation of the embryonic stem cell posing risk of tumorogenicity and teratoma formation. While research is on to overcome some of these shortfalls as of now, ESCs are not so far used therapeutically and have only remained an excellent platform for research.

Adult stem cells

Adult stem cells are found in most adult tissues. They are multi-potent - capable of differentiating into more than one cell type but not all cell types. The plasticity of an adult stem cell is described as its ability to expand beyond its potential irrespective of the parent cell from which it is derived [3]. For example, dental pulp stem cells not only develop into tooth tissue but also have the ability to differentiate into neuronal tissue.

Depending on their origin, adult stem cells can be further classified as haemopoetic stem cells (HSCs) and mesenchymal stem cells (MSCs). HSCs are obtained either from cord blood or peripheral blood. MSCs are those that originate from the mesoderm layer of the foetus and in the adult reside in a variety of tissues such as the bone marrow stem cells (BMSCc), limbal stem cells, hepatic stem cells, dermal stem cells, etc.

Stem cells have also been isolated from orofacial tissues which include adult tooth pulp tissue, pulp tissue of deciduous teeth, periodontal ligament, apical papilla, and buccal mucosa. Gronthos et al. have isolated stem cells from adult human dental pulp (DPSCs) that exhibit a similar immunophenotype to bone marrow stem cells. Stem cells from human exfoliated deciduous teeth (SHED) represent a unique population of multipotent stem cells that are easily accessible and are more immature in the cell hierarchy than the adult pulp stem cells [4]. Using a similar methodology, multipotent stem cells from the human periodontal ligament (PDLCs) have also been described [5]. Recently, a new population of mesenchymal stem cells (MSCs) residing in the apical papilla of incompletely developed teeth (SCAP) have been isolated and demonstrated in elegant studies [6,7,8].

Potential Applications in Dentistry. The regenerative potential of adult stem cells obtained from various sources including dental tissues has been of interest for clinicians over the past years and most research is directed toward achieving the following:

- Regeneration of damaged coronal dentin and pulp
- Regeneration of resorbed root, cervical or apical dentin, and repair perforations
- Periodontal regeneration
- Repair and replacement of bone in craniofacial defects
- Whole tooth regeneration.

Regeneration of damaged coronal dentin and pulp

To this date, no restorative material has been able to mimic all physical and mechanical properties of tooth tissue. Furthermore, we have not been successful in providing an ideal solution to certain situations, such as an immature tooth with extensive coronal destruction and reversible pulpitis. If the regeneration of tooth tissue is possible in these situations, it facilitates physiologic dentin deposition that forms an integral part of the tooth thereby restoring structural integrity, minimizing interfacial failure, microleakage, and other consequent complications. Similarly, young permanent teeth that require apexogenesis or apexification are the perfect candidates for the regeneration of pulp as they allow completion of both vertical and lateral root development, improving the long-term prognosis. However, pulp regeneration in fully formed teeth may not be of great benefit, although there is sufficient evidence to say that a restored vital tooth serves longer than a root-canal-treated one.Pulp tissue regeneration involves either delivery of autologous/ allogenic stem cells into the root canals or implantation of the pulp that is grown in the laboratory using stem cells. Both these techniques will have advantages and certain limitations that need further research. A landmark study conducted by Gronthoset al. demonstrated both in vitro and in vivo in animals that dental pulp stem cells (DPSCs) were capable of forming ectopic dentin and associated pulp tissue.

Periodontal regeneration

Regenerating the periodontium has always been a high priority in craniofacial regenerative biology. Due to the complex structure of the periodontium (consisting of hard and soft tissues), its complete regeneration has always remained a challenge. All the current regenerative techniques such as autologous bone grafts, allografts, or alloplastic materials have limitations and cannot be used in all clinical situations. Therefore, a cell-mediated bone regeneration technique will be a viable therapeutic alternative. Kawaguchi et al. demonstrated that the transplantation of ex vivo expanded autologous MSCs can regenerate new cementum, alveolar bone, and periodontal ligament in class III periodontal defects in dogs. Going a step further, periodontal ligament cells cultured in vitro were successfully reimplanted into periodontal defects in order to promote periodontal regeneration by Hasegawa et al. A subsequent study by the same group reported a similar approach in humans. This study reported firm evidence that stem cells can be used to regenerate a tissue as complex as the periodontium.

Repair and regeneration of bone in craniofacial defects

Craniofacial bone grafting procedures rely on autologous bone grafting, devitalized allogenic bone grafting (using bone from bone bank), and natural/synthetic osteoconductive biomaterials. Autologous bone grafting is limited by donor site morbidity and allogenic bone is often destroyed soon. A long-term outcome using biomaterials relies on their ability to encourage local cells to completely regenerate a defect and results are often not encouraging. If stem cells can be harvested in a scaffold and transplanted into a defect to regenerate the lost tissue, it can alleviate a lot of complications associated with the traditional techniques.

Abukawa et al. used a novel scaffold design with a new fabrication protocol to generate an autologous tissue engineered construct which was used to repair a segmental mandibular defect.

Whole tooth regeneration

A therapeutic option that was unthinkable a few years ago seems an achievable goal today. Even to this day, the replacement of missing teeth has limitations. Although, implants are a significant improvement over dentures and bridges, their fundamental limitation is the lack of natural structural relationship with the alveolar bone (absence of periodontal ligament). They rely on direct integration of bone on tooth surface which is indeed an unnatural relationship as compared with the natural tooth. Further, they are also associated with a lot of esthetic, functional, and surgical limitations that affect their prognosis. Nakao et al. recently engineered teeth ectopically and transplanted them into an anthropicsite in a mouse jaw.

On oral penicillin V prophylaxis and is neurologically normal. An accidental intra-arterial injection of benzathine penicillin is a possible but hazardous side effect of this drug. Benzathine penicillin and Procaine penicillin, both being opaque and viscous preparations for intramuscular injection, the visualization of the aspirated blood is difficult and hence, there is no absolute possibility of being completely sure of avoiding the intravascular injection of the drug [1]. A spectrum of injuries, sometimes permanent, to the gluteal region, the distal extremities, the perineum and the spinal cord, has been documented, which results from the inadvertent intra-arterial injection, probably due to vascular occlusion by the large crystals of the penicillin salts [2]. On further analysis of the literature, it was postulated that the patient had received an unintentional injection of Benzathine penicillin into the gluteal artery and that he subsequently developed the 'Nicolau syndrome', which has been described as 'livedoid dermatitis' – a very rare complication of the intramuscular injections which manifest as excruciating pain, immediately after the injection, followed by discolouration and oedema [3,4]. As the clinical features of such an accidental intra-arterial injection depend on the vessel into which the penicillin salt had been injected, dangerous and irreversible complications like progressive paralysis and paraplegia which are similar to transverse myelitis, have been described in the literature following the occlusion of the spinal vasculature. The earlier case reports have been documented in infants, wherein even profound complications like coma, convulsions and death have occurred [5].

Our case report reiterates the fact that the complications which are associated with an intramuscular injection of Benzathine penicillin, which have been described in the literature in the earlier decades and now have almost been forgotten, are still very significant. In peripheral health set ups where auxiliary health professionals administer the drug intramuscularly, these adverse events are very much possible and they could end up in very dangerous and sometimes lethal side effects. Hence, using penicillin preparations with caution, awareness of the occurrence of such complications and their immediate management is the need of the hour.

CONCLUSION

Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical and dental applications. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics, it is certain that the future is going to be exciting for all of us. We have moved on from the surgical model of care to the medical model and are likely to move onto the biological model of care. The need of the hour is high-quality research coupled with collaboration between basic scientists and the clinicians. A team effort engaging the expertise of the molecular biologists, immunologists, biomaterial scientists, cell biologists, matrix biologists, and practicing dental surgeons is crucial in attaining the desired goal. Stem cell therapy is no longer science fiction. Recent developments in the technique of stem cell isolation and expansion together with advances in growth factor biology and biodegradable polymer constructs have set a stage for successful tissue engineering of tooth/tooth-related tissues. Stem cell therapy has brought in a lot of optimistic hope amongst researchers, doctors, and not to forget the patients who are the chief supportive and beneficiary of this innovation.

REFERENCES

[1] Evans MJ, Kaufman MH. Establishment in culture of pluripotent cells from mouse embryos. *Nature* 1981;292:154-56
[2] Keller GM. In vitro differentiation of embryonic stem cells. *Curr Opin Cell Biol* 1995;7:862-69.
[3] Fortier LA. Stem cells, classification, controversies and clinical applications. *Vet Surg* 2005;34:415-23.
[4] Gronthos S, Mankani M, Brahim J, GehronRobey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs). 2000.
[5] Miura M, Gronthos S, Zhao M, Lu B, Fischer LW, Robey PG, et al. SHED. Stem cells from human exfoliated deciduous teeth. *ProcNatlAcadSci USA* 2003;100:5807-54.
[6] Seo B, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004;364:149-55.
[7] Sonoyama W, Liu Y, Fang D, Yamaza T, Seo BM, Zhang C, et al. Mesenchymal stem cell mediated functional tooth regeneration in Swine. *PLoS One* 2006;1:e79.
[8] Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: Pilot study. *J Endod* 2008;34:166-71.

AUTHOR(S):
1. Dr. K. Saraswathi Gopal
2. Dr. Arathy Manohar Lankupalli

PARTICULARS OF CONTRIBUTORS:
1. Professor and HOD, Department of Oral Medicine And Radiology, Meenakshi Ammal Dental College, Chennai, India.
2. P.G.Student Department of Oral Medicine and Radiology, Meenakshi Ammal Dental College, Chennai, India.

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. K. Saraswathi Gopal Professor and HOD,
Department of Oral Medicine and Radiology,
Meenakshi Ammal Dental College, Chennai.

FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Jul 28, 2011**
Date of Peer Review: **Sep 12, 2011**
Date of Acceptance: **Dec 22, 2011**
Date of Publishing: **Feb 15, 2012**