Review Article

Regenerative Capacity of Dental Pulp Stem Cells: A Systematic Review

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Objectives: The dental pulp contains undifferentiated mesenchymal cells, blood vessels and so on, which are responsible for routine functions of a tooth. The determination of stemness and regenerative properties using biomarkers and further application in routine practice may unravel its potential.

Materials and Methods: Inclusion criteria—original research articles published in English, from 2000 to 2019, were collected both manually and by electronic search from databases of Cochrane, Medline, Embase, and PubMed. Exclusion criteria—articles other than English and review manuscripts were omitted. The shortlisted articles were reviewed for specific biomarkers, to assess the regenerative potential, stemness, and lineage of dental pulp stem cells.

Results: Of 512 articles, 64 were selected and reviewed to determine the mesenchymal, neurogenic, vasculogenic, hematopoietic, and stem cell potential. On the basis of the search analysis, a panel of markers was proposed.

Conclusion: The application of proposed markers, on a pulpectomized tissue derived from human teeth, may be helpful to determine the regenerative potential and the usefulness in regenerative medicine and tissue engineering.

KEYWORDS: Biomarkers, dental pulp stem cells, regenerative medicine, stem cells, tissue engineering

INTRODUCTION

Dental pulp is a type of unique connective tissue that has an anatomical architecture closely restricted by its location within a rigid chamber of tooth. The dental pulp consists of cellular, noncellular components, collagen, and fibrillin fibers. The nonfibrous components include substances that are derived from the extracellular matrix, mainly glycosaminoglycan, proteoglycans, and other adhesion molecules. This matrix plays a pivotal role in the development, migration, division, shape, and function of the tissue. The presence of blood vessels and nerves plays an important role in the physiological functions of the tooth. It has varied functions ranging from detecting stimuli and also initiating and participating in response against insult.[1] Their regenerative capacity is explained on the basis of presence of various cellular constituents of the dental pulp, which includes odontoblasts, fibroblasts, defense, and undifferentiated cells.[2] The undifferentiated group of cells present in pulp tissue comes under the category of postnatal stem cells. Stem cells are seen in the pulp tissue of both adults and children, within the superficial cell-rich zone, underneath the Hoehl's cell layer. They are believed to originate from the neural crest cells and segregate into different cell types.[3,4]
Dental pulp stem cells (DPSCs) are desirable for their unique properties to differentiate into various cell types, which include dentin-producing odontoblasts, neural predecessor cells, chondroblasts, endothelium formative cells, lipocytes, myoblasts, and osteoblasts. DPSCs are mesenchymal cells that constitute one of the most broadly researched cells. Earlier studies have proved that DPSCs can form tissues such as dentin, pulp, and periodontal ligament fibers. These are proved to be a potential stem cell source for orthopedic and orofacial restoration, and it is postulated that these cells may contribute beyond the stomatognathic system.

Regenerative potentials of the dental pulp tissue have been established in various fields such as, cure of neuro-deficit disorders, cardiac-related disorders, muscular disorders (muscular dystrophy), genetic and lifestyle disorders, liver diseases, ophthalmic-related defects, immune diseases, diseases related to the orofacial, bone defects and infertility treatments. Hence based on the aforementioned facts, systematic review in DPSC was undertaken, which includes various biomarkers having regenerative potential and lineage, and with probable clinical applications were identified.

**MATERIALS AND METHODS**

This review was carried out based on the standard guidelines for making of a systematic review (Prisma Guidelines 2015) [Figure 1].

**Inclusion criteria**

Original research articles published in English in the year from 2000 to 2019 and related to the title were selected for the review.

**Exclusion criteria**

Articles other than English language and review manuscripts were excluded. The stem cell markers and regenerative markers were the main method of determination of the potentiality of the dental pulp tissue.

**Sources, search strategy, and study selection**

Various standardized search engines were used, such as PubMed, Cochrane Library, Embase, and Medline. In addition, a manual search was performed on the personalized collection of journals.
Table 1: The type of markers used by various authors and the interpretations derived\textsuperscript{[15-78]}

| S no. | Author name, year | Biomarkers used | Interpretation |
|-------|------------------|-----------------|----------------|
| 1     | Gronthos et al., 2000 | DPSCs (Differentiation Potential) Collagen type 1,2,3 MyoD Alpha SMA Neurofilamin MUC-1 (CD 146) Osteocalcin Osteonectin Bone sialoprotein Osteopontin AlkPhos PPAR-gamma FGF-2 CD 44, CD 45, CD 34, CD14 VCAM-1 (calcium adhesion molecule) Integrin beta-1 | Adipogenic, odontogenic, neurogenic, osteogenic, myoblasts formation, endothelial potency chondrogenic, cardiogenic potential |
| 2     | Karoaz et al., 2010 | Collagen type 2, SOX-9, collagen type 1, osteopontin, osteonectin, osteocalcin, beta III tubulin, NF, nestin, MAP proteins, alpha SMA, myosin IIa, myogenin, desmin Adipogenic markers— adipophillin, leptin | Regeneration of various structures |
| 3     | Karoaz et al., 2012 | STRO-1 | Positivity confirmed regenerative potential. Also neural crest origin of DPSC promoted neurogenic potential |
| 4     | Karoaz et al., 2011 | Cytokeratin 18 and 19 | Odontoblast differentiation and dentine repair. |
| 5     | Beatriz et al. | CD3, CD4, CD 5, CD 7, CD 8, CD 10, CD 11b, CD18, CD14, CD 15, CD 29, CD 33, CD 44, CD 45, CD71, CD 73, CD 90, CD106, CD 117, CD 123, CD 138, CD 146, CD 166 and HLA antigens. CD 9, CD10, CD13, CD29, CD44, CD56, CD59, CD71, CD73, CD90, CD105, CD106, CD117, CD146, CD166, CD 127, CD 11b, CD14, CD19, CD31, CD34, CD43, CD45, CD 150, OCT ¾ SOX2 NANO, c-myc KLF-4, LIN-28, STRO-1, SSEA-3, SSEA-4, TRA-1-60 | Regenerative potential to repair neurogenic, cardiac, hepatic, opthalmic, bony, and myogenic deficits |
| 6     | Atari et al., 2012, Abou-Asi et al., 2015 | HNF3beta\textsuperscript{c}, SSEA-4\textsuperscript{c}, Oct4\textsuperscript{c}, Nanog\textsuperscript{c}, FLK-1\textsuperscript{c}, Sox2\textsuperscript{c}, Lin28\textsuperscript{c}, Nestin\textsuperscript{c}, c- Myc\textsuperscript{c}, CD13\textsuperscript{c}, CD105\textsuperscript{c}, CD34\textsuperscript{c}, CD45\textsuperscript{c}, CD90\textsuperscript{c}, CD29\textsuperscript{c}, CD73\textsuperscript{c}, STRO-1\textsuperscript{c}, and CD146 | Potency to regenerate from DPSC’s demonstrated osteogenic induction |
| 7     | Ferro et al., 2012a | SSEA4, OCT3/4, NANO, SOX2, LIN28, CD13, CD105, CD34, CD45, CD90, CD29, CD73, STRO1, and CD146 | Demonstrated osteogenic induction |
| 8     | Ferro et al., 2012b | CD10, CD29, CD44, CD49a, CD49d, CD59, CD73, CD90, CD105 and CD133, CD117, CD 34,CD45, Oct4, Sox-2, and Nanog | Osteoblast differentiation, myocyte, hepatocyte, neural differentiation potential was highlighted. Hepatocytic differentiation potential |
| 9     | Ishkitiev et al., 2012 | Presence of OCT4, CD 117 and various other hepatocytic growth factors | Osteogenic and hepatocytic potential |
| S no. | Author name, year | Biomarkers used | Interpretation |
|-------|-------------------|-----------------|----------------|
| 10    | Miura et al., 2003 | STRO-1, CD 146, GFAP, nestin, neurofilament, beta-3 tubulin | Adipogenic, neurogenic, odontogenic, osteogenic, and myoblastic potential, endothelial potency, hepatocytes formation |
| 11    | Kerkis et al., 2006 | Nanog, Oct4, Nucleostemin, Slain-1, Jmjd1, Jmjd2, and Cyclin D1 | Ability to regenerate myogenic (skeletal) tissues |
| 12    | Wang et al., 2010  | STRO-1, CD29, CD90, CD146, CD34, vimentin, nestin, and TH, dentin sialoprotein, and betaIII-tubulin | Differ differentiation into neurogenic, odontogenic cells, and lipocytic structures |
| 13    | Wang et al., 2012  | STRO-1, CD 146, CD29, CD 105 | Cell proliferative indices and osteogenic and adipogenic potential were elicited |
| 14    | Akpınar et al., 2014 | CD3, CD4, CD13, CD14, CD29, CD34, CD44, CD45, CD73, CD90, CD106, CD117, CD146, CD166, HLA-DR, and HLA-ABC | Ability to derive from all stem cell lines. |
| 15    | Trivanoic et al., 2015 | Pluripotency markers (Nanog, Oct-4, SOX-2, and SSEA-4, CD90, CD44, CD73, and hematopoietic cells markers CD34 and CD45) | Higher proliferative indices |
| 16    | Nagako et al., 2012 | Alpha SMA, STRO-1, nestin | Regeneration in wound healing. |
| 17    | Feng Juan et al., 2014 | STRO-1 and CD 271 | Cardiovascular repair. Low Trilineage differentiation |
|       |                   | SSEA-4, CD 146, CD 49f, 3G5, STRO-4 | Tripotency, trilineage potency facilitates hematopoiesis, pericyte marker |
| 18    | Pereira et al., 2014 | STRO-1 | Proliferative capacity of MSCs isolated from normal and inflamed dental pulp |
| 19    | Alongi et al., 2014 | STRO-1, CD 90, CD 105, CD 146 | Inflamed dental pulps expressed higher levels of these markers |
| 20    | Evandro et al., 2017 | CD 73, CD 90, CD 105, CD 45 | Produced angiogenic proteins like endothelin, IGF, binding protein 3 (IL-3), pentraxin-3, serpin E (SE1), serpin F1 (SF1) |
| 21    | Paloma dias TELLES et al., 2010 | CD 31, VE-Cadherin, VEGFR-2- Endothelial markers | Expression of these markers, and presence of VEGF, helped organize capillary-sprouts |
| 22    | Akihiro et al., 2015 | STRO-1, ABCG2, CD90, alpha-smooth muscle actin, Bmi1, CD 31, CD90, CD 31/ CD 146 | Positivity of cells in the perivascular region |
| 23    | Shi and Gronthos et al., 2003 | STRO-1, CD 146 and Alpha smooth muscle actin | Niche of stem cells in the dental pulp |
| 24    | Shi et al., 2005 | CD14, CD34, CD44, CD45, CD106 CD146,3GS,STRO-1, a-SM actin Collagen Type-I, | Found hematopoietic stem cells in dental pulp |
|       |                   | Osteonectin, scleraxis, alkaline phosphatase, osteocalcin, osteopontin, collagen type-III, bone sialoprotein, dentin sialophosphoprotein | DPSCs have osteogenic potential |
| 25    | Sloan and Smith et al., 2007 | CD 29, CD44, CD105, CD 146, and STRO-1 | Multi-lineage differentiation potential |
| 26    | Struys et al., 2010 | CD 29, CD44, CD105, CD 146, and STRO-1 | Undifferentiated h DPSC’S-regenerative potential |
| 27    | W. Martens et al., 2012 | CD 29, CD44, CD105, CD177, CD146, and STRO-1 | Capable of deriving neural structures |
| 28    | Safford et al., 2002; Tropel et al., 2006 | Neural markers like nestin, beta- III tubulin, neurofilament, S100, synaptophysin, Vimentin | Success of differentiation to neurogenic structures |
| 29    | Tropel et al., 2006 | Neural markers | Cells with positivity showed fibroblastic behavior. |
| 30    | Alexanian et al., 2008 | STRO-1 | |
| S no. | Author name, year | Biomarkers used | Interpretation |
|-------|-------------------|-----------------|----------------|
| 31    | Arthur et al., 2008 | Neuronal-specific markers | Neurogenic potential of DPSC. DPSCs provide a accessible source of precursor stem cells |
| 32    | Kiraly et al., 2009 | Neural differentiation markers vimentin, nestin, N-tubulin, neurogenin-2 and neurofilament-M | Neurogenic potential |
| 33    | Karaöz et al., 2010 | Differentiation Markers—CD13, CD44, CD90, CD146 and CD166, CD3, CD8, CD11b, CD14,CD15, CD19, CD33,CD34, CD45, CD117, and HLA-DR | Adipogenic, osteogenic, chondrogenic, myogenic, and neurogenic potential |
| 34    | Nosrat et al., 2001 | PGP9.5, Protein 43, synaptophysin | Production and secretion of neurotrophic factors |
| 35    | Nosrat et al., 2004; 2008 | Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and GDNF | Huge potential to treat neurological disease. |
| 36    | Arthur et al., 2008 | Neurotrophic factors, like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line–derived neurotrophic factor (GDNF) beta III Tubulin | Differentiation to neural structures |
| 37    | Apel et al., 2009 | Neurotrophic factors NGF, GDNF, BDNF, and BMP2 | Neurogenic potential |
| 38    | Shi and Gronthos et al., 2003 | Endothelial cell marker and pericytic markers | Niches of cells, in the perivascular region, show positivity |
| 39    | Tecles et al., 2005 | Anti-BrdU antibody | Positivity surrounding the perivascular area. Has odontoblastic capacity and helps in repair during odontoblastic injury |
| 40    | Sloan and Smith 2007 | STRO-1, CD 146, alpha smooth muscle actin and the pericyte-associated antigen 3G5, collagen XVIII a1, IGF-2-cyclin-dependent kinase 6 | Positivity confirmed pluripotency of DPSC’s vasculogenic and myofibroblastic potential |
| 41    | Amera Alkasi et al., 2013 | CD105, CD166 | DPSCs show mesenchymal stem cell properties |
| 42    | Afshin Khorsand et al., 2013 | CD 90, CD 44, CD 146, SSEA-4, and anti-macrophage marker | Capable of differentiating to bone, cartilage, and adipose tissues |
| 43    | Bressan et al., 2012 | Collagen type I expressing osteopontin, RUNX, v WF VEGF, osteonectin, osteocalcin, CD 31, VEGF mRNAs | Osteogenic cells capable of producing an extracellular matrix is located |
| 44    | Chunwei Zhang et al., 2018 | CD 71, CK 14, integrin alpha-6 and PCNA | Transplanted DPSCs are inducted to form esophageal stem cells in vivo, to cure esophageal problems |
| 45    | Tomoatsu Kaneka et al., 2013 | CD146, CD 105, CD 166 | Density of stem cell associated marker higher in coronal pulp, suggests that coronal pulp harbors more stem cells |
| 46    | Huang et al., 2010 | Dentin sialophosphoprotein, bone sialoprotein, alkaline phosphatase, and CD105 | Multipotency is demonstrated by its of osteogenic, adipogenic, and chondrogenic capacity |
| 47    | Ivanovski et al., 2006 | CD 146 | The ability to generate and regenerate vascular and muscular components |
| 48    | Huang et al., 2009 | Oct4, Nanog, SSEA-3, SSEA-4, TRA-1–60, and TRA-1–81 | Multipotentiality |
| 49    | Demarco et al., 2011 | SHED express STRO-1 and CD146. Using different transcription factors (Oct4, Sox2, Klf4, Myc) | Positivity toward these markers helped in regenerative potential |
Two oral pathologists reviewed the articles and an experienced reviewer specialized in stem cell gave final decision.

Databases Keywords term and text word search
PubMed Dental pulp AND stem cells
Medline Immunohistochemistry AND dental pulp
Cochrane Immunohistochemistry AND stem cells
Embase Regeneration AND dental pulp
In vitro studies AND dental pulp
In vivo studies AND dental pulp
Methods AND stem cell regeneration
Biomarkers AND stem cell

| S no. | Author name, year | Biomarkers used | Interpretation |
|-------|-------------------|-----------------|----------------|
| 50    | Maurin et al., 2009 | MAP1B | Generate neural components |
| 51    | Montzka et al., 2009 | MAP1B, CD146,STRO-1 | Neurogenic potency |
| 52    | Askari et al., 2015 | Olig2 and GFAP (glial fibrillary acidic protein)—markers for neuronal precursors and astrocytes | DPSC-derived OPCs can differentiate into more mature oligodendrocytes |
| 53    | Kerkis et al., 2007 | Nanog, Oct4, nucleostemin, Slain-1, JmjD1, JmjD2, and Cyclin D1 | Ability to regenerate myogenic skeletal tissues |
| 54    | Ebrahimi et al., 2011 | Nanog, oct4, nucleostemin, slain-1, jmjD1a, jmjD2c, and cyclin D1 | Neurogenic potential |
| 55    | Tatullo et al., 2014 | STRO-1, CD29, CD44, CD73, CD90, CD105, CD146, CD166, and CD271 | Odontoblastic, osteoblastic, melanocytic, neurogenic, chondrocytic, and lipocytic potential of DPSCs derived |
| 56    | Kawashima et al., 2012 | STRO-1, CD29, CD44, CD73, CD90, CD105, CD146, CD166, and CD271. | Dentinogenic, osteogenic, myogenic, chondrogenic potency. Cornea, neural, and hair follicles can be regenerated |
| 57    | Yan et al. 2010b | Lin28, Nanog, Oct4, and Sox2, or c-Myc, Klf4, Oct4, and Sox2 | Forms induced pluripotent stem cells |
| 58    | Oda et al. 2010 | Sox2, Oct3/4, and Klf4 | iPSC generation using mesenchymal stem cells by retroviral transduction of Oct ¾, SOX-2, and Klf-4 without Myc |
| 59    | Tamaoki et al. 2010 | NANOG, SSEA-3, Tra-1-81 | iPSC cell Banks are aided by this boon |
| 60    | Yoo et al., 2013 | CD 34 | Precursor/progenitor cells are identified (endothelial progenitor cells) |
| 61    | Nosrat et al., 2004 | Neurotrophic factors, including nerve growth factor (NGF), BDNF, and GDNF | Capable of neurogenic curative and regenerative properties |
| 62    | Gronthos et al., 2000 | CD 14, CD44, CD 34, CD45, Integrin beta-1, MyoD, VCAM-1, alpha-SM Actin, MUC-18, neurofilamin, collagen-1, collagen-3, collagen-2, osteocalcin, BSP, osteonectin, osteopontin, PPAR gamma, AlkPhos, FGF-2 | Increased clonogenicity and proliferative and regenerative capacity |
| 63    | Talaat et al., 2015 | Markers dentin sialoprotein and bone sialoprotein | Lead to pulp regeneration and dentin pulp complex formation |
| 64    | Ferro et al., 2012 | Markers dentin sialoprotein CD 14, CD44, CD 34, CD45 | Proliferative and capable of regenerating a tissue |

Discussion
The dental pulp is an intricate tissue that has got multiple potentials and functions to protect the pulp against challenges such as caries or dental trauma. Michael Goldberg[12] had earlier proposed that the knowledge of the inbuilt defense mechanisms employed by the dental pulp has given similar ideas to induce pulp regeneration therapeutically. Ingle’s has observed that multiple growth factors act as important controllers in the instigation of each of the phases of tooth development.[13] This supports the idea of regenerating an entire dentine–pulp complex from the dental pulp tissue itself.
Though earlier studies have been conducted regarding its regenerative potential, a proper categorization of the stem cells derived has not been made.\textsuperscript{[14]} Hence review has been formulated on the following three criteria:

1. To determine the maximum number of immunohistochemical markers that were used in determining the potency of the pulpal tissue
2. To categorize the markers based on the respective properties such as mesenchymal, multi-lineage potency, vasculogenic, neurogenic, osteogenic, muscularogenic, dentinogenic, and hematopoietic, thereby confirming the pluripotent nature of the pulpal tissue
3. To derive a standardized protocol of panel of markers.

Markers used by various authors and its application in the pulp are systematically analyzed in this review [Table 1]. On the basis of the results, the multi-lineage potency of the dental pulp tissue predicted by various markers has been tabulated [Table 2].

A panel of markers is proposed based on the markers used frequently by different authors, which shows the multi-lineage capacity and to support our aim of this review [Table 3].

\textbf{CONCLUSION}

DPSC has a multi-lineage capacity, proved by various studies. The pulp tissue, which is considered as biological waste following extraction and endodontic treatment, can be harvested for the study. DPSC being mesenchymal and neuroectodermal origin has great potency for various therapeutic and regenerative purposes. It is imperative to study about this tiny tissue and its potential. On the basis of our review, we suggest that preservation of dental pulp tissue and subjecting them to the panel of biomarkers such as CD146, CD 73, CD 105, STRO-1, and SOX-2 will unravel its regenerative potential and lineage. The limitation of this analysis is that the panel of markers proposed is yet to apply practically in a pulp tissue to confirm its viability.

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Nil.

\textbf{Conflicts of interest}

There are no conflicts of interest.
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